European consensus for starting and stopping enzyme replacement therapy in adult patients with Pompe disease: a 10-year experience

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Background and purpose: Pompe disease is a rare inheritable muscle disorder for which enzyme replacement therapy (ERT) has been available since 2006. Uniform criteria for starting and stopping ERT in adult patients were developed and reported here.
Methods: Three consensus meetings were organized through the European Pompe Consortium, a network of experts from 11 European countries in the field of Pompe disease. A systematic review of the literature was undertaken to determine the effectiveness of ERT in adult patients on a range of clinical outcome measures and quality of life. A narrative synthesis is presented.
Results: Consensus was reached on how the diagnosis of Pompe disease should be confirmed, when treatment should be started, reasons for stopping treatment and the use of ERT during pregnancy. This was based on expert opinion and supported by the literature. One clinical trial and 43 observational studies, covering a total of 586 individual adult patients, provided evidence of a beneficial effect of ERT at group level. At individual patient level, the response to treatment varied, but factors associated with a patient's response to ERT were not described in many studies. Eleven observational studies focused on more severely affected patients, suggesting that ERT can also be beneficial in these patients. There are no studies on the effects of ERT in pre-symptomatic patients.
Conclusions: This is the first European consensus recommendation for starting and stopping ERT in adult patients with Pompe disease, based on the extensive experience of experts from different countries.

Introduction

Pompe disease, or glycogen storage disease type II, is a rare, inheritable, multisystemic disorder with a predominant muscle involvement. The disease is caused by deficiency of lysosomal acid α-glucosidase, which leads to impaired lysosomal glycogen breakdown and,

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subsequently, accumulation of glycogen in body tissues. Pompe disease presents as a broad clinical spectrum. Infants, presenting as floppy babies with hypertrophic cardiomyopathy, usually die within the first year of life from cardiorespiratory failure if untreated. Children and adults typically present with an axial and limb-girdle pattern of muscle weakness and respiratory involvement; eventually most of these patients become wheelchair bound and ventilator dependent [1,2].

In 2006, enzyme replacement therapy (ERT) with human recombinant acid α-glucosidase (Myozyme®) became available for all patients in Europe and the USA. In infants, treatment generally improves cardiorespiratory function and motor function, and prolongs survival [3–6]. In older children and adults, ERT improves or stabilizes skeletal muscle strength, muscle function, respiratory function and also survival [7–16]. However, the magnitude of the therapeutic response varies among individual patients [15,17].

Guidance on when to start and stop ERT in patients with Pompe disease is important, especially because many treating physicians will be unfamiliar with the disease and treatment costs are high. Further, this life-long treatment has a large impact on patients' lives; infusions are given every other week and take about 4 h. In most countries patients need to visit the hospital for their infusions, although in some countries, such as the UK and the Netherlands, home-based ERT is frequently used but only after enzyme therapy has shown to be safe during a period where treatment is given in the hospital.

Recommendations for treating and/or managing adult patients with Pompe disease have been composed for several countries [18–24], but general European guidelines do not exist. In 2014 the European Pompe Consortium was formed during the 208th European Neuromuscular Centre international workshop. Through this consortium, we brought together a group of experts from 11 different European countries, all with long-standing experience in treating and following substantial numbers of patients with Pompe disease, to develop recommendations on starting and stopping ERT in adult patients. The resulting European consensus recommendations, based on their shared clinical experience and available evidence, are reported in this article.

Methods

Consensus meetings and e-mails

This consensus recommendation was developed by the European Pompe Consortium in a number of consecutive meetings organized between September 2014 and March 2016, and finalized by e-mail communication. A total of 34 experts from 11 European countries participated in the consensus meetings. Experts were invited to the meetings based on their clinical experience in treating and following large groups of patients with Pompe disease, and in performing research on this disease. In addition, an epidemiologist, a basic scientist and a patient representative participated. In September 2014, the first meeting was held, laying the groundwork for the recommendations [25]. Following this, two further meetings were held and the criteria were further elaborated. Consensus regarding the exact phrasing of the criteria was reached by e-mail after the third meeting. Consensus was based on agreement amongst all participants.

The initial consensus meeting started with presentations reviewing published guidelines and national practice, providing a background to the discussions. Discussion sessions were organized around specific topics. We intensively discussed the criteria for diagnostic confirmation. On starting treatment, topics included whether pre-symptomatic patients and severely affected patients should be started on treatment. The possibility of an initial treatment period of 2 years, during which a physician can assess whether treatment is beneficial for an individual patient, was considered. On stopping treatment, a focus point was how to define a lack of response to treatment. Finally, the topic of ERT during pregnancy and/or lactation received attention. The evidence available from the literature relating to any of the above points was presented alongside the consensus agreement and is also included in this article.

Search strategy

We performed a systematic review of the published literature providing information on the effects of ERT in adult patients with Pompe disease. Six bibliographic databases [Embase.com, Medline (Ovid), Web-of-Science, PubMed, Cochrane Central and Google Scholar] were searched to identify relevant studies published up to 28 April 2016. Terms relating to the disease (Pompe disease, glycogen storage disease type 2, acid maltase deficiency and variants thereof) were combined with terms for treatment (ERT, alglucosidase alfa and variants thereof). We did not apply any language restriction at this stage, but restricted the search to studies on humans and adults, and excluded conference abstracts. The full search strategies are provided in Appendix S1.

Studies to be included had to describe clinical outcome measures (motor performance, respiratory function, muscle strength), health-related quality of life or survival of adult patients with Pompe disease followed during treatment. Effects on other clinical assessments, not directly pertaining to the characterizing symptoms of Pompe disease (e.g. gastrointestinal symptoms, eye tests), were excluded, as were data on safety, antibodies, body composition and magnetic resonance imaging. All types of studies, whether trials or observational studies, were included. Only full journal articles in English were included, i.e. conference abstracts and journal articles in other languages were omitted. Titles and abstracts of all documents identified were screened for the above criteria and full-text versions retrieved for those fulfilling the criteria and those lacking abstracts.

Information was extracted using a pre-defined Excel table. Information on the effects of ERT was extracted, where possible for adult patients only. Specific attention was given to the disease severity of patients included in these studies to identify studies focusing on the effects of ERT in more severely affected and/or pre-symptomatic patients. In addition, articles presenting patient(s) with Pompe disease receiving ERT during pregnancy and/or lactation were identified and information extracted.

Studies were evaluated for inclusion by one reviewer, with 13% assessed by a second reviewer, identifying no omissions by the main reviewer. Additionally, all experts were asked to confirm that they did not miss any studies for their country. Two independent reviewers performed the data extraction. Because of the expected heterogeneity of the data, no attempt was made to pool the outcomes and a descriptive synthesis was undertaken. We estimated the total number of patients in the studies, taking into account that some patients participated in multiple studies. Overlap of patients was identified by contacting the authors (European studies) or comparing the patient characteristics (Japan, USA).

Results

Available evidence and national practice

Out of 981 references identified initially, 44 studies were included, which provided information on the effects of ERT for the specified outcomes (Fig. 1). In addition, four studies were identified that concerned pregnant patients with Pompe disease who were treated with ERT during their pregnancy.

Table 1 shows the results of the 44 studies reporting effects of ERT in adult patients, from 26 separate patient populations (lead authors were contacted to exclude double counting of patients). After excluding

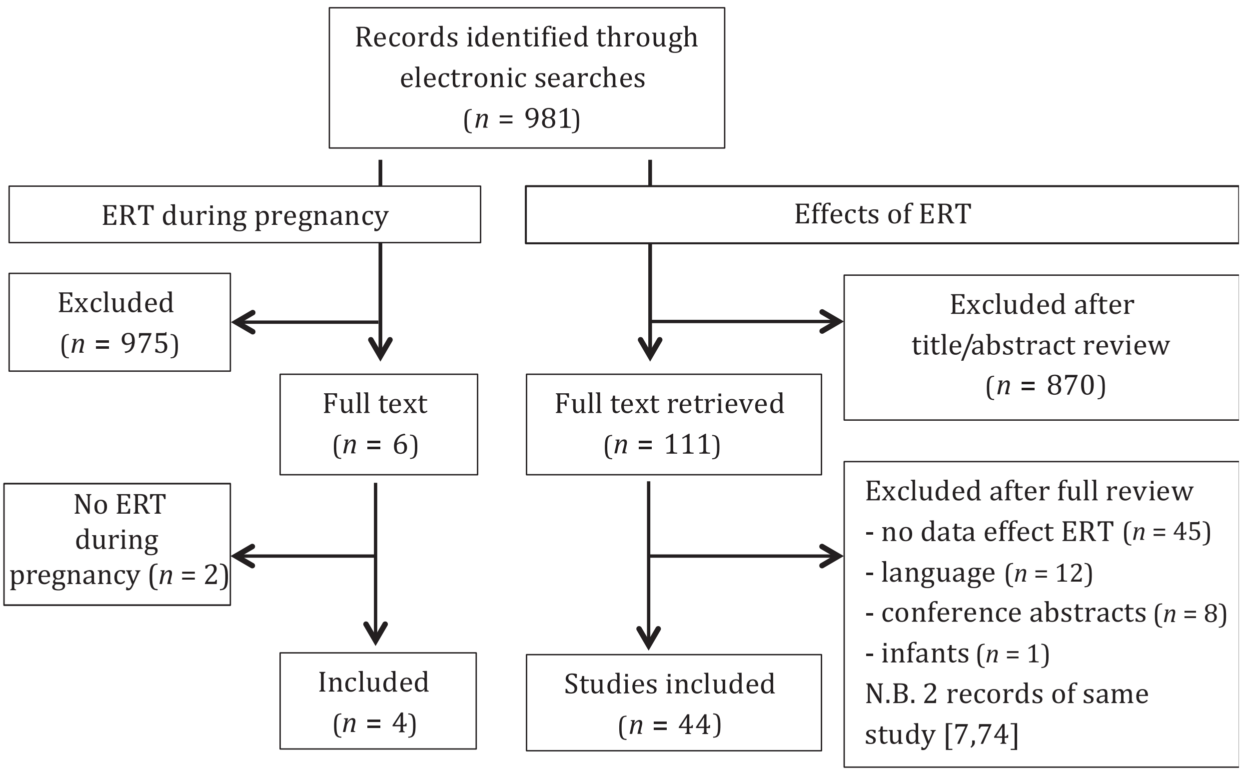

Figure 1 Flowchart of studies included in the systematic review. ERT, enzyme replacement therapy.

Table 1 Clinical studies on the effects of enzyme replacement therapy (ERT) in adults with Pompe disease

Patient population	Study	Comparison	No. of patients: Total	No. of patients: ERT	No. of patients: Adult	Age (year)	ERT (months)	Outcomes under treatment[a]: Motor performance	Respiratory function	Muscle strength	Quality of Life	Survival
LOTS trial	vd Ploeg 2010 [15]	placebo	90	60	most	10–70	18	+(6-MWT)	+(FVC,MEP); 0(MIP)	0(QMT)	0 (SF-36 PCS)	
Extension	vd Ploeg 2012 [14	baseline	81	55[b]&26	most	NA	24[b]&6	≈(6-MWT)[b]	≈(FVC);↑(MI/EP)[b]	↑(QMT arm); ≈(leg)[b]		
IPA patients	Güngör 2013 [11]	Cox	283	204	all	19–81	48 (2–96)					+
IPA patients	Güngör 2013B [26]	NC	163	all	all	24–76	36 (6–96)				↑ (FSS)	
IPA patients	Güngör 2016 [27]	NC	174	all	all	24–76	48 (6–96)				↑ (SF-36 PCS); ≈(SF-36 MCS, RHS)	
Switzerland	Hundsberger 2013 [21]	baseline	7	all	all	43[h]	3–61+12	↑(6-MWT,n=6)	≈(FVC)	≈(MRC)		
MCS Germany	Strothotte 2010 [13]	baseline	44	all	all	21–69	12	↑(6-MWT); ≈(WGM,TT)	≈(FVC)	≈(MRC)	≈(SF-36)	
Extension MCS	Regnery 2012 [12]	baseline	38	all	all	23–69	36	≈(6-MWT,TT)	≈(FVC)	≈(MRC)	≈(SF-36)	
Part of MCS	Vielhaber 2011 [57]	baseline	2	all	all	41–42	24	*See MCS*	*See MCS*	*See MCS*	*see MCS*	
Not in MCS	Merk 2009 [58]	baseline	4	all	all	39–68	6	≈(6-MWT,n=2)	↑ (MIP, n=3)		no data shown	
Denmark	Andreassen 2014 [59]	baseline	4	all	all	39–59	48 (24–72)	↑(6-MWT)	Varied (VC)	Varied (Biodex)		
Finland	Korpela 2009 [41]	baseline	1	all	all	20	12	≈(10MWT)	≈(VC)	↑(grip)		
France (Paris)	Orlikowski 2011 [30]	baseline	5	all	all	28–62	12	≈(MFM)	≈(SVCsit,sup, MI/EP)		↑ (SF-36, FSS)	
France (Aix)	Gesquière 2015 [60]	baseline	2	all	all	31,38	9 (6–12)	Varied (6-MWT); ≈(10MWT)	≈(FVC)			
Greece	Papadimas 2011 [31]	baseline	5	all	all	37–72	12 (6–38)		≈(VCsit,sup,n=4)	≈(MRC)	↑ (FSS, n=4)	
MCS Italy	Angelini 2012 [8]	baseline	74	all	most	7–72	36 (12–54)	↑(6-MWT);≈(WGM)	≈(FVC)			
Part of MCS[c]	Angelini 2009 [35]	baseline	11	all	all	na	12 (3–18)	*See MCS*	*See MCS*			
Part of MCS	Angelini 2012B [61]	baseline	40	all	most	5–80	12	*See MCS*	*See MCS*			
Part of MCS	Bembi 2010 [9]	baseline	24	all	17	48±11[d]	36	*See MCS*	*See MCS*			
Part of MCS[c]	Ravaglia 2008 [42]	NC	1	all	all	49	12	↑(10MWT)	↑ (VC)	↑(MRC,HHD)		
Part of MCS[c]	Ravaglia 2009 [62]	baseline	13	all	all	57±12	12	*See MCS*	*See MCS*			
Part of MCS[c]	Ravaglia 2010 [63]	baseline	11	all	all	54±11	18/24	*See MCS*	*See MCS*	*See Ravaglia 2012*		
Part of MCS[c]	Ravaglia 2012 [64]	baseline	16	all	all	28–81	18/24	*See MCS*	*See MCS*	↑(HHD)		
Part of MCS	Vianello 2013 [28]	CC	14	8	all	18–65	36 (27–43)	*See MCS*	*See MCS*			
Part of MCS	Marzorati 2012 [65]	baseline	4	all	all	45 ± 6	12	*See MCS*	*See MCS*			
Part of MCS	Marzorati 2012B [66]	baseline	1	all	all	50	24	*See MCS*	*See MCS*			
Not in MCS[e]	Montagnese 2015 [67]	baseline	30	14	all	36–72	32 (12–60)	≈(6-MWT, WGM)	≈(FVC)			
Not in MCS[e]	Crescimanno 2015 [68]	baseline	8	4 (data)	all	31–72	36	↑ (6-MWT)	↓(FVC)			
Not in MCS	Rossi 2007 [43]	baseline	3	all	1	19[d]	5	NA[d]	NA[d]	NA[d]		
Japan (Tokyo)	Kobayashi 2010 [40]	baseline	4	all	all	17–44	12	≈(WGM)		↑(MMT)		
Japan (Osaka)	Sugai 2010 [45]	baseline	1	all	all	26	12			↑(HHD)		
Japan (NCH)	Furusawa 2012 [39]	baseline	5	all	all	32–66	24		↑(FVC)	≈(MMT); ↑(HHD)		
In above	Furusawa 2014 [69]	baseline	1	all	all	37	48		*See Furusawa 2012*	*See Furusawa 2012*		
Japan (Kyoto)	Isayama 2014 [70]	baseline	1	all	all	30	66	↓(6-MWT)	↑(FVC)	≈(MRC), varied (HHD)		

(continued)

Table 1 *(Continued)*

			No. of patients					Outcomes under treatment[a]				
Patient population	Study	Comparison	Total	ERT	Adult	Age (year)	ERT (months)	Motor performance	Respiratory function	Muscle strength	Quality of Life	Survival
South-Korea	Park 2015 [71]	baseline	5	all	all	NA	9 (3–11)	Varied (6-MWT,n=4)	≈(FVC)	≈(MRC)		
Dutch main	de Vries 2012 [10]	baseline/NC	69/49	all	all	26–76	23 (5–47)	≈(QMFT)	≈(FVCsit); ↓(FVCsup)	↑(MRC,HHD)		
Part main	de Vries 2010 [72]	baseline	4	all	all	50–63	33	*see de Vries 2012*	*see de Vries 2012*	*see de Vries 2012*		
Not in main	Winkel 2004 [73]	baseline	3	all	1	32[d]	36[d]	≈(GMFM)[d]	≈(VC)[d]	↑(MRC,HHD)[d]		
Extension [73]	v Capelle 2008 [46]	baseline	3	all	1	32[d]	96[d]	≈(GMFM)[d]	≈(VC)[d]	≈(HHD)[d]	↑(SF-36,RHS,FSS)[d]	
MCS UK	Anderson 2014 [7,74]	baseline	62	59[f]	all	16–74	16 (0–37)[f]	↑(6-MWT)	≈(FVC)	↑(MRC)		
Partly in MCS	Stepien 2016 [32]	baseline	22	all	all	16–64	60	No baseline	≈(FVCsit,sup)		≈(SF-36 PCS&MCS)	
Not in MCS	Sayeed 2015 [44]	baseline	2	all	all	67	36		≈(FVC)			
US	Case 2008 [38]	baseline	1	all	all	61	24	↑(TT)	≈(FVC, 18 months)			
US	Patel 2012 [50]	baseline	3	all	all	37–57	40 (16–59)	↓(6-MWT, TT)	↓(FVC,n=2)	Varied (MRC,n=2)	↓(SF-36 PCS)	
Total[g]: 44 studies in 26 separate patient populations			1349 patients, 586 after excluding overlap				Average: 2.8 year	6MWT: 13 separate populations (n=281)	(F)VC: 21 separate populations (*n*=364)	Any: 16 separate populations (*n*=275)	Any: 7 separate populations (*n*=282)	

Only the first author of each study is given; studies from the same country (or international setting) are alternately shaded in grey/white. MCS, multi-centre study; *n*, number of patients; NA, not available; 6-MWT, six minute walk test; TT, timed tests; 10MWT, 10 meter walk test; QMFT, quick motor function test; (G)MFM, (gross) motor function measure; WGM, Walter Gardner Medwin scale; (F)VC, (forced) vital capacity (if unspecified then in upright position; sit, in sitting positon; sup, in supine position); SVC, slow vital capacity; MIP/MEP, minimum inspiratory/expiratory pressure; MRC, Manual Muscle Testing according to the Medical Research Council grading; HHD, Hand Held Dynamometry; MMT, manual muscle testing other than according to MRC; QMT, quantative muscle testing; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; SF-36 PCS, physical component summary score of the SF-36; SF-36 MCS, mental component summary score of the SF-36; RHS, Rotterdam Handicap Scale; FSS, Fatigue Severity Scale; Comparison: placebo, the study compares outcomes under treatment to outcomes observed in patients treated with placebo; baseline, comparison is made with the patients' baseline status; NC, comparison is to the natural course period of the same patients; Cox, comparison is to time untreated (time-dependent Cox proportional hazards model); CC, comparison is with untreated controls (case control study); [a]Outcomes under treatment are reported as: ↑, improvement; ↓, deterioration; ≈, stabilization; except for trials and CC where: +, positive effect; –, negative effect; 0, no effect; [b]Data for 55 late-onset treatment study (LOTS) patients treated for 24 months; [c]Most patients from these studies were included in the Italian MCS; [d]Data reported are for adult patient(s) only; [e]Only one or two patients were included in the Italian MCS; [f]At recruitment; [g]An estimate of the total number of individual patients (i.e. counting each patient only once) was made. Overlap of patients in studies was identified by: (i) contacting study authors (Europe, LOTS), (ii) assessing individual patient characteristics (Japan, USA) and (iii) adjusting for the national coverage [overlap between International Pompe Association (IPA) patient population and German and UK studies]; [h]median value.

overlapping patients, the total number of individual patients was 586. The average treatment duration observed in the studies varied from 5 months to 8 years, with a weighted average of 2.8 years. One placebo-controlled randomized clinical trial was identified: the late-onset treatment study (LOTS) [15]. All other studies were observational, most following patients from start of treatment, four comparing with the time before treatment started (‘natural course’ follow-up) [10,11,26,27] and one comparing with a historical control group [28]. A total of 31 studies were from Europe, six from Asia, two from North America and five were multinational. The multinational studies comprised patients from several countries in Europe, North America and Australia, and included the LOTS trial and its extension, and three studies based on the International Pompe Association survey [29], which is a survey that monitors patient-reported outcomes.

Figure 2a summarizes the response to ERT found at group level in the 26 study populations, weighted by population size, whereas Fig. 2b depicts the patients’ individual responses, as far as these were reported in the studies. The majority of studies showed that, at group level, the 6-min walk test (6-MWT), muscle strength and health-related quality of life improved or stabilized. For vital capacity, a stabilization was observed at group level (Fig. 2a). Given the progressive nature of Pompe disease, it is likely that a stabilization of respiratory function at group level also reflects a positive effect of ERT. Most studies assessed vital capacity in an upright position, while only few included assessments on vital capacity in while only supine position [10,30–32].

At the individual level, the response to treatment in these studies varied. Individual responses were not reported in all studies. Those that did report data showed that 76% of patients improved or remained stable on the 6-MWT, 70% on vital capacity and 90%

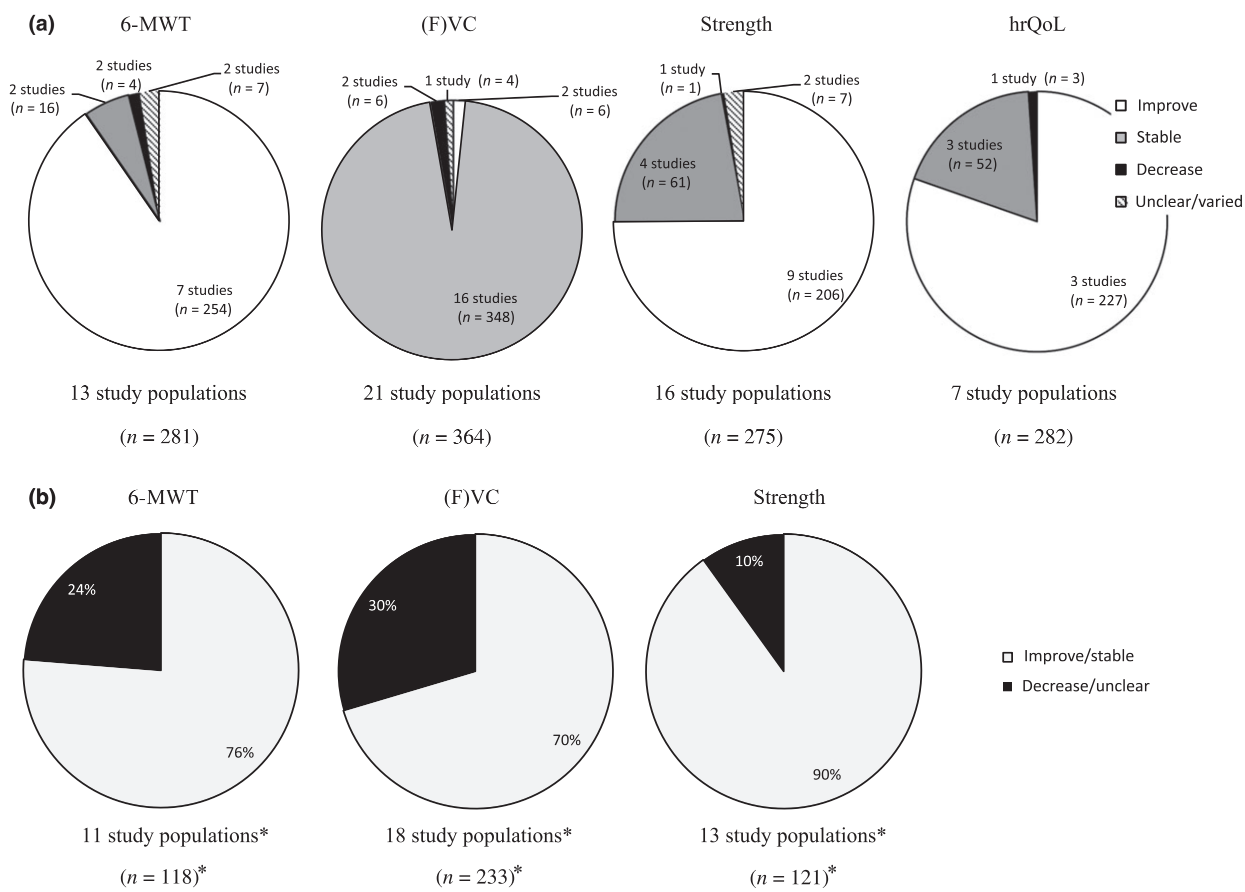

Figure 2 (a) Response to ERT observed at group level in 26 study populations (44 studies), weighted by size. (b) Response to ERT observed in individual patients in 26 study populations (44 studies). 6-MWT, six minute walk test; (F)VC, (forced) vital capacity; Strength, muscle strength; hrQoL, health-related Quality of Life; n, number of patients. *In (a) patient numbers represent the total number of patients included in the studies reporting results at group level for the respective outcome measures (see for details Table 1), while in (b) only those who actually performed the respective tests are included. Individual responses were not reported for the 6-MWT and (F)VC in studies [14,15] and [7,74], and for strength not in [14,15], [7,74] and [12,13].

on muscle strength (Fig. 2b). The larger studies on health-related quality of life did not report individual patient responses, so no results were reported here.

Factors associated with a good or poor response to treatment were reported in two studies [10,15]. Patients with a better clinical status at baseline responded better to treatment on some outcome measures in both studies, whereas the observational study [10] also suggested that women may benefit more from ERT in terms of muscle strength compared with men, and younger patients in terms of forced vital capacity (FVC) in a supine position compared with older patients.

Table 2 shows the criteria currently applied in the 11 participating countries with respect to starting and stopping treatment. All countries required patients to have a confirmed diagnosis and skeletal muscle weakness and/or respiratory symptoms before starting treatment. With respect to stopping treatment there was more variation, with some countries not specifying any stop criteria.

Confirmation of diagnosis

Diagnosis has to be performed by a certified laboratory. Before starting ERT the diagnosis should be confirmed by enzyme analysis in leukocytes, fibroblasts or skeletal muscle and/or genetically by mutation analysis. As the group is aware of examples where patients who were later found not to have Pompe disease were started on ERT, confirmation by both enzymatic and genetic testing should preferably be attempted. Dried-blood-spot testing has recently become available and is a good test for screening for Pompe disease. However, it always requires diagnostic confirmation [33]. Mutation analysis can be inconclusive due to the detection of new variants of unknown pathogenicity or uncertainty about variations being on separate alleles (in trans). In addition, variations may be deep intronic and lead to cryptic splicing and be missed. Such mutations should be searched for accurately [34].

Pre-symptomatic patients

All published studies assessing the effects of ERT focused on patients with a confirmed diagnosis who were symptomatic, i.e. had a minimum level of skeletal and/or respiratory involvement. One study included one pre-symptomatic patient, but individual data were not presented [35]. Follow-up of seven pre-symptomatic patients in France showed that Pompe disease can remain clinically silent for years [36,37].

Hence, there is currently insufficient evidence to support starting ERT in pre-symptomatic patients. We recommend that these patients are monitored every 6 months in the first year and once per year thereafter in an attempt to identify disease progression early and to start ERT in a timely fashion. Treatment should not be started in the absence of both skeletal muscle weakness (assessed by muscle strength tests or impairments in daily living) and respiratory involvement (FVC < 80%). This recommendation to monitor pre-symptomatic patients includes patients who experience fatigue or myalgia, have elevated creatine kinase levels or show minimal pathological findings on magnetic resonance imaging or muscle biopsy in the absence of skeletal muscle weakness and/or respiratory involvement. Further studies are needed to determine whether starting treatment based on these non-specific signs and symptoms is beneficial.

Monitoring should consist of at least a minimal set of clinical assessments, including manual muscle testing using the Medical Research Council grading scale, 6-MWT, timed tests (10-m walk, climb four steps, stand up from supine and stand from chair), FVC in a sitting and supine position, maximal inspiratory/expiratory pressure and ventilation use. More information on the selection of these assessments is presented in a workshop report [25].

Severely affected patients

Although some studies suggest that ERT is more beneficial if started early in the course of disease [8,10,13,15], there were also a number of studies assessing the effects of ERT specifically in more severely affected patients. Eleven studies (36 patients) focused on patients who were invasively ventilated, required ventilation during part of the day or had an FVC in a supine position below 30%, and/or were fully wheelchair dependent or able to walk <40 m [28,30,38–46]. These studies indicate that respiratory function and muscle strength can also improve/stabilize in these patients. One patient who was described as being in a terminal stage of the disease when starting treatment died, as did one patient who was ventilated and confined to bed, had a history of frequent pneumothorax, and was severely emaciated [40,43].

Also for patients who are wheelchair bound and/or ventilator dependent, it remains very important to retain their present level of independence and ability to perform activities of daily life. Given that there is some evidence that more severely affected patients also benefit from ERT, it was agreed that ERT can be started in these patients. However, the consensus was that, in principle, ERT should not be started in patients who have another significant life-threatening illness in an advanced stage or who have virtually no remaining skeletal or respiratory muscle function.

Table 2 National practice with respect to starting and stopping ERT in adult Pompe patients

	Belgium	Denmark	France	Germany	Italy	Netherlands	Spain	UK	Swiss	Austria
Approach	National guidelines [56]	National guidelines	National guidelines	National guidelines [24]		Decision to start and stop treatment is made in a multidisciplinary team meeting	National guidelines [18]	Provisional guidelines [75]	National guidelines [21]	Individual decision or by national multidisciplinary metabolic team
Start ERT:	Diagnosed Symptomatic Not if: limited LE due to comorbidities Not if: no clinical impact	Diagnosed Symptomatic	Diagnosed Symptomatic Consents to monitoring	Diagnosed Symptomatic	Diagnosed Symptomatic	Diagnosed Symptomatic	Diagnosed Symptomatic	Diagnosed Symptomatic Consents to monitoring	Diagnosed Symptomatic	Diagnosed
Stop ERT:	Patient wish Severe IARs Lack effect Non-compliance Severe comorbidity/complications	Patient wish Severe IARs Deterioration	Patient wish Severe IARs Clinical worsening, considering patient opinion Severe comorbidity	Patient wish Severe IARs	Patient wish Severe IARs	Patient wish Severe IARs	Patient wish Severe IARs	*Not well defined*	Decline Non- compliance Severe comorbidity	*Not well defined*

Diagnosed, confirmed diagnosis, Symptomatic, muscle weakness and/or respiratory involvement; Lack effect, lack of improvement/stabilisation; Severe comorbidity, if a disease occurs which is life threatening or leading to invalidity; IAR, infusion associated reactions, LE, life expectancy.

Initial treatment period needed to evaluate effects of enzyme replacement therapy

The group recommended the use of an initial treatment period of 2 years, after which the effect of treatment will be evaluated. Based on the studies reviewed, an effect of ERT should be observed within this period. To allow such evaluation to take place, start criteria should include the commitment of the patient and physician to regular monitoring. The patient should be evaluated using at least the minimal set of clinical assessments mentioned above [25].

An improvement or stabilization in motor and/or respiratory function (assessed using the minimal set of assessments described above) suggests that the treatment is having an effect and should be continued. Usually the patient is only followed from the start of treatment. If assessments are also available for the period prior to starting treatment, then a slowing of a patient's disease progression can also be interpreted as an improvement and suggestive of a positive treatment effect.

If the patient shows a substantial deterioration in both motor and respiratory functions, stopping treatment should be discussed. If the patient has only been monitored from start of treatment, there is no proper way to distinguish whether this observed deterioration means that ERT is not effective or whether ERT effectively reduces the speed of deterioration. Therefore, it was agreed that restarting treatment could be considered if disease progression appears to be enhanced after ERT has been stopped.

Effect of antibodies

Antibody formation against ERT may counteract the effect of treatment in adult patients, as it has been shown to do in infants with Pompe disease [47,48]. Two studies in children and adults with Pompe disease show that only a small proportion of these patients develop high antibody titers against ERT [49,50]. In some of these cases, the effect of ERT was counteracted, but in several this was not the case. In the rare cases where high antibody titers do interfere with the effect of ERT in adult patients, stopping treatment should be considered.

No evidence to stop enzyme replacement therapy during pregnancy and lactation

Four case reports have been published on patients who used ERT during pregnancy and/or lactation, including a total of four individual patients [51–54]. One patient had a spontaneous miscarriage at week 14, without further information on the cause. The remaining three patients showed deterioration in mobility and respiratory function during the pregnancy, which was shown to improve or resolve in the two patients who were followed for 6–12 months after delivery. Three babies were delivered by Caesarean section, without complications. Two were followed for 6–12 months after delivery and developed normally. Alglucosidose alfa levels were shown to be elevated in breast milk until 24 h after infusion [52]. Although there is currently no evidence that ERT affects the unborn fetus, the decision to continue or discontinue ERT should be left to the discretion of the treating physician and patient. For safety we recommend that breastfeeding is avoided in the first 24 h after infusion.

Recommendation

Based on the available evidence, clinical experience and discussion, consensus was reached regarding when to start and stop treatment.

Treatment should be started in patients who meet all of the following criteria:

1) The patient should have a confirmed diagnosis of Pompe disease, as established by enzyme activity testing in leukocytes, fibroblasts or skeletal muscle and/or demonstration of pathogenic mutations in both alleles of the GAA gene.
   Note. A positive dried-blood-spot screening test should always be followed by one of these tests for confirmation of the diagnosis.
2) The patient should be symptomatic, i.e. should have skeletal muscle weakness or respiratory muscle involvement as observed using clinical assessments (see [25]).
3) The patient should commit to regular treatment (every other week) and regular monitoring (at least once per year) to evaluate his/her response to treatment.
4) The clinician should commit to regular treatment and monitoring.
5) The patient should have residual skeletal and respiratory muscle function, which is considered functionally relevant and clinically important for the patient to maintain or improve.
6) The patient should not have another life-threatening illness that is in an advanced stage, where treatment to sustain life is inappropriate.

Stopping treatment should be considered for any one of the following reasons:

1) The patient suffers from severe infusion-associated reactions that cannot be managed properly.
2) High antibody titers are detected that significantly counteract the effect of ERT.
3) The patient wishes to stop ERT.

4) The patient does not comply with regular infusions or yearly clinical assessments.
5) The patient has another life-threatening illness that is in an advanced stage, where treatment to sustain life is inappropriate.
6) There is no indication that skeletal muscle function and/or respiratory function have stabilized or improved in the first 2 years after start of treatment, as assessed using clinical assessments (see [25]).
   N.B. If after stopping treatment the disease deteriorates faster than during treatment, restarting ERT can be considered.

Continuation of ERT can be considered during pregnancy and lactation.

Discussion

This is the European Pompe Consortium's consensus recommendation for starting and stopping ERT in adult patients with Pompe disease. It is based on the long-standing clinical experience of 34 experts from 11 European countries and the available evidence reported in the literature. The experts involved in this recommendation all have extensive experience in treating patients with Pompe disease, and care for large numbers of patients.

Enzyme replacement therapy became available for patients in Europe and the USA in 2006. Studies in neonates showing improved survival were key to market approval [3,6,55]; not many data on adult patients were available at the time. The placebo-controlled LOTS trial, which studied children and adults with Pompe disease started in 2005/2006. In the 10 years since then a large amount of evidence has been accrued on adult patients suggesting that ERT is beneficial in this group. Although almost all studies are observational in nature, the relatively large number of patients studied and the comparison to disease progression without treatment included in a few of these studies provide substantial evidence for the beneficial effect of ERT in adult patients with Pompe disease. The average follow-up during treatment was 2–3 years in the reported studies. Studies reporting a longer follow-up are required to further assess the effects of long-term treatment with ERT.

Studies indicate that there is individual variation in the effect of treatment and it has been suggested that starting treatment early is beneficial. Although more severely affected patients are likely to have a higher degree of muscle damage and have already lost some functional abilities, they are not necessarily unresponsive to therapy and have been shown to improve under ERT. At present, there is a lack of verified prognostic factors to help identify which patients would benefit more or less from treatment or when treatment is no longer useful. Such knowledge is key to a sensible implementation of ERT. Further research on prognostic factors is needed, but requires large-scale studies, which can only be achieved by collaborating internationally. The European Pompe Consortium intends to work together on such studies.

There are many commonalities between this recommendation and published national guidance and practice. For example, all countries and published guidance require a confirmed diagnosis and presence of symptoms to start treatment. The exact specification of which tests should be used to confirm a diagnosis differs somewhat. Our recommendation is that the diagnosis of Pompe disease is based on enzymatic testing and/or genetic confirmation. A positive dried-blood-spot result, however, should always be confirmed by another test [33].

Although no previously published guidelines suggest that pre-symptomatic patients should be treated, some indicate that treatment can be considered in pre-symptomatic patients with abnormal muscle imaging or biopsy results [20,22]. Although there is currently no evidence to show whether pre-symptomatic patients benefit from treatment, and it has been shown that they may remain pre-symptomatic for years [36,37], such patients may already be losing muscle mass, which they may not be able to regain. It is thus important to obtain more evidence to assess whether such patients would benefit from treatment, but the high drug costs may hamper such studies.

Several national practices and published recommendations do include some criteria for withdrawing treatment [20–22,24,56], but none mention the detection of high antibody levels against alglucosidase alfa that counteract the treatment effect as a reason to stop treatment. The effect of antibodies does seem to be much higher in infants than in adults [49]. Most also specify that patients should be followed to monitor the treatment effect, but not all consider the lack of a treatment effect to be a reason for stopping treatment. The requirement that patients and doctors commit to the regular follow-up is an important element of the recommendation, and was first included in the UK and Brazilian guidance.

Future consortium activities and research priorities

The consortium will review these recommendations every 2 years. For this purpose new evidence will be assessed and discussed at consortium meetings. The most urgent research priorities are to determine the effect of long-term treatment and gain insight into prognostic factors. Future studies should aim to incorporate the minimal set of outcome measures and include supine FVC in addition to FVC in a sitting position.

Conclusion

This is the first European consensus recommendation for starting and stopping ERT in adult patients with Pompe disease. It is based on the extensive experience of experts from different countries.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Details of the search strategy.

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Appendix 1: The European Pompe Consortium

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