Real-life Effects of Enzyme Replacement Therapy in Adults with Late-Onset Pompe Disease: Multicentric Retrospective Study

Dr. Helena Schubert[1], Dr. Miguel Azevedo[2]
[1]Department of Clinical Pharmacology, University Hospital Zurich, Zurich, Switzerland
[2]Institute of Rare Disorders and Therapeutics, University of Lisbon, Lisbon, Portugal
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Abstract
Pompes disease is an infrequent lysosomal storage disease that is brought on by a deficiency in acid alpha-glucosidase, resulting in muscle weakness that develops gradually and respiratory impairment. This retrospective multicenter study aims at assessing the clinical effects of enzyme replacement therapy (ERT) in 52 adult patients with late-onset Pompe disease (LOPD) during the 3-year treatment. It involved an analysis of data of five European specialty centers, with emphasis on the changes of forced vital capacity (FVC), 6-minute walk distance (6MWD), and adverse events. ERT was linked to the statistically significant mean changes of 9 percent in FVC and 14 percent in 6MWD ($p < 0.05$). All but one adverse event was a mild infusion reaction and no patient discontinued. These data confirm the long-term effectiveness and safety of ERT to enhance the respiratory function and mobility in adult LOPD patients, which provides the persistence of access to specialized pharmacotherapy as an approach to managing rare diseases.

Keywords: ***Pompes disease, late-onset Pompes disease, Enzyme replacement therapy, Forced vital capacity, 6-minute walk distance, Rare disease, Pharmacotherapy, Respiratory function, Functional capacity, Real-world evidence***

1. Introduction

1.1 Pompes Disease and LOPD Overview

Glycogen storage disease type II (GSD-II) or Pompes disease is an infrequent, hereditary, lysosomal storage disease which is caused by the insufficiency of acid alpha-glucosidase (GAA) enzyme, which is involved in the digestion of glycogen in lysosomes. This buildup of glycogen in different tissues especially muscles causes progressive weakness of the muscles, respiratory disturbance, and involvement of the heart. There are two types of Pompes disease; infantile-onset and late-onset Pompes disease (LOPD).

Late-onset Pompe disease (LOPD) is an instance of the disease in which the symptoms appear late in life, usually after the first year of life. In contrast to infantile-onset form, which is clinically severe, with cardiac and respiratory symptoms evident at birth and the disease being frequently lethal during the first year of life, LOPD has more insidious onset and skeletal muscles and respiratory involvement may be the primary symptoms. Progressive muscle weakness is a frequent symptom in individuals with LOPD that has a drastic effect on mobility, respiratory ability, significantly decreasing the quality of life and causing early death in some individuals.(1)

1.2 Mechanism and Role of Enzyme Replacement Therapy (ERT)

Enzyme replacement therapy (ERT) is the approved standard treatment of Pompe disease including LOPD. ERT is the use of a recombinant version of acid alpha-glucosidase (the enzyme that is defective in Pompes disease) to aid in the breakdown of glycogen in the lysosomes and thus ERT lightens the burden of glycogen build up in the tissues. The therapy is expected to replenish the activity of enzymes and avoid the worsening of muscle and respiratory weakness due to the amelioration of the lysosomal activity and muscle conditions.

ERT has proven to be disease slowing in LOPD patients and capable of Functional outcome measures, especially concerning respiratory Status (forced vital capacity (FVC)) and muscle strength (6-minute walk distance (6MWD)). Treatment is well-tolerated, but some mild adverse effects may be experienced by a patient, including infusion reactions. ERT is not a full reversal of the damage done by the buildup of glycogen, despite the benefits, there is variability in how well ERT works, particularly regarding long-term outcomes, amongst different patients.(2)

1.3 Restrictions of Clinical Trials on Rare Diseases

The limited amount of patients with rare diseases, including Pompe disease, and the heterogeneity of the disease pose a big challenge to clinical trials. The rare disease studies that are characterized by small sample sizes cannot provide the statistical power, and they are not representative of the full patient experience. In addition, randomized

controlled trials (RCTs) regarded as the gold standard in measuring treatment efficacy may be difficult to carry out because of recruitment problems, ethical issues and the long term treatment and follow up that has to take place.

Placebo-controlled studies are not always possible or ethical when treatments, such as ERT, exist which have proved to be of benefit in a substantial number of patients. Moreover, this is because Pompes disease is long-term and follow-ups have to be done over a long period to comprehend the proficiency and safety of therapeutic procedures such as ERT, which cannot be possible within a brief period of clinical trials.(3)

1.4 Significance of Real-World Outcome Studies

The findings of a clinical trial in rare diseases are limited; therefore, real-world outcome studies are gaining prominence. Such studies offer information on real-life clinical practice and constitute a wider and more varied population of patients, with multiple comorbidities, who might not be able to pass the rigid inclusion criteria of clinical trials. Long-term efficacy, safety and tolerability of a treatment such as ERT, however, require real-world studies to assess the applicability in routine practice.

These kinds of study also assist in the validation of the results obtained in clinical trials and give some information about the heterogeneity of the responses observed in diverse populations. Additionally, they are capable of providing insight into the practical advantages of treatments within the care environments that are regularly underrepresented in controlled clinical trials.

1.5 Objective and Rationale of the Study

This study aims at assessing the effectiveness of enzyme replacement therapy (ERT) in adult patients with late-onset Pompe disease (LOPD) in real life. This study will help in evaluating the clinical efficacy, safety, and improvement in functions of long-term ERT use by the analysis of data collected in 52 patients in five European centers. The major outcomes will be the changes in forced vital capacity (FVC), 6-minute walk distance (6MWD), and the profile of adverse events. The purpose of the study is to offer real-life data regarding the functional ERT advantages, supporting once again that ERT is a treatment alternative to be used in LOPD patients and it shows the long-term safety of ERT in real-life clinical practice. The study aims at examining the effectiveness of ERT in various patients groups, as it will capture data pertaining to various centres and this data will be instrumental in the general pharmacotherapy of rare diseases.(4)

2. Materials and methods

2.1 Study design

It is a retrospective, multicentric, observational study that has been conducted in five expert centers. The research aims to evaluate the clinical effectiveness (in the real world setting) of enzyme replacement therapy (ERT) in adults with late-onset Pompes disease (LOPD). The retrospective design allows using the data of the patients who have already undergone treatment with ERT and whose follow-up can be effective in the context of the long-term treatment outcomes in a real clinical practice.

Its multicenter format was chosen because it was necessary to guarantee that the data of a broad spectrum of LOPD patients were derived and, therefore, the enhanced external validity of the results to diverse clinical environments. The article is based upon the real life evidence-based on the routine clinical practice and it is focused on the effects produced by ERT on the key functional outcomes which comprise the respiratory status and mobility following the 3 years of the examination. The observational nature of the study means that the patients were not assigned randomly to the different treatment regiments but rather the study represented a retrospective review of the outcomes which were attributed to the ERT which the patients were receiving as a part of their routine care settings. The design will provide data regarding effectiveness and safety of ERT in long-term real life clinical practice which cannot be determined in controlled clinical trials because of the rareness of the diseases. The research makes patient population more varied as it employs data of multiple centers that reflect diversity of clinical practices and experiences of different patients.(5)

2.2 Precences and Moral Consents of the Study

The research trial was performed at five European specialty centers, in which all of them have specialised in the management of patients having rare genetic illnesses and Pompes disease in particular. The centers involved are spread among various European states, and this fact contributes to the sample being extensive in geographical distribution of LOPD patients.

The list of participating centers implies:

1. Center 1: French specialist center of genetic disorders.
2. Center 2: German renowned hospital of metabolic diseases.
3. Center 3: Italian institute of neuromuscular diseases.
4. Center 4: Spanish center of National Pompe disease.
5. Center 5: UK University hospital, rare disease, and neurology center.

Information was related to individual patients regarding enzyme replacement therapy (ERT) in routine clinical care in each center. The centers were chosen due to their clinical experience, perceived experience in management of Pompes disease and availability of the patients record that would meet the eligibility rules of the study.

The ethical conditions before the start of the study were ensured through the approval of the study by Institutional Review Board (IRB) or Ethics Committee of each center. The study was conducted based on the ethical standards or guidelines of a research that involves human subjects and thus privacy and confidentiality of all the patients was taken into account during the study. The access and use of the data were allowed by the data protection authorities and all the patient data were anonymized to maintain confidentiality.(6)

Taking into consideration the fact that the study was retrospective in nature, it was determined that the patients would not be asked to consent according to the ethics of retrospective chart review as long as the confidentiality of the patients could be ensured and that the data would be anonymized.

2.3 Selections Criteria of the Patients

The reason behind the inclusion and exclusion criteria of the patients was to take those individuals who had received treatment through enzyme replacement therapy (ERT) of late-onset Pompes disease (LOPD) in the real-life clinical practice, and this would help in making the results obtained applicable to the general clinical practices.

Inclusion Criteria:

- Age: Adults (> = 18 years old) with late-onset Pompes disease (LOPD).
- Diagnosis: LOPD has been definitely diagnosed and acid alpha-glucosidase (GAA) deficiency is documented (by genetic testing or by enzyme quantitation).
- ERT Treatment: These are the patients that received enzyme replacement therapy (ERT) and were on therapy a minimum of 6 months before the study and had clinical data to enable a retrospective analysis.
- Clinical Records: Availability of clinical records with the baseline and follow-up data on forced vital capacity (FVC), 6-minute walk distance (6MWD), and adverse event profiles.(7)

Exclusion Criteria:

- Infantile-onset Pompe disease: Patients with infantile-onset Pompes disease were excluded because this type of the disease tends to take a different clinical course and therapy is tends to be administered.
- No ERT treatment: Patients that had not received treatment with ERT, or had received alternative treatment (gene therapy, experimental drugs, etc.) were not permitted.
- Missing data on at least one of the vital clinical parameters of FVC, 6MWD or adverse events: Patients who had missing data on at least one of the vital clinical parameters of FVC, 6MWD or adverse events were not analysed to provide uniformity and completeness of the analysis.
- Severe comorbidities: Patients with severe comorbid conditions, who could confound the interpretation of the results (e.g., severe heart failure, malignancies, etc.) were excluded.

Such inclusion and exclusion criteria were intended to ensure that the study receives the appropriate type of patients who had received the treatment with ERT and whose clinical data would provide feasible evidence on the efficacy and safety of such treatment in the real-life setting.

2.4 Intervention

The intervention in the case of the study was enzyme replacement therapy (ERT) with the recombinant form of the acid alpha-glucosidase (GAA), which is the enzyme that is defective and causes Pompes disease in the patients. The exact formulation of the enzyme replacement therapy given was as per the standard procedures of ERT per participating center.(8)

ERT dosage and frequency:

The dose of ERT administered in this study on patients was the normal recommended dose on adult patients with LOPD of 2.5 mg/kg of body weight.

Frequency: The ERT was performing fortnightly as per the routine treatment process. Such a dosing regimen is proven efficient to maintain the functional improvements acquired at the time of initial treatment.

Duration:

The patients were treated by ERT during at least 6 months and the average patient was treated during up to 3 years. This enabled a sufficient time of determining the long term effect of ERT on respiratory and mobility status.

The intervention was in line with the current clinical guidelines regarding the management of late-onset Pompe disease and reflected real-life practice between the enrolling centers.

2.5 Outcome Measures

The primary end points of study were based on general clinical parameters upon which the functional status of a patient with Pompes disease is decided:

Forced Vital Capacity (FVC): FVC was taken to represent the respiratory functions and it was measured in liters (L). The respiratory decay is a significant source of morbidity in Pompes patients and consequently, this test is a major outcome measure in trials of Pompes disease.

6-Minute Walk Distance (6MWD): It involves measurement of the distance that a patient can walk in the 6 minutes, and it serves as an assessment of functional mobility and muscle strength. The deterioration in 6MWD is generally connected to progressive muscle weakness in Pompes disease.(9)

Adverse Event Documentation: All the adverse events (AEs) observed by the patients during the treatment process were documented. AEs were categorized according to CTCAE v5.0 (Common Terminology Criteria for Adverse Events) and analyzed in regard to their severity, duration and correlation with the treatment.

The reason to chose these outcome measures is because these are outcome measures that are established in the literature as outcome measures of efficacy and safety of treatment in Pompes disease and other neuromuscular disease.

2.6 Statistics Analysis

Descriptive statistics and inferential statistical procedures were applied so as to interpret data. Central tendency and variability of the outcomes of FVC and 6MWD underwent descriptive statistics of the mean, standard deviation (SD), and percent change. The difference of these parameters between the baseline and follow up visits were significant as determined by paired t-tests or non-parametric tests (Wilcoxon signed-rank test).

Significance Threshold: All hypothesis testing used a p-value less than 0.05 as statistical significant.

Software Used: The statistical analysis was performed in SPSS statistics (version 25.0) and R software (version 3.6) that are sophisticated statistical modeling software packages.

In addition, multivariate regressions were done to identify the variables that may be utilized to predict the superior outcomes or adverse events, and they included the age, baseline functional capacity, and time on ERT. This has allowed the study to consider prognostic factors based on which treatment decisions would be made were it a case of clinical practice.

3. Results

3.1 Baseline Characteristics of the Patients

The study involving 52 adult patients with late-onset Pompes disease (LOPD) was examined. These patients received enzyme replacement therapy (ERT) during at least 6 months in five European centres. The cohort baseline characteristics are as follows:

Table 1: Baseline Characteristics of the Patients

Characteristic	Value (mean ± SD)
Age	45.6 ± 12.4 years
Gender	
- Male	24 (46%)
- Female	28 (54%)
Disease Duration (years)	8.2 ± 4.1
ECOG Performance Status (PS)	
- 0 (Fully active)	32 (62%)
- 1 (Restricted in physically strenuous activity)	20 (38%)
Comorbidities	
- Hypertension	15 (29%)
- Diabetes mellitus	7 (13%)
- Cardiomyopathy	5 (10%)

Characteristic	Value (mean ± SD)
- Asthma	4 (8%)
- Other (e.g., osteoarthritis)	6 (12%)

The patients had a middle-aged cohort with a mean age of 45.6 years and a standard deviation of 12.4 years. The vast majority of the patients were women (54%), and the average duration of the disease was 8.2 years. The baseline functional status of the patients was determined using ECOG Performance Status (PS), of which most (62%) of the patients had an ECOG PS of 0, meaning that they were fully active and could only be restricted in activities that were physically demanding.(10)

The patients had frequent comorbidities of hypertension (29%) and diabetes mellitus (13%), and this finding is congruent with the increasing prevalence of those diseases in the general adult population. Cardiomyopathy was noticed in one-tenth of the patients, and this observation represents a typical feature of Pompes disease since heart involvement is typical of this disorder, but the severity of this complication is lesser in late-onset patients than in infantile forms.

3.2 Shift in Functional Parameters

The key results of focus in this trial were the variations in functional parameters, namely, forced vital capacity (FVC) and 6-minute walk distance (6MWD), between the baseline and follow-up at 12, 24, and 36 months of the ERT treatment.

FVC (%) Baseline-Follow up.

Forced vital capacity (FVC) was calculated in percentages of the normal values which are predicted. The mean FVC at baseline was 68.2 +/- 12.6 percent. Mean FVC improvement after 3 yrs of ERT treatment was 9%, and the follow up value was 74.5 +/- 11.8 percent. This was a significant change, p-value < 0.05, and it showed a clinically important decrease in the difficulty of respiratory efforts.

Table 2: FVC (%) Baseline-Follow up.

Time Point	Mean FVC (%)	Change from Baseline (%)
Baseline	68.2 ± 12.6	-
12 months	71.1 ± 11.3	2.9%
24 months	72.8 ± 11.0	4.6%
36 months	74.5 ± 11.8	9%

This increase of FVC is a main predictor of improved pulmonary activity and shows that ERT positively influences the strength of the respiratory muscles, which is essential to handle the respiratory complications typical of LOPD patients.

6MWD -Baseline vs. Follow-up

The function mobility and muscle strength were measured with the help of the 6-minute walk distance (6MWD) test. The baseline 6MWD was 315 +/- 85 meters. Patients demonstrated the improvement of mobility and functional capacity, with the 6MWD increasing by 14% after 3 years of ERT and achieving the final value of 359 98 meters ($p < 0.05$).

Table 3: 6MWD -Baseline vs. Follow-up

Time Point	Mean 6MWD (m)	Change from Baseline (m)
Baseline	315 ± 85	-
12 months	330 ± 90	15 meters
24 months	340 ± 92	25 meters
36 months	359 ± 98	44 meters

The improvement in 6MWD by 14% indicates that the patients have gained much walking capacity and muscle activity that is crucial to the independence and quality of life of LOPD patients.(11)

3.3 Safety and Tolerability

The safety and tolerability of enzyme replacement therapy (ERT) were evaluated regarding the incidences and severity of adverse events (AEs) observed over the 3 years of treatment. The adverse events were graded based on the Common Terminology Criteria for Adverse Events (CTCAE v5.0).

Adverse Events Frequency and Severity

In general, the adverse events were mild to moderate with the most frequent one being infusion-related reaction that included fever, headache, chills, and nausea. To report mild infusion reactions in 40 percent of the patients and they generally disappeared within hours after treatment. There were no reports of serious adverse events like anaphylaxis in the course of the study.

Table4: Adverse Events Frequency and Severity

Adverse Event	Frequency (%)	Severity
Mild Infusion Reactions	40%	Mild (Grade 1)
Headache	20%	Mild (Grade 1)
Fatigue	18%	Mild to Moderate
Nausea	12%	Mild (Grade 1)
Chills	10%	Mild (Grade 1)

Infusion-Related Reactions

Infusion-related reactions were the most frequent adverse events occurring in 40 percent of patients. These were mostly fever, chills and headache but the reactions were of mild (Grade 1) and temporary nature. One-eighth of the patients also reported fatigue, which may be connected to the immune system reaction or the influence of the treatment on the muscle activity.(12)

Treatment Discontinuations

Notably, none of the patients stopped treatment because of an adverse event in the course of the study. This indicates that ERT can be well-tolerated in long-term use, and its side effects are manageable, and do not cause discontinuation of the treatment. The safety of ERT in adult LOPD patients is also supported by the lack of any major adverse events and the low incidence of discontinuation due to any reason.

4. Conclusion

4.1 Overview of Important Results

This research paper gives real life data on the efficacy, safety and tolerability outcome of enzyme replacement therapy (ERT) in adults with late-onset Pompe disease (LOPD). Main results of this multicenter retrospective analysis are illustrating that ERT results in considerable functional enhancements in patients, especially in respiratory capability (measured by forced vital capacity, FVC) and mobility (measured by 6-minute walk distance, 6MWD). The study demonstrated statistically significant and clinically relevant improvements in FVC (9%) and 6MWD (14%) over a treatment period of 3 years.

Furthermore, the research identified that ERT was generally tolerable and the majority of the adverse outcomes were mild infusion-related reactions, which did not require discontinuation of the treatment. Notably, there were no severe incidents, which additionally proves the safety of ERT use in LOPD patients in the long-term. Such results support the clinical usefulness of ERT, which is in the enhancement of functional capacity and quality of life in adult patients with LOPD.

4.2 Long-Term ERT Benefits in Adult LOPD reinforcement.

This study lends significant implications to the long-term effectiveness of enzyme replacement therapy (ERT) among adult patients with LOPD particularly when it comes to disease progression. The 9 % increment in FVC shows a continued amelioration of the respiratory status that is of paramount importance in patients with LOPD as they are at high risk of developing respiratory failure as the disease progressively causes muscle weakness. The key to enhancing patient survival and quality of life, decreasing the need of ventilatory assistance, and avoiding additional complications of respiratory insufficiency is to preserve or enhance respiratory status over time.

Correspondingly, the 14% increase in 6MWD results in a high degree of physical mobility enhancement, which translates to the increased muscle strength and endurance. In the case of the LOPD patients, functional mobility maintenance or improvement enables more autonomous participation in daily activities, which is crucial to maintaining life quality of the progressive disease. These outcomes not only support the effectiveness of ERT in functional outcomes, but also indicate that long-term treatment may postpone the occurrence of physical disability and lead to the better overall patient outcomes.

Moreover, the favourable safety and tolerability profile of ERT in the present study over the long-term follows previous observations and confirms that the treatment is a viable option to be used by adult patients with LOPD. Since none of the patients stopped treatment because of the side effects, the study signifies the feasibility of ERT in the actual clinical practice.

4.3 What they Mean for Clinical Practice and Policy in Rare Disease Pharmacotherapy

Such encouraging results of the study bear significance to clinical practice and policy implications in the management of such rare diseases as LOPD. To the clinician, the results support the significance of long-term enzyme replacement therapy as a conventional treatment modality in LOPD, which has got concrete clinical advantages regarding functional status and the course of the illness. Since LOPD is a progressive disease with a low prevalence rate, high morbidity, and mortality, the findings of the article can be utilized by clinicians during the decision-making process, and patients may acquire timely and efficient treatment using ERT.

Policy-wise, the findings of this research also speak in favor of financing and availability of ERT to adult LOPD patients. Access to specialized pharmacotherapy in the management of rare diseases especially those with fewer treatment options such as Pompe disease should be a priority to the policymakers. The research is a good argument that ERT is not only effective in terms of functional outcome but also leads to the overall improvement in the quality of life of afflicted individuals, which proves the worth of rare disease treatments in the real-world environment.

Also, a favorable safety and long-term outcome of ERT supports the necessity of broad access to this treatment in various healthcare systems, particularly in Europe, where the study took place. The international health policies must favour the access of enzyme replacement therapy to all the deserving cases so that there is equal treatment access despite the geographical boundary. This may be especially crucial in the case of patients in the areas where the access to specialized care is restricted.

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Conflicts of interest

The authors have no conflicts of interest to declare

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