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ORIGINAL COMMUNICATION

Comparison of recent pivotal recommendations for the diagnosis and treatment of late-onset Pompe disease using diagnostic nodes—the Pompe disease burden scale

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Abstract

Pompe disease is a rare autosomal-recessive disorder characterised by limb-girdle myopathy and respiratory weakness in the late-onset form (LOPD). Various mutations in the acid alpha-glucosidase gene lead to toxic lysosomal and extra-lysosomal glycogen accumulation in all organs due to ineffective glycogen clearance by the encoded enzyme. Only one randomized trial demonstrated beneficial effects of respiratory function and meters walked in the 6-min walking test with enzyme replacement therapy (ERT). These results were confirmed in several retrospective and prospective observations and in meta-analyses. Due to a potential lifelong therapy, moderate efficacy and high treatment costs time of ERT initiation and cessation is an ongoing matter of debate. So far, several national and international recommendations have been published with different criteria concerning diagnosis, initiation and cessation of ERT in LOPD. We therefore formally analysed recent published recommendations and consensus statements of LOPD using diagnostic nodes (DODES) as a special software tool. With DODES, an objective analysis becomes possible if the content of the recommendations is represented as algorithms using cross-compatible elements. This analysis formally disclosed both, areas of great heterogeneity and concordance for the diagnosis and management of LOPD and paved the way for a Pompe disease burden scale focussing on ERT initiation. According to this investigation further clinical research should concentrate on ERT in pre-symptomatic and severely affected LOPD patients and on cessation criteria for ERT as these issues are areas of international uncertainty and discordance.

Keywords Pompe disease · Enzyme replacement therapy · ERT initiation · ERT cessation · Diagnostic nodes · Guidelines

Introduction

Pompe disease is a rare autosomal-recessive disorder caused by mutations of the acid alpha-glucosidase (GAA) gene [1]. The prevalence is country-specific and estimated to be as low as 1: 40.000 in the Dutch population and up to 1: 283.000 in Europe [2]. Manifestation of the disease varies greatly; the infantile-onset Pompe disease (IOPD) form occurring in new-borns with no residual enzyme activity presents with severe cardiomyopathy, respiratory failure and a floppy infant phenotype [3]. Enzyme replacement therapy (ERT) with recombinant human glucosidase alpha (rh-GAA) prevents IOPD patients from dying within the first year of life [4], but leads to a new treatment-induced clinical phenotype with cognitive impairment, speech difficulties and motor impairment [5, 6]. The late-onset Pompe disease form (LOPD) is phenotypically more heterogeneous and the onset of clinical symptoms may occur from early childhood to very late adulthood associated with a high prevalence of the

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c.− 32 to 13 T > G genotype [1, 7]. Proximal limb-girdle myopathy, axial weakness and diaphragmatic insufficiency are the clinical hallmarks but vary substantially depending on the residual GAA activity, which is related with the severity of the mutation [8]. Natural progression studies demonstrated significant impairment in the course of the disease leading to pain, fatigue, humanistic burden, wheelchair use, ventilation dependency and even premature death [9–13]. To date, only one randomized trial demonstrated efficacy of ERT in LOPD with significant improvements in the 6-min walking test (6-MWT) and stabilization of respiratory function especially during the first 3–6 months of ERT [14]. Recently, a prospective study also demonstrated efficacy of ERT of skeletal muscle function and stabilization of respiratory function over a period of 5 years with a peak between 2 and 3 years compared with the estimated natural progression [15].

However, one third of LOPD patients may not benefit from ERT [16] and there is still no prognostic or predictive marker of disease progression or treatment response [17, 18]. Hence, beside medical objections and regulatory affairs the time of ERT initiation, duration and cessation with regard to treatment burden and financial toxicity are highly controversial and ethically demanding [17, 19]. Several countries [20–24] or even continents [25] have published academically driven recommendations and consensuses to regulate access of ERT in LOPD. Comparing and analysing these consensuses may be a major step towards harmonization of the management LOPD worldwide including the best medical use of ERT [26].

As these recommendations are published as manuscripts, an automated comparison is not feasible. However, when their content is represented by algorithms using cross-compatible elements [27], an objective analysis becomes possible [28]. Such an analysis will not generate new primary data, but might serve as a source of new information [29], potentially uncovering areas of controversy and consensus in a clinical setting [30, 31], which is presented here for the diagnosis and treatment of LOPD.

Methods

The Pubmed database of the US National Library of Medicine was searched for national and/or medical-society-driven guidelines/recommendations/consensus from 1st January 2013 to 31st December 2018 written in English. Additionally, the bibliography of the identified articles was screened for relevant further articles. The search terms included: Pompe disease, glycogen storage disease type II, acid maltase deficiency, glycogenosis type II, recommendations, consensus, management, diagnosis and guidelines. The articles were reviewed by clinical experts (TH, KMR, DL, BS) for diagnostic procedures, treatment decision criteria, follow-up assessment recommendations and treatment cessation criteria. Treatment recommendations were extracted and represented as decision trees, as previously described [27, 30, 32]. The decision criteria were unified based on the objective consensus methodology [28]. Each article was represented as an individual decision tree (not shown). Consensus for each possible parameter combination was extracted to create a tree containing recommendations from all papers (Fig. 1) analogous to the methodology implemented previously in expert opinion or centre policy decision making. Based on the extracted decision criteria a single scale was built which allows for an unambiguous statement from the paper analysed for each element of the scale (Fig. 1, Table 1).

Results

Six papers meeting the inclusion criteria were identified and analysed [20–25]. The publication from South Africa contains only a diagnostic pathway and was therefore excluded from further analysis [24]. Only the European recommendation was based on a formal consensus process and a review of the literature [25], whereas the other national/regional recommendations relied on expert opinions (with or without a formal task force/expert panel) and a literature research, only [20–23]. Three consensus papers were directly or indirectly sponsored by industry [21, 23, 24]. By analysing all relevant papers three main areas of recommendations were identified. These were the diagnostic confirmation of LOPD, criteria for the initiation of ERT with rh-GAA and ERT cessation. However, ERT cessation criteria were only mentioned in two papers [22, 25]. ERT in the important context of pregnancy was commented on in one paper [25].

Confirmation of diagnosis

For diagnostic purposes all consensus papers (Table 2) demand a characteristic clinical phenotype (i.e., limb-girdle myopathy with or without diaphragmatic insufficiency) as being suspicious for LOPD. Patients with this clinical picture should be screened for GAA activity based on all recommendations. All papers, beside one [22], recommend the dried blood spot assay (DBS assay) as an adequate screening tool (Table 2) [33]. If a low enzyme activity on a DBS assay is detected all recommendations request a secondary confirmatory GAA enzyme assay, which is further specified in one paper only [23] (Table 2). Genetic confirmation is advised in three papers [20, 21, 25] and considered optional in two [22, 23], especially if a second GAA-assay is normal [23]. Four papers claim a second GAA-assay as a gold-standard test in case of doubt, either

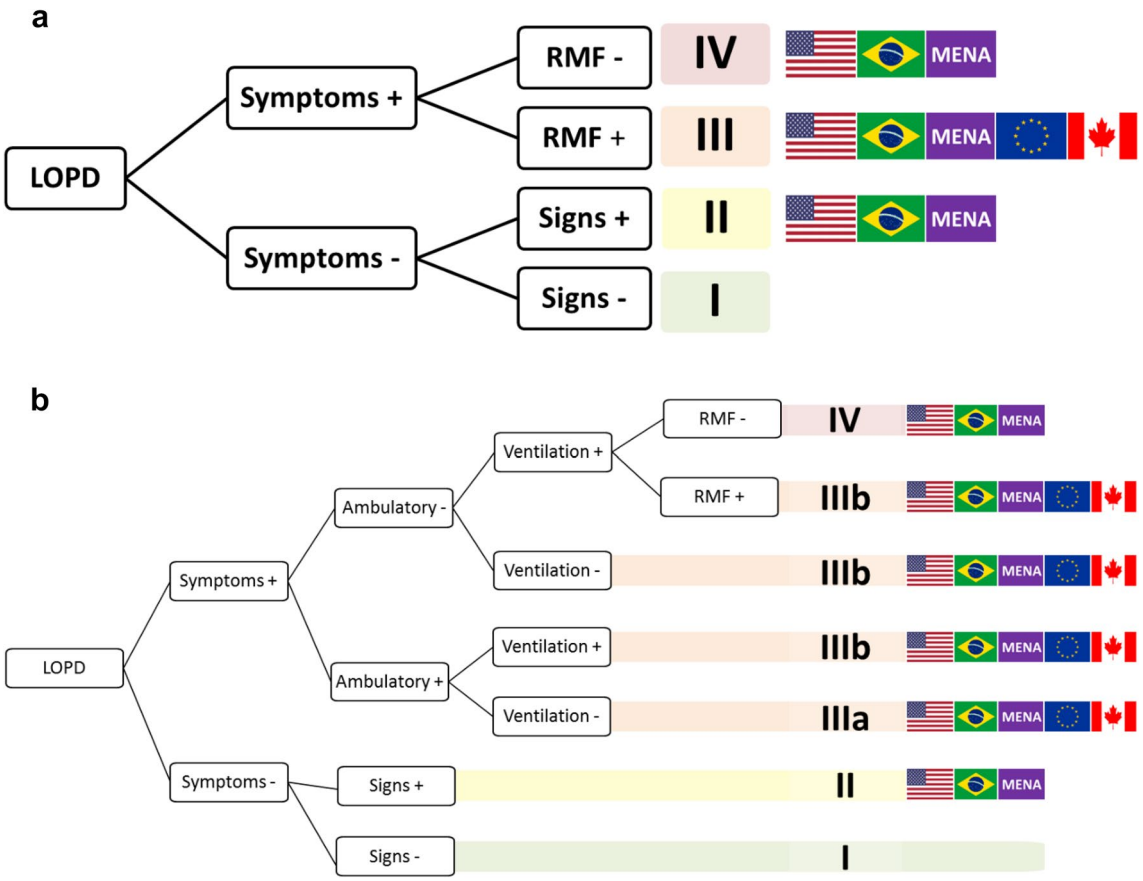

Fig. 1 Minimal (**a**) and optimized decision tree (**b**) representing the pivotal conditions for initiation of ERT derived from different recommendations using DODES leading to the Pompe disease burden scale (PDBS). *LOPD* late-onset Pompe disease, + present, − absent, *ventilation* invasive ventilation, *RMF* relevant residual muscle function, *MENA* middle east and North Africa

Table 1 Pompe disease burden scale (PDBS; tabular view)

Parameter	PDBS
Diagnosis only[a] (pre-symptomatic)	1
Signs only[b] (clinical and/or paraclinical)	2
Symptoms[c]	3a
Symptoms plus non-ambulatory and/or invasive ventilation	3b
No residual muscle function	4

[a]Diagnosis made by screening, i.e., siblings or relatives, incidental findings

[b]Clinical and/or paraclinical signs (i.e., signs by examination, muscle MRI, lung function tests, muscle biopsy)

[c]Complaints reported by the patient

from fibroblast culture or muscle biopsy [21, 23] or from a different tissue (not further specified) [20, 22]. The European consensus, however, considers the combination of a pathological GAA-assay in combination with genetic confirmation the gold standard [25].

ERT start criteria

All recommendations relied on a confirmed diagnosis of LOPD before initiation of ERT. However, start criteria for ERT greatly vary across the recommendations. Some of them are ambiguous leaving room for interpretation (i.e., no differentiation between clinical signs and patient-reported symptoms), some being more specific. Decision tree analysis revealed fundamental differences in ERT start criteria (Fig. 1). Stricter recommendations acknowledge that only symptomatic patients may qualify for treatment [20, 25] whereas others recommend ERT treatment also in patients with signs only (i.e., abnormal muscle MRI, raised creatine kinase or muscle biopsy) [21–23]. This addresses the issue of pre-symptomatic patients occasionally diagnosed by newborn screening, in case of an affected sibling, elevated CK-levels and subsequent confirmation of the diagnosis LOPB. Derived from our analysis we developed the "Pompe Disease Burden Scale" (PDBS, Fig. 1, Table 1). From a methodological point of view the PDBS discriminates four main disease stages (I–IV) and exactly represents the spectrum of

Table 2 Overview of mandatory diagnostic procedures in LOPD

Region	Clinical phenotype	DBS	Alternative GAA-assay	Genetic analysis	Gold standard
USA 2012	+	n.a	+	Optional	Second GAA-assay
South Africa 2014	+	+	+	n.a	Second GAA-assay
MENA 2015	+	+	+	+	f-GAA-assay, if genetic is not informative
Brazil 2016	+	+	+ leucocytes	Optional, if second GAA-assay is normal	f, m-GAA-assay, if genetic is not informative
Canada 2016	+	+	+	+	GAA-assay, if genetic is not informative
Europe 2017	+	+	+	+	GAA-assay and genetic

+ mandatory, *m-GAA* GAA-assay from muscle biopsy, *f-GAA-assay* GAA-assay from fibroblast cultures, *informative* detection of two pathogenic mutations, *MENA* middle east and North Africa, *DBS* dried blood spot assay

ERT starting criteria in LOPD derived from the publications analysed here (Fig. 1). PDBS I includes individuals with neither signs nor symptoms (subsequent confirmed diagnosis of LOPB by new-born screening or screening after diagnosis of an affected sibling). PDBS II includes LOPD patients with clinical and/or paraclinical signs (i.e., muscle MRI findings, CK-elevation, muscle biopsy findings) but still being pre-symptomatic without even minimal skeletal muscle dysfunction or respiratory involvement [25].

From a clinical view and with respect to the detailed differentiation of the disease stage in some papers a detailed PDBS stage III seems more appropriate (Fig. 1). Therefore, we propose to subdivide the PDBS stage III in one category "a", which represents ambulatory patients without the need for invasive ventilation and the category "b", which also includes non-ambulatory patients with/or without mechanical ventilation as differentiation of these conditions is clinically relevant. Non-invasive ventilation does not play a role in the decision to start ERT or not. Hence, the PDBS covers pre-symptomatic (PDBS I), mildly to moderate affected (PDBS II+III) as well as severely affected patient without relevant residual muscle function (PDBS IV) (Fig. 1, Table 1). Of note, patients with PDBS II and IV were not included in the LOTS study but were suggested for ERT treatment in various recommendations (Fig. 1). This issue was discussed in the US consensus [22]. Additionally, two papers demand at least minimal functionally relevant and measurable muscle function as a key criterion for ERT included in the PDBS stages III or IIIb [20, 25] (Fig. 1a, b).

None of the papers advised ERT solely on lab results, like a definitive diagnosis derived from genetic and/or enzymatic analysis in cases of an affected family member or on new-born screening (PDBS I) (Fig. 1). Interestingly, two out of five papers recommended ERT in pre-symptomatic patients with a definite diagnosis and in combination with objective clinical (abnormal only on examination) and/or paraclinical signs (i.e., muscle abnormalities on MRI scans without symptoms in the patient history), only (PDBS II). If a patient presents with a typical clinical phenotype with proximal weakness or pulmonary symptoms and a definite diagnosis of LOPD (PDBS III) all papers recommended ERT. Hence, the differentiation and definition of signs versus symptoms is relevant in the context treatment initiation especially in LOPD in contrast to IOPD, where babies are immediately treated by clinical signs only (cardiomyopathy, and floppy infant phenotype). Clinical signs are based on a patient examination, while symptoms are given by the patient describing his complaints. Nevertheless, this is a conundrum of misunderstanding and misinterpretation [34]. All recommendations consented of LOPD patients to be treated, if they are symptomatic irrespective of the need for a wheelchair and/or invasive ventilation (PDBS III or III a, b; Fig. 1). Finally, like the discrepancies of treatment initiation for patients with very low disease burden (PDBS II) this holds also true for the treatment of patients with no residual muscle function (PDBS IV).

ERT cessation criteria

As shown in Table 3 various criteria for the cessation of ERT could be extracted [20, 21, 25]. The most important criterion is ERT inefficacy. However, only two out of five papers mentioned a time interval, after which treatment efficacy should be assessed in general (Table 3). The MENA (middle east, North Africa) and Brazilian consensus additionally advised a 12-months treatment course in severely affected patients which were not further characterized [21, 23]. Furthermore, most cessation criteria remained vague and did not define limits of the level of clinical decline in paraclinical tests. The necessity of adherence to the infusion intervals and regular assessment procedures were only mentioned in two guidelines [20, 25]. The same two papers took the presence of high sustained anti-GAA antibodies (HSAT) into account [35], which may abrogate treatment efficacy at high titres on the one hand and being a source of allergic infusion reactions on the other hand.

Table 3 Cessation criteria for ERT in LOPD

Criteria	Europe 2017	USA 2012	CAN 2016	MENA 2015	BRA 2016
Adherence	+	−	+	−	−
Infusion reaction	+	−	+	−	−
Severe comorbidity	+	−	+	−	−
HSAT	+	−	+	−	−
ERT-efficacy	After 24 months	After 12 months	+	After 12 months	After 12 months

MENA middle east and North Africa, + present, − not defined, *HSAT* high sustained antibodies against rh-GAA

Pregnancy

Due to the physical changes in body shape and weight gain, pregnant LOPD patients are at risk of symptom deterioration [25]. Therefore, continuation or even initiation of ERT may be important. From seven reported pregnancies in the literature only one patient experienced a miscarriage and all other women gave birth to healthy babies [25, 36, 37]. Alglucosidase alfa was not elevated in breast milk [38] and based on evidence from the literature ERT might not be harmful to the foetus, but further evidence is needed to draw definite conclusions.

Discussion

Several guidelines, recommendations and papers on the diagnosis and treatment of LOPD have been published, reflecting the current knowledge and the clinical practice of this rare disease. However, most evidence relies on the only prospective randomized trial with ERT (LOTS) [14]. Therefore, in theory, no guideline can be established based on more than one RCT trial. All other knowledge of ERT in LOPD is derived from retrospective or prospective observations [39] and meta-analyses [40]. In a medical area of low evidence, as in the case of LOPD, eminence and expert opinions become evident [29]. This additional source of knowledge is often constituted in national or international recommendations. However, these recommendations are limited in different ways like the type of health care system, reimbursement concepts, availability of diagnostic or therapeutic measures among others [41].

In this paper we analysed recent pivotal recommendations of LOPD and extracted the most relevant clinical issues like diagnosis, initiation and cessation of ERT. For diagnostic purposes all papers claimed a combination of a typical clinical phenotype and paraclinical tests as unequivocally necessary for the definite diagnosis of LOPD and a prerequisite for starting ERT (Table 2). Interestingly, the gold standard differed from genetic confirmation to a second GAA-assay or combination of both. Obviously, region-specific facilities, availabilities and transportation issues must be considered when considering a supranational recommendation. Furthermore, the dilemma of non-informative, i.e., variations of yet unknown significance in the second GAA allele or false-negative genetic analysis (i.e., non-screened intronic sequences, promotor methylation, and deletions) must be considered. This issue can at least be circumvented by the choice of a second GAA-assay from a different tissue source as a confirmatory test also ruling out the unnecessary treatment of heterozygote gene carriers harbouring only one pathological mutation in the GAA gene. Furthermore, molecular analysis has also the potential to disclose GAA pseudo-deficiency which is associated with specific gene variations being the culprit for false-positive results, i.e., in new-born screening programs [42].

Beside a definitive diagnosis the timing and duration of ERT is a critical issue. A potentially lifelong treatment, the time-consuming burden of therapy (4–5 h infusions every other week), regular assessment procedures and high treatment costs must be considered. Up to now, no accepted biomarker has been validated in LOPD, which could predict a response to ERT or not. Such a biomarker would be well appreciated in the controversy discussion of ERT initiation in pre-symptomatic LOPD patients (PDBS I and II). Since approximately one third of LOPD patients do not benefit from ERT [39, 40] and pulmonary symptoms respond less well to ERT compared to musculoskeletal symptoms [15, 40, 43, 44], a thorough evaluation of the potential benefits of ERT and a discussion when to start treatment is highly relevant [45, 46]. More research and derived clear-cut recommendations in this context are of utmost importance, to guide patients, physicians and regulatory agencies through this process and to develop the best medical use of ERT [19]. In general, stricter recommendations start later with ERT and stop earlier (Fig. 1, Table 3) [20, 25].

Most recommendations propose ERT initiation early, when symptom burden is low and as ERT might be most effective in relatively mildly affected muscles. Hence, the inclusion criteria from the LOTS study [47] are not represented in all analysed recommendations. The same holds true for the recommendation to start treatment in severely affected patients and those with the need for invasive ventilation. However, the potential benefit of ERT in this

population is extensively discussed in the European consensus and refers to the analysis of 36 severely affected patients from 11 studies from the literature out of the whole study population of 586 patients [25]. ERT initiation is recommended in symptomatic LOPD patients of PDBS III (a and b) for a time period ranging from 1 to 2 years (Table 3), after which efficacy defined as stabilisation or improvement must be demonstrated. However, one might also consider slowing of the disease as a treatment goal, especially in patients with fast progression of clinical symptoms and a longer time period beyond 2 years after which ERT efficacy might become evident [15, 40].

The minimal criterion for ERT in this situation is residual, functionally relevant muscle strength which was also mentioned in the Canadian recommendation [20, 25]. At present, the evidence for ERT initiation with a pre-symptomatic PDBS (I and II) and severely affected patients (PDBS IV) remains an area of obvious controversy (Fig. 1, Table 3) [48].

ERT in pre-symptomatic patients and those without disease signs but reported symptoms also remain a great matter of debate, not only reflected in the comparison of the recommendations analysed here (Fig. 1) but also in the literature [34]. This issue remains open as there is no clear delineation between reported symptoms compared to clinical signs. In this context, the absence of a prospective and/or a predictive disease-specific marker for the benefit of ERT is annoying. One could imagine a wide spectrum of different criteria from isolated hyper-CK-emia, structural changes in muscle MRI, or reported fatigue and pain as treatment relevant. However, some of these criteria seem to be more objective than others [49] and might substantially differ in terms of subjective recognition of being ill or not. Furthermore, evidence of late morbidity like dilatative cerebral vasculopathy and leukoencephalopathy might also argue for early treatment [50], if ERT would be able to reach at least cerebral arteries [51]. Of note, patients might not recognize any clinical impairment in life-time, but might be confronted with significant therapeutic burden and potentially short-term (nephrotic syndrome and allergic reaction) or even long-term side effects (leukoencephalopathy) [6, 51]. In this context we propose to follow the patients of PDBS I and II by regular assessment every 6–12 months and initiate ERT if symptoms arise (progression to PDBS III) [25].

In conclusion, our analysis of recent clinical recommendations about diagnosis and management of LOPD using DODES discloses areas of concordance and even more important controversy, which might serve as a basis for a supranational recommendation of a rare disease like LOPD. Taking a mixed spectrum of evidence and excellence into account may also serve as a tool to disclose potentially important future research topics. Our analysis suggests that further efforts should focus on gaining more evidence for the treatment of pre-symptomatic and severely affected LOPD patients and cessation criteria for ERT.

Compliance with ethical standards

Conflicts of interest TH served as a scientific advisor for and received institutional grants from Sanofi Genzyme (Switzerland). BS is a scientific advisor of Audentes Therapeutics. Lupin Therapeutics and Nexien BioPharma, Inc. He received speaker honoraria from Sanofi Genzyme, Amicus therapeutics, and Kedrion. He received unrestricted research grants from Sanofi Genzyme and Grennovation. KMR was a scientific advisor for Sanofi Genzyme (Switzerland) and Biogen Switzerland AG; and has received speaker honoraria from Sanofi Genzyme (Switzerland) and Shire Switzerland GmbH. DL declares no conflict of interest. PMP received institutional research or educational grants from AstraZeneca, Celgene, Sanofi Genzyme and Roche.

Ethical approval The manuscript does not contain clinical studies or patient data and was done as a literature analysis. Therefore, no formal IRB approval was submitted.

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