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REVIEW

Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review

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Abstract Glycogen storage disease type 2/Pompe disease is a progressive muscle disorder with a wide range of phenotypic presentations, caused by an inherited deficiency of acid alpha-glucosidase. Since 2004 only a limited number of patients have been treated with recombinant human alpha-glucosidase from rabbit milk whereas since 2006 enzyme replacement therapy (ERT) with alglucosidase alfa has been licensed for the treatment of Pompe disease. This systematic review evaluates the clinical efficacy and safety of alglucosidase alfa treatment of juvenile and adult patients with late-onset Pompe disease (LOPD). Studies of alglucosidase alfa treatment of LOPD patients—published up to January 2012—were identified by electronic searching of the EMBASE and MEDLINE databases, and manual searching of the reference lists. Data on ERT outcomes were extracted from selected papers and analyzed descriptively. No statistical analysis was performed owing to data heterogeneity. Twenty-one studies containing clinical data from 368 LOPD patients were analyzed. Overall, at least two-thirds of patients were stabilized or had improved creatine kinase levels and muscular and/or respiratory function following treatment with alglucosidase alfa. ERT was well tolerated; most adverse events were mild or moderate infusion-related reactions. In conclusion, alglucosidase alfa treatment is effective and well tolerated and attenuates progression of LOPD in most patients. Further research is required to investigate factors such as age at diagnosis, phenotypic presentation, and genotypic characteristics, identification of which may enable better clinical and therapeutic management of LOPD patients.

Keywords Late-onset Pompe disease (LOPD) · Glycogen storage disease type 2 · Enzyme replacement therapy · Alglucosidase alfa · Systematic review

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Introduction

Glycogen storage disease type 2/Pompe disease is a rare, progressive muscle disorder caused by a deficiency of acid alpha-glucosidase (GAA). In patients with Pompe disease, glycogen gradually accumulates in muscle cells causing irreversible muscle damage and a range of clinical signs and symptoms including respiratory insufficiency and skeletal muscle weakness. Overall incidence ranges from 1 in 33,000 to 1 in 300,000, depending on geographic region and ethnicity [3, 6, 18].

Pompe disease may present with different clinical entities depending on the age of onset: two classical phenotypes have been described as infantile and late-onset forms. The infantile onset generally shows predominant cardiorespiratory involvement with muscle hypotonia and exitus by the first 2 years of life. The late-onset form may present with variable rates of progression and different clinical patterns, for example isolated hyperCKemia, muscle weakness with a limb-girdle distribution and/or acute respiratory dysfunction [11, 34, 38].

In 2004, few patients started enzyme replacement therapy (ERT) with recombinant human rabbit milk GAA [37]. In 2006, ERT with alglucosidase alfa (Myozyme®, Genzyme

Corporation, a Sanofi Company, Cambridge MA, USA) was approved in the European Union and, subsequently, in the US as treatment for Pompe disease. Alglucosidase alfa treatment has been shown to improve prognosis in infants and late-onset Pompe disease (LOPD) patients [2, 14, 26, 30, 35]. However, few patients have clinical data available owing to the rarity of the condition and to the recent introduction of ERT in many countries. Data on longer term treatment (>3 years) are now becoming available. Therefore, we carried out a systematic review of published clinical studies to provide an overview of the safety and efficacy of alglucosidase alfa treatment in patients with LOPD. Novel treatment options for Pompe disease are briefly discussed.

Methods

Search strategy

Electronic literature searches of the EMBASE and MEDLINE databases were performed on January 9, 2012 to identify all clinical studies published in English on patients with LOPD. The National Library of Medicine Medical Subject Headings "enzyme replacement therapy" and "glycogen storage disease type II" were used with the keywords "alglucosidase", "adult", "juvenile", and "Pompe disease". The electronic literature search was performed including all subterms and derivative forms of the search terms.

Inclusion and exclusion criteria

Clinical studies involving patients with Pompe disease aged ≥2 years were included. Non-human clinical studies and studies of infantile-onset Pompe disease were excluded. In addition to clinical trials and cohort studies, case reports, observational studies, and statistical analyses were considered for inclusion in the analysis owing to the small population of LOPD patients.

Both authors independently reviewed the titles and abstracts of all retrieved records for eligibility and relevance. Full copies of all papers that met the inclusion criteria were reassessed for relevance against the inclusion criteria. A manual search of reference lists and personal resources was also performed to identify any relevant articles missed in the electronic searches. Papers that did not present clinical data were excluded, and any duplicate presentation of clinical data was identified. No statistical analyses were possible owing to the heterogeneity of the patient populations and the endpoint data extracted.

Data extraction

The final subset of retrieved papers was analyzed to identify data addressing the safety and efficacy of alglucosidase alfa in patients with LOPD. In addition to summarizing patient characteristics and treatment duration for each clinical study, data on the following outcomes were extracted: creative kinase (CK) levels; motor function, as assessed using the 6-min walking test (6MWT) and ambulatory status; respiratory assessment, by evaluation of forced vital capacity (FVC) and ventilatory support requirement; quality of life (QoL); and adverse events (AEs). Data on each outcome (apart from safety) were summarized as "improved", "stabilized", or "declined", on the basis of a comparison with clinical status at the start of ERT. AEs were descriptively summarized.

Results

Descriptive summary of search results

The electronic search of EMBASE and MEDLINE identified a total of 352 records and the manual search of reference lists identified a further 17 papers. Removal of duplicate publications led to the generation of a "long list" of 351 records. A total of 304 records were excluded as they did not present clinical data, resulting in a "short list" of 47 records that were assessed for eligibility. From this subset, three papers were excluded because they contained data also presented in other publications, and a further 23 papers were excluded because of lack of relevance according to the selection criteria. Therefore, a final total of 21 papers were included. The overall outcomes from these studies are summarized in Table 1, and notable AEs are shown in Table 2.

Patient characteristics

The identified studies contained data on 368 patients with LOPD whose characteristics are summarized in Table 3. Of these patients, individual data were available for 27 juvenile patients (age range: 2–17 years old) and 251 adult patients; data on the age of Pompe disease onset were not available for 74 patients. Most of the patients received alglucosidase alfa at a dose of 20 mg/kg every other week, although the three patients included in a 2004 study by Winkel et al. [37] and a 2008 follow-up study, by van Capelle et al. [32], were transitioned from recombinant human rabbit milk alpha-glucosidase (20 mg/kg weekly) during the first 3 years of treatment to alglucosidase alfa (30–40 mg/kg biweekly) over the last 5 years.

Creatine kinase levels

CK levels are elevated in patients with LOPD, and their reduction is considered a useful indicator for diagnosis and

Table 1 Summary of clinical studies included in the literature review

Study	*n*	CK levels	Motor performance (6MWT) (*n*)	Ambulation status (*n*)	Respiratory status (FVC, VC, SVC, FEV_1) (*n*)	Need for ventilator support (*n*)	Quality of life (*n*)
Regnery et al. [26]	38	Decreased	Improved	Unchanged	Decreased	Unchanged	Stable
Angelini et al. [2]	74	Decreased	Improved	NR	Improved	Improved (6) Worsened (2)	NR
Hobson-Webb et al. [12]	12	NR	NR	Improved	NR	NR	NR
Furusawa et al. [10]	5	Decreased	NR	NR	Improved	Stable	NR
de Vries et al. [8]	1	NR	NR	NR	Improved	Stable	Improved (1)
Yang et al. [39]	15	NR	NR	NR	Improved/stable	NR	Improved
Orlikowski et al. [20]	5	NR	NR	Improved	Improved (2) Worsened (3)	Worsened (IV)	Improved
Vielhaber et al. [36]	2	Decreased	Improved	NR	Improved	NR	Improved
Papadimas et al. [21]	5	NR	NR	Improved	Improved	NR	NR
Bembi et al. [4]	24	Decreased	Improved	Improved (1)	Improved/stable	Improved	NR
Ravaglia et al. [25]	11	Decreased	Improved	NR	Improved	NR	NR
van Capelle et al. [33]	5	NR	Improved	NR	Improved	NR	NR
Ravaglia et al. [24]	14	NR	NR	NR	NR	NR	NR
van der Ploeg et al. [35]	90	NR	Improved	NR	Improved	NR	Stable
Strothotte et al. [30]	44	Decreased	Improved	NR	Improved	NR	Stable
Korpela et al. [16]	1	Decreased	NR	Improved	Improved	NR	NR
Angelini et al. [1]	11	NR	Improved	NR	Improved (1)	NR	Improved (3)
Merk et al. [19]	4	Decreased	Improved (1)	Improved (2)	Improved (2)	Improved (1)	Improved
van Capelle et al. [32]	3	NR	NR	Improved	NR	Improved	NR
Rossi et al. [27]	1	Increased	NR	NR	NR	NR	NR
Winkel et al. [37]	3	Decreased	NR	Improved	Improved	Improved (1)	NR

The descriptive summary of each clinical outcome (e.g., decreased, improved, stable) is a reflection of the trend observed in this study where mean values are not presented in the original publications

6MWT 6-min walking test, *CK* creatine kinase, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *IV* invasive ventilation, *NR* not reported, *SVC* slow vital capacity, *VC* vital capacity

response to treatment. In our analysis, 86.7 % (91/105) of patients were reported to have elevated CK levels at baseline [4, 10, 12, 16, 19, 21, 30, 36]. Data on changes in CK levels during ERT were available for 138 individual patients from eight studies [2, 10, 16, 19, 21, 27, 30, 36]. Among those patients, CK levels decreased in 69.6 %, stabilized in 10.9 %, and increased, relative to baseline, in 19.6 % of patients. Regnery et al. [26] presented 36-month treatment outcomes for the same cohort of patients initially reported by Strothotte et al. [30]. Although Regnery et al. [26] did not cite individual patient CK levels, they reported a significant mean decrease of 8.8 % from baseline. In addition, Winkel et al. [37] reported a significant decrease in CK levels after 3 years of treatment with recombinant human rabbit milk alpha-glucosidase in three patients with elevated enzyme values (from 1,560 to 545 IU).

Motor performances

In patients with Pompe disease, the 6MWT—universally accepted in clinical trials—was the main outcome measure for which data were extracted to determine changes in motor performance. As an indicator of disease progression in untreated patients, the mean 6MWT distance decreased by 3 meters over 78 weeks in the placebo arm of the only randomized, placebo-controlled trial of 90 LOPD patients [35]. In our analysis, 6MWT data were available for 122 treated patients from seven studies [1, 2, 4, 19, 26, 30, 33]. Of these, 77.9 % improved, 8.2 % stabilized, and 13.9 % declined. The mean improvement in walking distance reported ranged from 10 meters to 149 meters, and most of the patients showed a 6MWT improvement as treatment continued after the first year. However, the analyzed data

Table 2 Summary of the notable adverse events included in the literature review

Study	Notable adverse events
Regnery et al. [26]	Mild/moderate infusion reactions: erythema, tachycardia, reduced oxygen saturation, exanthema, globus pharyngis, pruritus
Angelini et al. [2]	Mild infusion site erythema, facial erythema, itch, flu-like symptoms, bronchospasm
Furusawa et al. [10]	Mild infusion-related skin rash
	Severe emphysema and pneumothorax (1 patient)
Orlikowski et al. [20]	Severe tracheal hemorrhage (fatal) (1 patient)
	Mild/moderate infusion site erythema; pyrexia, muscle cramp
Vielhaber et al. [36]	Mild skin rash
Bembi et al. [4]	Mild/moderate bronchospasm, skin rash
	Serious pneumothorax (1 patient)
van Capelle et al. [33]	No infusion site reactions were observed
van der Ploeg et al. [35]	Mild/moderate: urticaria, flushing, hyperhidrosis, chest discomfort, vomiting, raised blood pressure
	Severe tongue edema (1 patient)
Strothotte et al. [30]	Erythema, tachycardia, drop of oxygen saturation, exanthema, globus pharyngis, and pruritus; hand edema, acute hearing loss, herpes simplex infection, pollakisuria, prickling in the muscles, and hypertensive crisis
Angelini et al. [1]	Facial edema, oral paresthesia, tachycardia
van Capelle et al. [32][a]	Infusion-site reaction, chills (1 patient)
Winkel et al. [37][b]	Infusion-site reactions, mild and transient skin reactions (1 patient)

[a] Patients were transitioned from recombinant human rabbit milk alpha-glucosidase (20 mg/kg weekly) to alglucosidase alfa (30–40 mg/kg biweekly)

[b] Patients were treated with recombinant human rabbit milk alpha-glucosidase at 10–20 mg/kg weekly

Table 3 Late-onset Pompe disease patient characteristics ($n = 368$)

Characteristics	n (%)
Gender[a]	
Male	168 (48)
Female	185 (52)
Age at start of treatment[b]	
<8 years	3 (1)
8–17 years	24 (9)
18–39 years	65 (26)
40–59 years	111 (44)
≥60 years	51 (20)
Treatment duration[c]	
<12 months	13 (4)
12–23 months	177 (52)
24–35 months	32 (9)
≥36 months	118 (35)

[a] Data on gender were not available for 15 patients

[b] Individual data on age at start of treatment were not available for 114 patients

[c] Data on duration of treatment were not available for 28 patients, and 49 patients were reported twice at different time points

showed no clear correlation between a longer duration of treatment and further improvements in motor function (Fig. 1). Although we did not study the same patients at different time points, our analysis suggests that longer duration of treatment did not improve 6MWT in those patients who declined during the first 12–23 months of treatment (14.3 % declined in the first 12–23 months versus 16.7 % at >36 months). In addition, in a study comparing different time points, the mean outcomes of 36-month treatment in 38 patients revealed some deterioration of motor function after 2 years (mean 6MWT distance declined from 356.4 meters at 24 months to 325.6 meters at 36 months) [26].

Ambulation status

In untreated LOPD patients, the probability of wheelchair use increases—on average—by 13 % each year after diagnosis [11].

In our analysis, 115 treated patients were reported to have an impaired baseline ambulatory status; of these patients, 1.7 % were bedridden, 25.2 % used a wheelchair, 70.4 % had walking difficulties requiring assistance or using walking aids, and 2.6 % had impaired walking. Although most of the studies did not take changes in ambulatory status from baseline into account, an ambulatory improvement was reported in seven patients (6.1 %) [4, 16, 19–21]. Among the improvements reported, one bedridden patient was able to sit in a wheelchair [20], three

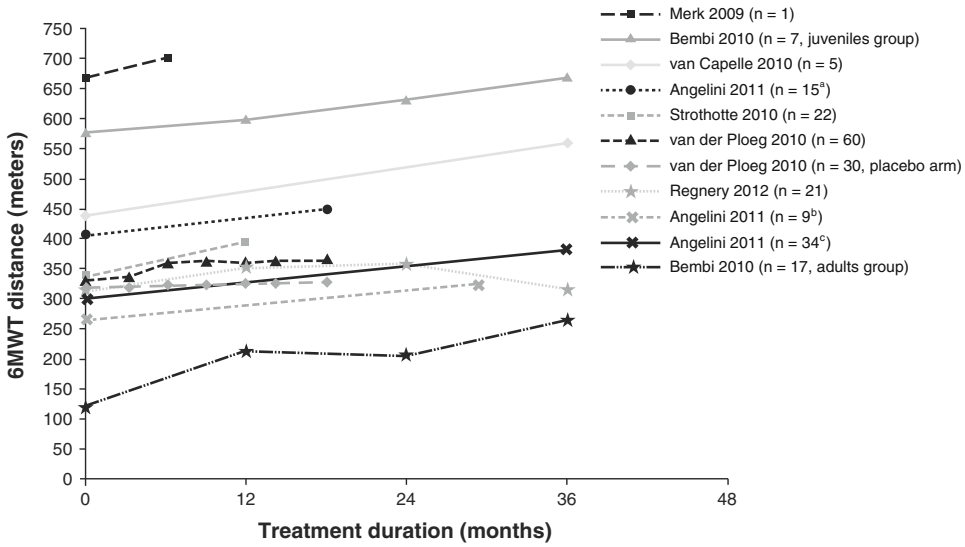

Fig. 1 Change in motor performances during ERT using the 6MWT. [a]ERT duration of 12–23 months. [b]ERT duration of 24–35 months. [c]ERT duration of ≥36 months

wheelchair-bound patients were able to walk short distances [4, 16, 20], and one wheelchair-bound patient abandoned wheelchair use [32]. In addition, Winkel et al. [37] reported on a wheelchair-bound patient who could walk without assistance after 72 weeks of treatment with weekly doses of recombinant human rabbit milk alpha-glucosidase.

Respiratory status

In untreated LOPD patients, respiratory dysfunction develops in >70 %, with a mean reduction in vital capacity (VC) of approximately 1.5 % per year following diagnosis [34]. Individual FVC data were available for 124 treated LOPD patients [1, 2, 10, 30, 33, 36]. Of these patients, FVC improved in 51.6 %, stabilized in 13.7 %, and declined in 34.7 %. There was no clear correlation between length of treatment and improvement in respiratory function (Fig. 2). A mean decline in FVC of 3.08 % was reported after 36 months of treatment in 38 adults with Pompe disease [26]. Pulmonary function improved in two of three patients in the 3-year study by Winkel et al. [37], with one patient showing an improvement of VC from 9 to 16 % of normal after 3 years of treatment with recombinant human rabbit milk alpha-glucosidase.

Ventilatory support

In untreated patients, the likelihood of needing either non-invasive or invasive ventilation increases by an average of 8 % each year following diagnosis [11]. Data on changes in ventilatory support were available for 66 patients [2, 4, 10, 19, 20, 26, 39]. Of these patients, ERT resulted in an improvement in 59.1 % of patients, with 36.4 % of patients achieving stabilization and only 4.5 % declining. Among the patients receiving non-invasive ventilation, 64.1 % improved, 32.1 % stabilized, and 3.8 % declined, whereas among the patients who were receiving invasive ventilatory support, 38.5 % improved, 53.8 % stabilized, and 7.7 % declined. Overall, seven of 28 patients required non-invasive ventilation with a mean duration of 10.29 ± 1.28 h, and six of 28 patients required 24-h invasive ventilation; no reduction in the number of hours of ventilation was observed during 36 months of ERT [26]. The most significant improvements included three patients who recovered from tracheostomy [4], and eight patients (including a tracheostomized adolescent girl) who were able to completely stop ventilation support [2, 4]. In addition, in the cohort of patients studied by Angelini et al. [2], 21 patients showed a significant reduction of 3.5 h/day of ventilatory support.

Quality of life

QoL was assessed in 176 treated patients [1, 19, 20, 26, 30, 33, 35, 36, 39]. Overall, 144 patients (81.8 %) had QoL scores that were below the general population norms at baseline. No assessment tools have been designed to specifically measure the impact of clinical improvements on QoL in patients with LOPD; however, the general short-form questionnaire, SF-36, was used to assess 156 patients with LOPD who had received alglucosidase alfa treatment. Thirteen patients (8.3 %) reported an overall improvement in QoL scores: three (23.1 %) reported improvements in both mental and physical component scores whereas one (7.7 %) reported improvements only in the physical component score, two (15.4 %) showed improved mental component scores, and three (23.1 %) reported improved bodily pain. As for the remaining four patients, there were no details about which of the component scores specifically improved. In a recent

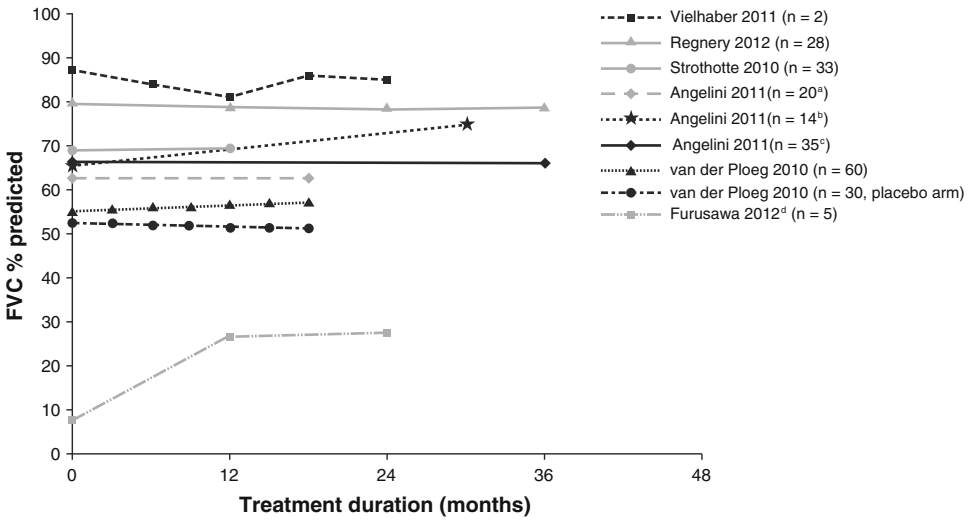

Fig. 2 Change in respiratory function during ERT using FVC. [a]ERT duration of 12–23 months. [b]ERT duration of 24–35 months. [c]ERT duration of ≥36 months. [d]Average FVC % values: 0.0–46.1 before ERT; 9.3–51.2 at 1 year; 7.7–66.1 at 2 years

paper, mean SF-36 scores were found to be unchanged after 36 months of treatment [26]. Improvements in QoL were reported by van Capelle et al. [32] for two patients transitioned over 5 years from recombinant human rabbit milk alpha-glucosidase to alglucosidase alfa.

Safety

Thirteen studies—comprising a total of 303 individual patients—included information on alglucosidase alfa safety [1, 2, 4, 10, 20, 26, 27, 30, 32, 33, 35–37]. Single AEs were reported for 38 patients only; of these, most events (34 patients) were mild to moderate in severity and included infusion-related reactions to alglucosidase alfa (Table 2).

Severe or serious AEs were reported in only four patients (Table 2). These comprised of one fatal tracheal hemorrhage [20]; one case of severe emphysema and pneumothorax during treatment [10]; one case of pneumothorax, which led to tracheostomy of the patient [4]; and one case with severe tongue edema [35].

Data on the development of antibodies to alglucosidase alfa (immunoglobulin [Ig]G and IgE titers) were available for 128 patients [2, 8, 10, 20, 26, 27, 33, 35]. Among 121 of these patients who converted to low IgG titers, three had anaphylactic reactions and two developed IgE antibodies to alglucosidase alfa [35]. The impact of IgG antibodies on clinical outcomes was not studied; however, Regnery et al. [26] reported an adult female patient who developed IgG antibody titers of up to 1:819,000 leading to a decline in her neuromuscular status and subsequent discontinuation of ERT.

Discussion

The results of our systematic review indicate that CK levels, motor performance, respiratory function, and the need for ambulatory and/or ventilatory support improve or stabilize in at least two-thirds of patients with LOPD receiving ERT with alglucosidase alfa. Considering the progressive nature of this disease, clinical stabilization has to be considered a positive treatment outcome, and it is plausible to conclude that alglucosidase alfa is an effective treatment for most patients with LOPD.

However, up to a third of patients do not show improvements during treatment, and these patients experience deterioration of muscular and respiratory functions. The factors underlying this variation in clinical response require further investigation as it is unclear whether it is due to phenotypic and pathogenetic factors associated with Pompe disease or to a diagnostic delay that may postpone an earlier start of treatment. Moreover, a recent report of long-term treatment outcomes (>36 months) indicates that many patients with LOPD improve for 1–2 years on ERT before their clinical condition stabilizes or, in a few cases, later begins to deteriorate after 2–3 years on treatment [26]. This could not be evaluated as part of the quantifiable outcomes in this analysis because only the latest time point for which data were reported was selected when extracting data from each study.

In our analysis, there was no trend suggesting that longer treatment would continuously improve the percentage of responders (improved or stabilized disease), with the mean 6MWT distance declining from baseline in 14.3 % of patients who were treated for 12–23 months and in 16.7 % of patients treated for >36 months. Although most of the patients experienced an improvement in FVC after treatment for >12 months, treatment for >24 months was not associated with any further improvement in the proportion of responding patients.

Alglucosidase alfa treatment was generally well tolerated; most AEs were related to the treatment infusion and were mild-to-moderate in severity. Most of the patients

who received ERT developed IgG antibodies against alglucosidase alfa. To date, their clinical effect has not been fully elucidated and will require further investigations. Regnery et al. [26] recommend that patients undergoing ERT receive immunological monitoring, particularly patients with an unexpected decline in clinical status during treatment.

Although our analysis provides an important update on the clinical efficacy, safety, and tolerability of ERT with alglucosidase alfa, direct comparisons between studies remain difficult owing to the variety of outcomes reported. General agreement on a set of standardized outcome measures will facilitate comparisons between future clinical studies on Pompe disease and related meta-analyses of datasets.

Our literature analysis highlights the lack of long-term data on treatment outcomes in patients with LOPD. It is essential to continue to collect data on cohorts of LOPD patients to allow identification of phenotypic and genotypic factors that could be predictors of therapeutic response. Studies of the natural history of the disease in LOPD patients have shown that the skeletal muscle condition deteriorates in a variable—but often rapid—manner, unless the patients receive treatment [34, 37]. Recently published evidence highlights the multisystemic pathology of the condition, with cardio-cerebrovascular complications reported in approximately one-third of patients [28]. This emphasizes the importance of an early diagnosis of Pompe disease, as some studies have indicated that prompt initiation of ERT may maximize the clinical benefits of treatment [14, 30, 35]. Recently published guidelines from the American Association of Neuromuscular and Electrodiagnostic Medicine [7] recommend that all patients with Pompe disease receive ERT at diagnosis if there is evidence of clinical symptoms, whereas presymptomatic individuals have to be regularly monitored (i.e., every 6 months) in order to start ERT when they become objectively affected.

Study limitations

Our analysis is subject to several limitations. The heterogeneity of the clinical outcomes for which data were collected prevented any formal statistical analyses from being carried out. Furthermore, the outcomes presented in the selected studies varied, reducing the size of the data sets for the endpoints considered. There was also the potential for a publication bias toward positive articles, although this can be considered relatively unlikely given the very small number of patients with LOPD.

Adjunctive treatment options

The response to alglucosidase alfa therapy in patients with LOPD is less marked than that seen in patients with the infantile form, possibly due to an attenuated skeletal muscle response, but also potentially related to prognostic factors such as delayed diagnosis and progressive muscle degeneration. Enhancing the expression of the cation-independent mannose-6-phosphatase (CI-MPR) receptor may improve the uptake of GAA by muscle cells, increasing treatment efficacy [15]. Alternative ERT options that have shown improved potency at clearing tissue glycogen levels in Pompe mice hold promise for the future management of Pompe disease. These therapies are currently being considered for clinical trials or are in phase I/II development, and involve chemically conjugating a ligand onto recombinant human (rh) GAA to enhance its recognition by CI-MPR (neo-GAA; Genzyme Corporation, a Sanofi Company, Cambridge, MA, USA) [40], and a chimeric fusion protein of insulin-like growth factor 2 and GAA (BMN701; BioMarin Pharmaceutical Inc., Novato, CA, USA) [5].

Another approach involves the use of small molecule chaperones to increase the amount of active enzyme in lysosomes [22]. Early in-vivo studies also indicate that chaperones may work synergistically with ERT [23]. Other preclinical treatment approaches include substrate reduction therapy to reduce the amount of glycogen synthesis [9] and gene therapy to restore GAA activity levels [17].

Introduction of a protein-rich diet and alanine supplements in addition to exercise therapy may also reduce protein degradation in the muscles of patients with Pompe disease [29]. Finally, a supervised program of physical therapy and moderate aerobic exercise has been shown to enhance the benefits of ERT on motor function and muscle strength [31]. Jones et al. [13] also showed an improvement of inspiratory and expiratory parameters after specific respiratory training in two patients.

In conclusion, the findings of our analysis indicate that alglucosidase alfa treatment offers an effective, safe, and well tolerated therapy that attenuates clinical progression in most patients with LOPD. Further research is required to identify factors that may predict therapeutic response. Possible future combined therapies may help all patients with LOPD.

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Conflicts of interest AT and BS are members of the Pompe Global Advisory Board, sustained by Genzyme, and received reimbursement for participation to the board meetings and invited lectures.

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