The impact of interrupting enzyme replacement therapy in late-onset Pompe disease

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Abstract
Background Late-onset Pompe disease (LOPD) is a rare autosomal recessive disorder caused by mutations in the GAA gene, leading to progressive weakness of locomotor and respiratory muscles. Enzyme replacement therapy (ERT), administered every second week, has been proven to slow down disease progression and stabilize pulmonary function. Due to the COVID-19 pandemic in Germany, ERT was interrupted at our centre for 29 days. As reports on ERT discontinuation in LOPD are rare, our study aimed to analyse the impact of ERT interruption on the change in clinical outcome.

Methods We performed a prospective cohort study in 12 LOPD patients. Clinical assessments were performed after ERT interruption and after the next three consecutive infusions. We assessed motor function by muscle strength testing, a 6-minute-walk-test, pulmonary function tests, and adverse events. For statistical analysis, an estimated baseline was calculated based on the individual yearly decline.

Results The mean time of ERT interruption was 49.42 days (SD ± 12.54). During ERT interruption, seven patients reported 14 adverse events and two of them were severe. Frequent symptoms were reduced muscle endurance/increased muscle fatigability and shortness of breath/worsening of breathing impairment. After ERT interruption, significant deterioration was found for MIP%pred (p = 0.026) and MRC%pred, as well as a trend to clinical deterioration in FVC%pred and the 6MWT%pred.

Conclusion Interruption of ERT was associated with a deterioration in the core clinical outcome measures. Therefore, an interruption of ERT should be kept as short as possible.

Keywords Interruption of enzyme replacement therapy · Clinical outcome · Glycogen storage disease type 2 · Pompe disease

Introduction
Pompe disease (glycogen storage disease type II, acid maltase deficiency) is a rare autosomal recessive neuromuscular disease that results from mutations in the GAA gene, which encodes the enzyme acid alpha-glucosidase (GAA) [1]. Reduced or absent GAA activity results in lysosomal accumulation of glycogen predominantly in muscle cells, but also smooth muscle cells and motor neurons [2]. Pompe disease is characterized by slowly progressive axial and proximal muscle weakness, combined with ventilatory insufficiency with the need for mechanical ventilation at later disease stages. Enzyme replacement therapy (ERT) has been approved since 2006, demonstrating a slowing of disease progression and stabilization of pulmonary function in clinical trials [3–5]. For adult Pompe patients (LOPD), ERT is usually administered by infusion every 2 weeks with 20 mg/kg body weight [5, 6].

COVID-19 causes a severe acute respiratory syndrome [7], and the pandemic and so called ‘lockdowns’ have caused enormous health, economic, and social consequences in many countries [8–10]. In March 2020, the government of Bavaria, Germany, announced a partial lockdown for university hospitals from mid of March 2020 until mid of April 2020 (29 days), which also covered the suspension of treatment of non-emergency therapies for inpatients and
outpatients encompassing regular ERT infusions for LOPD patients.

Reports on the clinical impact of discontinuing ERT in LOPD are rare. Based on natural history studies, a yearly decline in pulmonary function (FVC) in sitting (1.0%) and supine position (1.3%) and in muscle strength (MRC) of 1.3% is estimated [11]. One retrospective study analysed seven patients with an ERT interrupted period between 3.1 and 59.3 months. Most of the patients showed a clinically meaningful decline in respiratory function and all patients in the 6-minute walk test. After ERT restart, a stabilisation in pulmonary function and stabilisation or improvement in the 6MWT was noted [12, 13]. However, reports on shorter treatment interruptions are lacking. Therefore, we analysed the clinical outcome of LOPD patients after short-term treatment interruption and after the ERT resumption for the next three consecutive ERT infusions.

Methods

Study setting and inclusion criteria

We conducted a prospective single-centre observational cohort study in patients with late-onset Pompe disease who discontinued ERT due to the COVID-19 pandemic in Munich, Germany. We assessed the clinical outcome after interruption and after the resumption of three consecutive ERT infusions. Inclusion criteria were (1) a genetically confirmed diagnosis for LOPD, (2) regular biweekly ERT administrations in the past 12 months, (3) interruption of ERT for more than 2 infusions, and (4) data of ≥ 3 retrospective yearly assessments before the COVID-19 pandemic lockdown. The assessments were performed within the national POMPE Registry programme, approved by the Ethics Committee of the Landesaerztekammer Rheinland-Pfalz (no. 7/04929). All patients gave written informed consent for participation in this registry. Yearly routine assessments within this registry programme and, if applicable, additional assessments for safety were performed within the standards of care and in accordance with ethical standards (Declaration of Helsinki 1975). During the lockdown period, all patients were contacted by telephone on the day of the planned ERT and asked for adverse events and disease-related symptoms. Prior to clinical assessments at t₀ and t₁ as well as prior to ERT infusions, patients were examined regarding temperature and vital signs and had to complete questionnaires regarding symptoms suggestive of any infection during the past ten days.

Data collection

For the evaluation of the clinical impact of ERT interruption, we calculated differences between the estimated baseline before ERT interruption (BLₑ), before (t₀) and three infusions after the resumption of ERT (t₁) (Fig. 1). We collected data from the following assessments: muscle strength test (Medical Research Council, MRC) of predicted %, the six-minute-walk-test in meters and predicted %, manometry (maximum inspiratory and expiratory pressure, both in cm H₂O and predicted %) and spirometry (forced vital capacity in sitting and supine position) in litres and predicted % as well as FVCₕ₀ (decrease from FVCₕ to FVCₕ₉) for the assessment of diaphragmatic weakness.

Estimated baseline (BLₑ)

Due to the unpredicted COVID-19-pandemic lockdown, sudden ERT cessation, different lengths of time between clinical assessments in standard of care and the beginning of the ERT interruption, we calculated an estimated baseline (BLₑ). This was based on historical assessments of the individual yearly progression of the disease and the days since the last assessment. This simple corrective mathematical approach made it possible to create a uniform and adjusted individual baseline for comparison (MCₖ = mean change of assessed value in %predicted):

\[
\text{Mean yearly change } MCₖ \ [\%\text{pred}] = \left( \frac{R₃ - R₄}{\Delta \text{days}} \right) \frac{365}{R₄ - R₃} + \frac{R₂ - R₃}{\Delta \text{days}} \frac{365}{R₃ - R₂} + \frac{R₁ - R₂}{\Delta \text{days}} \frac{365}{R₂ - R₁} \right) / 3
\]
Study procedures and clinical assessments

Muscle strength

The modified Medical Research Council (MRC) grading scale (0–5) was used to determine the skeletal muscle strength [14]. For the MRC sum score (maximum score 80), the following muscle groups were included: neck flexor and extensor, right and left shoulder abductors, elbow flexor and extensors, hip flexors and extensors, knee flexor and extensors. Values are presented as % of predicted.

6-minute-walk-test

Distance walked in the 6-minute-walk-test (6MWT) as a measurement of functional endurance was recorded in meters and converted to the percentage of the predicted of normal. The test was performed according to the ATS guidelines [15, 16].

Pulmonary function assessments

Lung function test included spirometry (forced vital capacity, FVC) in an upright/sitting (FVCs) and supine position (FVCsup) and manometry (maximal inspiratory pressure, MIP; maximal expiratory pressure, MEP). Values of FVCs, MIP and MEP are presented as % of predicted, adjusted for age, height and sex, as applicable, according to published regression formulas [17, 18]. For assessment of diaphragm weakness, we calculated the reduction in FVC from sitting to the supine position, FVCdrop [19].

Statistical analysis

To measure the impact of an ERT interruption, we compared the values of muscle strength, 6MWT, spirometry and manometry at three different time points (BLc, t0 and t1). Descriptive and explorative analysis was performed for demographic data and characteristics. The normal distribution was tested by Shapiro–Wilk-test. For all metric, normally distributed values, a quantitative linear model with paired two-sided students’ t-test was performed. The significance level was set at p < 0.05. For metric values not normally distributed we used the Wilcoxon-rank-test. Linear regression models were used to assess whether independent variables had an impact on the changes after ERT interruption, measured by MRC%pred, FVC%pred, MIP%pred, MEP%pred and 6MWT%pred. For statistical analysis, we used SPSS statistics version 25.

Results

Patient’s characteristics

Thirteen patients consented to participate. Twelve patients met the inclusion criteria and were analysed (female 58.3%). One patient had to be excluded because the required minimum of three historical examinations had not been performed. All included patients received ERT every second week without relevant side-effects at our outpatient clinic for mean of 7.56 years (SD ± 4.79). Descriptive analysis of the cohort is summarized in Table 1. Due to two serious adverse events in two patients after t0, two patients were not able to perform assessments at t1.

Adverse events

Seven patients reported 14 adverse events (AEs), two of them were classified as severe. The most frequent symptoms were reduced muscle endurance/increased muscle fatigability in six patients (50%), and shortness of breath/worsening of breathing impairment in three patients (25%). AEs and their description are summarized in Table 2. Twelve AEs have been classified as possibly related to the interruption

Table 1  Patient characteristics

| Patient characteristics (n = 12) | Mean ± SD | Median | range |
|---------------------------------|-----------|--------|-------|
| Sex                             | Female: n = 7 (58.3%) |
| Age at BLc [years]              | 51.07 ± 16.62 | 50.17  | 24.60–80.00 |
| Age at diagnosis [years]        | 41.07 ± 17.75 | 43.82  | 7.56–65.91  |
| Age at start of ERT [years]     | 43.47 ± 17.36 | 44.19  | 12.16–66.73 |
| Years on ERT until discontinuation [years] | 7.56 ± 4.79 | 7.25   | 0.42–13.26 |
| Duration of ERT interruption [days] | 49.42 ± 12.54 | 42.00  | 36–70     |
of ERT. One female reported four AEs. Interestingly, this patient was one of the clinically mildest affected patients (MRC 95% predicted, FVC 84% predicted). AE No. 13 (fracture due to fall) and No. 14 (fracture due to fall) occurred in two males. Due to the description by the patients and evaluation of the event, these were classified as not related to the ERT interruption, whereas AE No. 7 (fall) in another female patient was possibly related to ERT interruption, as she complained about the deterioration of her muscle strength due to ERT discontinuation 14 days after her last infusion. None of the patients reported any symptom suggestive for COVID-19-infection during the period of ERT cessation and t1.

### Impact of ERT discontinuation and restart of ERT on clinical outcomes

The mean time of ERT interruption was 49.42 days (SD ± 12.54; 36–70 days), and the mean time after restart of ERT between t0 and t1 was 43.90 ± 5.59 days (median 42.00; range 35–56). Except for MIP%pred, we could not detect a significant change in the assessments after ERT discontinuation (BLe–t0) or after the restart of ERT (t0–t1).

### Table 2 Summary of reported adverse events after interruption of ERT or after restart of ERT

| No. of reported AEs | AE no | Description | Patient no | Grade  | Time of occurrence | Relation to ERT interruption |
|---------------------|-------|-------------|------------|--------|--------------------|-------------------------------|
| 1                   | SAE 13| Bone fracture due to fall | 6          | Severe | 22 days after restart of ERT | Not related |
| 1                   | SAE 14| Bone fracture due to fall | 7          | Severe | 14 days after restart of infusion | Not related |
| 6                   | AE 1, 2, 4, 8, 10, 12 | Reduced muscle endurance/increased muscle fatigability | 1, 2, 3, 5, 6 | Moderate | Mean 33 days after last infusion | Possibly related |
| 3                   | AE 3, 9, 11 | Shortness of breath/worsening of breathing impairment | 2, 4, 6 | Moderate | Mean 34 days after last ERT | Possibly related |
| 3                   | AE 7, 13, 14 | Fall | 3, 6, 7 | Moderate | AE 7: 14 days after last infusion AE 13: 22 days after restart of infusion AE 14: 56 days after restart of ERT | AE 7: possibly related AE 13: not related AE 14: not related |
| 1                   | AE 5  | Increased exercise-related muscle pain | 2          | Moderate | 15 days after last infusion | Possibly related |
| 1                   | AE 6  | Burning sensation in extremities during prolonged exercise and sitting | 2          | Mild  | 27 days after last infusion | Possibly related |

### Table 3 Mean values of spirometry, manometry, muscle strength test and 6MWT at BLe, t0 and t1

| Test | BLe ± SD (n) | t0 ± SD (n) | p value (BLe–t0) | t1 ± SD (n) | p value (t0–t1) |
|------|--------------|-------------|-----------------|-------------|----------------|
| FVC%pred | 72.92 ± 15.10 (12) | 69.83 ± 14.05 (12) | 0.207 | 69.68 ± 14.72 (10) | 0.721 |
| FVCdrop [%] | −33.62 ± 10.18 (10) | −31.67 ± 12.77 (12) | 0.898 | −29.69 ± 13.21 (10) | 0.315 |
| MIP%pred | 64.39 ± 20.83 (6) | 63.60 ± 21.79 (12) | 0.026 | 63.53 ± 22.98 (10) | 0.910 |
| MEP%pred | 80.43 ± 30.93 (6) | 79.93 ± 26.63 (12) | 0.556 | 84.02 ± 27.46 (10) | 0.185 |
| MRC%pred | 82.77 ± 11.82 (9) | 82.51 ± 12.64 (11) | 0.889 | 82.71 ± 13.72 (10) | 0.217 |
| 6MWT%pred | 65.15 ± 27.08 (11) | 68.19 ± 22.45 (10) | 0.453 | 67.37 ± 15.20 (7) | 0.525 |

Values are provided as Mean ± SD (N). BLe, estimated baseline, t0 before re-start of ERT, t1 3 infusions after re-start of ERT; all variables at BLe, t0 and t1 were normally distributed, we used the students’ t-test for the comparison of paired samples in all cases, %pred percent of predicted of normal, FVC forced vital capacity, MIP maximum inspiratory pressure, MEP maximum expiratory pressure, MRC medical research council, 6MWT 6-minute walk-test.
MEP%pred in two patients (2.7% and 13.1%), MRC%pred in three patients (2.1–9.9%) and in 6MWT%pred in three patients (0.3–15.8%) (supplements table S2). Outcome assessments at the three time points BL\(_e\), \(t_0\) and \(t_1\) are summarized in Table 3 and displayed in Figs. 2 and 3. Raw data per patient are summarized in supplementary tables S2 and S3. In linear regression modelling, we investigated the associations between changes in outcome measures from BL\(_e\) to \(t_0\) and the following independent parameters: the number of days of ERT interruption (Δ INT), the number of years on ERT (Δ ERT) and the age at the start of ERT (S ERT). The change of MRC%pred from BL\(_e\) to \(t_0\) was associated with Δ INT (adjusted \(R^2 = 0.91, p = 0.002\)) and in the overall model (adjusted \(R^2 = 0.88, p = 0.021\)). Change in MIP%pred was associated with all independent parameters in the overall model (\(\beta_1(\Delta \text{ INT}) + \beta_2(\Delta \text{ ERT}) + \beta_3(\text{ S ERT}); \) adjusted \(R^2 = 0.99, p = 0.002\)) (supplementary table S1). In other models, none was associated with the change of outcome measures from BL\(_e\) to \(t_0\).

**Discussion**

This analysis was performed to evaluate the effects of a short-term interruption of enzyme replacement therapy in patients with genetically confirmed late-onset Pompe disease. Interruption of ERT in Pompe disease for a shorter duration has rarely been investigated. Today, however, emerging events such as the COVID-19 pandemic are becoming increasingly important for patients with chronic diseases who need to receive regular therapies. An interruption of these therapies may cause a clinical deterioration and, in a worst-case scenario, irreversible disease progression. Therefore, we investigated the clinical outcome after a short-term ERT interruption in LOPD. In particular, changes were calculated by a defined baseline examination followed by outcome measures. The unpredictable COVID-19 pandemic resulted in a partial lockdown in Munich, Germany. Thus an actual group or individual baseline was not available. Therefore, we calculated an estimated baseline (BL\(_e\)) to create a...
uniform and adjusted baseline for all 12 patients comparing changes after this short-term ERT discontinuation. Using an estimated baseline including results of assessments over at least three previous years, we determined disease progression by avoiding interfering factors that could influence baseline values e.g. motivation, and concomitant diseases. Consequently, we assume that our calculated estimated baselines reflect useful and suitable values for our investigation.

In our cohort, the mean period of treatment interruption was 49.42 days (SD ± 12.54 days). Due to infusion schedules and patient’s concern of an increased risk of SARS-CoV2-infection in hospitals after the lockdown, interruption of ERT was up to 70 days in two patients. Overall, we saw a trend to deterioration after ERT interruption in objective assessments, predominantly in FVC<sub>pred</sub>, FVC<sub>drop</sub>, MIP<sub>pred</sub>, and 6MWT<sub>pred</sub>. Significant changes were only found for MIP<sub>pred</sub> and MRC<sub>pred</sub> in the regression models. Muscle strength, assessed by MRC<sub>pred</sub>, showed significant deterioration in the linear regression model based on the number of days of ERT interruption (supplementary table S1).

Both significant changes correspond to the most frequently reported adverse events by the patients.

From the patient’s perspective, we have noticed an increased rate of AE’s reported by the patients during therapy interruption, with the most frequent symptoms “reduced muscle endurance/increased muscle fatigability” and “shortness of breath/worsening of breathing impairment” in 75% of our patients. On average, the time from the last day of infusion and occurrence of the AE “reduced muscle endurance/increased muscle fatigability” was 33 days and for the AE “shortness of breath/worsening of breathing impairment” was 34 days, respectively. Both findings may be interpreted as related to ERT interruption. Six patients (50%) reported a “reduced muscle endurance or increased muscle fatigability” during ERT interruption. In seven patients (58%), we noted a deterioration in the six-minute-walk-test (6MWT<sub>pred</sub>) but for the whole cohort, these changes were not significant. In the regression analysis, changes in the 6MWT<sub>pred</sub> were not associated with age of onset, years of ERT, or days of ERT interruption.
A slight but significant change was found for MIP$_{\text{pred}}$ after ERT interruption at the group level. The significant change in MIP$_{\text{pred}}$ may be explained by the fact that manometry of respiratory muscles detects changes earlier than FVC assessments [20, 21]. A worsening of breathing impairment was stated in three patients, but subgroup analysis did not reveal a significant deterioration in FVC$_{\text{pred}}$, MIP$_{\text{pred}}$ or MEP$_{\text{pred}}$ in those. Besides this, a deterioration of $>10\%$ in FVC$_{\text{pred}}$ was found in three patients (25%), but only one of these patients (no. 9) reported a worsening of breathing impairment. In regression models, we found an association between MIP$_{\text{pred}}$ at the group level, however not for the number of days of interruption, the number of years on ERT, nor years since ERT start. When analysing the individual results, it was also noticeable that some patients had improved in some assessments after the ERT interruption. Even if the individual improvements are not statistically significant, this is still an interesting result. Although a linear trend is rarely observed in a clinical course especially cally significant, this is still an interesting result. Even if the individual improvements are not statistically significant, this is still an interesting result. Although a linear trend is rarely observed in a clinical course especially in neuromuscular diseases, many factors may contribute to intermittent deteriorations or improvements. Frequent factors in daily clinical routine are affective components that may lead to an improved motivation after therapy cessation or learning effects in assessments that are performed more often than in routine diagnostics.

We cannot exclude a psychological factor contributing to the subjective deterioration in 75% of our patients. In the context of the COVID-19 pandemic, an increasing number of depressive and anxiety disorders across a high number of countries has been described [22], which certainly has an impact on both, subjective and objective assessment scales. Nevertheless, the reported adverse events of reduced muscle endurance and reduced/worsened pulmonary function correspond to the findings in objective measurements, even if some of them did not reach statistical significance. This highlights whether statistically significant deterioration in assessments truly reflects a clinical meaningful deterioration.

Our observations underscore the clinical benefits of regularly administered ERT in late-onset Pompe disease, which are based on clinical outcome measures and subjective reports from the patients. Correlating our findings and former reports, where a relevant decline in FVC and 6MWT after ERT interruption of 3.1 and 59.3 months was described [13], we can conclude that even a short-term interruption of ERT shows a trend to a clinical decline and should be avoided. This is not only relevant for objective outcome assessments, but also in terms of quality of life in this chronic progressive disease. Our results may also help to advise patients who may have to interrupt their regular treatment for a shorter period, e.g. holidays, travel, or hospitalization where ERT is unavailable. Further studies are necessary to evaluate changes in specific, validated patient-reported outcome measures covering depressive and anxiety symptoms.

**Conclusion**

Emerging events, such as the COVID-19 pandemic, are becoming increasingly important for patients with chronic diseases who are at risk of not receiving their necessary therapy. Interruption of ERT in LOPD should be avoided or kept as short as possible, as our cohort showed a significant decline in MIP$_{\text{pred}}$, MRC$_{\text{pred}}$ and a trend to clinical deterioration in FVC$_{\text{pred}}$ and the 6MWT$_{\text{pred}}$ in objective outcome measures and an increased rate of adverse events. Further studies are necessary to evaluate the impact of interrupting ERT on clinical outcomes in LOPD more in detail.

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**Author contributions** SW: Statistical analysis and interpretation of data, discussion of results, critical revision of the manuscript for intellectual content, first and final manuscript draft. Guarantor who accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. KG: Statistical analysis and interpretation of data, discussion of results, critical revision of the manuscript for intellectual content. CW: Data aquisition, discussion of results, critical revision of the manuscript for intellectual content. KE: Data aquisition, discussion of results, critical revision of the manuscript for intellectual content. FM: Data aquisition, discussion of results, critical revision of the manuscript for intellectual content. BS: Discussion of results, critical revision of the manuscript for intellectual content.

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**Data availability** The anonymised participant data presented here are available upon request from the correspondent author (stephan.wenninger@med.uni-muenchen.de).

**Compliance with ethical standards**

**Conflict of interest** All authors report no disclosures regarding this study. SW has received research grant by the DGM—Deutsche Gesellschaft für Muskellkranke e.V. He has served on advisory boards for Alexion Pharma, CSL Behring and Sanofi Genzyme GmbH. He received funding for travel or speaker Honoraria from Sanofi-Aventis Germany GmbH; SH Glykogenose Gesellschaft; AbbVie Germany GmbH; Recordati Pharma GmbH; CSLBehring GmbH; Alexion Pharma GmbH; Desitin Germany; Akcea GmbH. BS has served on advisory boards for Amicus Therapeutics, Audentes, Nexien, Spark, and Sanofi Genzyme; he has undertaken contracted Page 21/25 unrestricted research for Greenovation Biopharm, Sanofi Genzyme, Amicus; and has received honoraria from Kedrion and Alexion, and travel expenses from Amicus and Sanofi Genzyme. FM received funding for travel or speaker Honoraria from Sanofi-Aventis Germany GmbH and...
SH Glykogenose Gesellschaft. The other authors have no conflicts of interest to declare.

**Ethics approval** The assessments in this study were performed with in the national POMPE Registry program, approved by the Medical Ethics Committee of the Landesaerztetkammer Rheinland-Pfalz (no. 7/04929) and conducted in accordance with the ethical standards recognized internationally.

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