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ORIGINAL COMMUNICATION

36-Months follow-up assessment after cessation and resuming of enzyme replacement therapy in late onset Pompe disease: data from the Swiss Pompe Registry

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Abstract

Introduction Although not curative, enzyme replacement therapy (ERT) with recombinant human acid alpha-glucosidase enzyme has shown to be effective in the treatment of late-onset Pompe disease (LOPD). For this potentially life-long treatment, little is known on the clinical effect of cessation and resuming ERT. Due to a Swiss supreme court decision on ERT reimbursement, a temporary stop of ERT occurred in our study population. The aim of this study was to report the 36-months follow-up assessments after resuming ERT.

Methods After resuming ERT, seven patients suffering from genetically and enzymatically confirmed LOPD had periodic, mandatory, prospective assessments of pulmonary function tests, muscle strength summary scores, distances walked in timed walking tests, and patient-reported questionnaires. Data were statistically analyzed for significant differences between time points at ERT cessation, at ERT resuming, and 36 months thereafter.

Results After resuming ERT forced vital capacity ($p=0.007$) and distance walked in the 6 min walk test (6-MWT, $p=0.011$) significantly increased at 36 months. Compared to before ERT cessation, distance walked in 6-MWT at 36 months still remained significantly lower ($p=0.005$). Self-reported scores in the fatigue severity scale significantly declined at 36 months after resuming ERT ($p=0.019$). No other functional or reported parameter significantly changed at 36 months after resuming ERT.

Conclusions Our data suggests that long-term interruption of ERT in LOPD may lead to deterioration of clinical meaningful parameters and quality of life. In addition, a clinical restoration after ERT cessation is possible for most of the LOPD patients within a 36 months follow-up.

Keywords Muscle disease · Metabolic disease · Pompe disease · GSD II · Enzyme replacement therapy

Introduction

Pompe disease is a lysosomal storage disease with an autosomal-recessive inheritance. Various mutations in the acid alpha-glucosidase (GAA) gene lead to reduced lysosomal activity of the GAA enzyme in various organs with a preponderance in proximal skeletal muscle. As a consequence lysosomal glycogen accumulates and eventually leads to cellular dysfunction, cell architecture disruption, and ultimately to cell death [1]. Structural cell changes are enhanced by dysfunction of autophagy [1, 2] leading to a structural myopathy with the combination of diaphragmatic insufficiency and a limb girdle distribution. Late onset Pompe disease (LOPD) has a variable phenotype with a wide range of disease onset depending on the type of mutation and hence

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residual enzyme activity [3]. Enzyme replacement therapy (ERT) with recombinant human GAA (rhGAA) has shown to be effective in the treatment of Pompe disease, leading to a stabilisation of respiratory function (forced vital capacity, FVC), improvement in meters walked in the 6 min walk test (6-MWT), and increasing overall survival (e.g. [4–7]).

Enzyme replacement therapy is not curative, hence a potentially life-long administration will be necessary. This is associated with high costs and therapeutic burden (i.e. drug side effects, intravenous infusions every other week, limited personal travelling flexibility due to regular infusions). Therefore, some national healthcare authorities legislated strict inclusion criteria and predefined follow-up evaluation for reimbursement of ERT. In Switzerland, a prospective registry ("Swiss Pompe Registry") was established to monitor treatment success and limit prescription authority only to specialised physicians and tertiary hospitals [8]. The Swiss Pompe registry was a prerequisite for reimbursement of rhGAA and evolved out of a temporarily reimbursement stop of nearly 12 months duration following a supreme court decision [9]. Being an unprecedented and unique population follow-up assessment of the affected patients revealed durable decline in respiratory function and meters walked in the 6-MWT during the temporary cessation of ERT [10]. Here, we report on long-term follow-up assessments after re-treatment with rhGAA of this unique patient population.

Methods

Subjects

Seven patients with genetically confirmed LOPD were enrolled in two neuromuscular reference centres in Switzerland. The patient population was recently described elsewhere [10]. In short, enrolled patients were symptomatic, but not invasively ventilated and/or severely affected as measured by 2–4 points on the modified ranking scale (mRS) [11], were treated with rhGAA (Myozyme®, 20 mg/kg body weight every other week) before the supreme court judgement, and had a minimum of a 36 months treatment period with rhGAA after cessation.

Clinical assessments

Prospective and mandatory assessment of all patients was performed as outlined in the Swiss Pompe registry [8] every 6 months after resuming ERT, and consisted of evaluation of (1) distance walked in 6-MWT [12], (2) time needed to complete a walking distance of 10 m (10 m walk test; 10 m-WT [13]), (3) pulmonary function tests [percent predicted forced vital capacity (FVC) in upright position, maximal inspiratory pressure (MIP), sniff nasal inspiratory pressure (SNIP)], (4) sum score on a manual muscle strength testing according to the medical research council (MRC) grading scale (0, minimum; 180, maximum; 36 muscle functions tested), (5) patient reported outcome and daily life activities assessed with the Fatigue Severity Scale (FSS) [14] and the Rotterdam Handicap Scale (RHS) [15]. Before cessation of ERT, only FVC and 6-MWT have been monitored.

Statistics

The prospective and standardized assessments have been performed as a consequence of reimbursement regulations for ERT in Switzerland, and not as part of a clinical study protocol. After assessments, data were registered in the previously reported "Swiss Pompe Registry" [8]. For this study, data from the registry were analysed retrospectively. Paired t-tests for comparing the mean of the each outcomes (FVC, 6-MWT, MRC, 10 m-WT, SNIP, MIP, WGMS, FSS, RHS) observed at resuming (t0) versus 36 months of ERT (t3) were used to examine the null-hypothesis of no difference in the means between t0 and t3. Additionally, we compared the mean of the pivotal FVC and 6-MWT assessments at the time of treatment cessation (tc) versus t3 to investigate if patients regain or exceed performance after a period of long-term cessation of ERT. For an overview on the different time points see Fig. 1.

A p value < 0.05 was considered to yield substantial evidence against the null hypothesis that there is no difference in the mean of the outcomes observed at two different follow-up assessments. No correction for multiple testing was applied as this is an explorative analysis, and therefore, the global error-rate (or significance level) is not controlled. Descriptive statistics, assessment value trajectories for individual patients, and box-plots further illustrate the data for each follow-up visit.

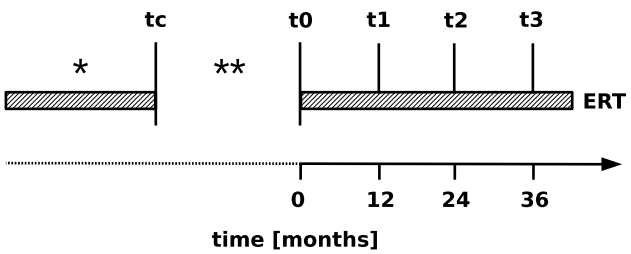

Fig. 1 Overview on time course of enzyme replacement therapy (ERT) and clinical assessments. *ERT period before cessation, the period length was different for each patient; **period without ERT, the period length was different for each patient; tc, time point of ERT cessation due to supreme court judgement; t0, time point of resuming ERT; t1, t2, t3, time point at 12, 24, and 36 months after resuming ERT

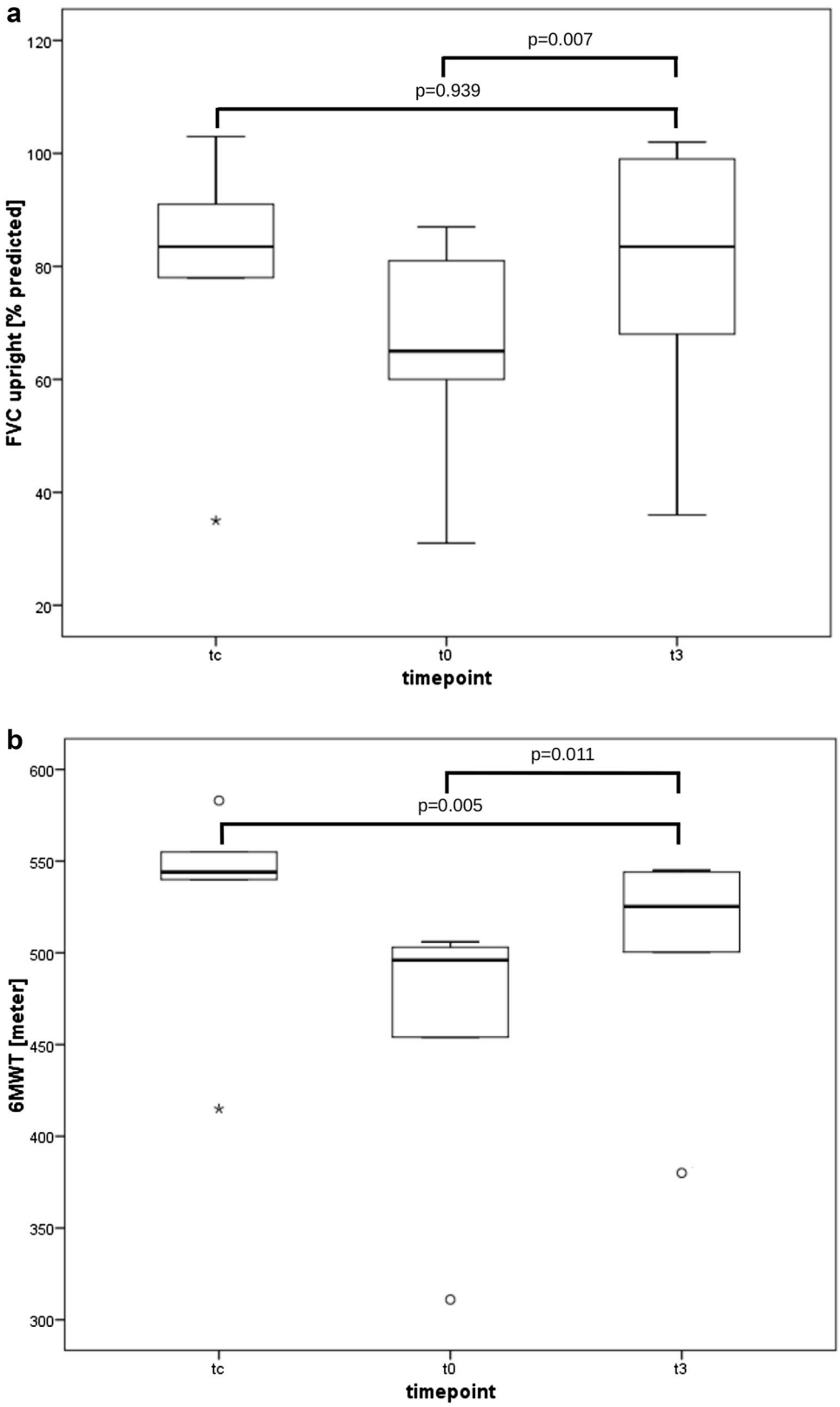

Fig. 2 Follow-up of pivotal values for forced vital capacity (FVC) and distance walked on the 6 min walk test (6-MWT) before cessation (tc), and at 0 (t0) and 36 months (t3) after resuming enzyme replacement therapy (ERT). **a** Predicted FVC in upright position, **b** distance walked in the 6-MWT. Patient reported fatigue severity scale (FSS) score. Statistical analysis were performed using the paired *t* test. On each box, the central horizontal bar indicates the median, the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively, and the whiskers extend to the inter-quartile range. Asterisk and open circle denote respective outliers. Note that one patient was wheelchair-bound and could not perform the tests

Results

The patient population ($n=7$, four females) has been described in detail previously [10]. Duration of initial ERT until cessation (at tc) was 3.1–61.3 months. Duration of ERT-free interval until resuming (at t0) was 3.1–59.3 months. All 7 patients were still on ERT at 36 months after resuming treatment (t3). At 36 months (t3) compared to 12 months (t1), no patient changed the ventilation status (4 with, and 3 without non-invasive ventilation), nor the ambulatory status (one patient with wheelchair). No adverse or side effects were noticed in all patients. One patient could not participate in FVC measurements and walking tests due to the ambulatory status (wheelchair bound).

FVC and 6-MWT at ERT cessation (tc) and during 36 months after resuming ERT (t0, t3)

The time course of FVC and 6-MWT for individual patients at tc, t0, and t1 have been reported previously [10]. After resuming ERT, mean values of FVC increased until the end of the observation period (t0 vs t3, $p=0.007$), reaching values similar to before cessation of ERT (tc vs t3, n.s.), see Fig. 2a. For mean values of 6-MWT, again an increase after resuming ERT until the end of the observation period was noticed (t0 vs t3, $p=0.011$), but mean values still remained lower compared to before cessation of ERT (tc vs t3, $p=0.005$), see Fig. 2b.

Comprehensive assessment after resuming ERT (t0–t3)

After resuming ERT, mean values of MRC, MIP, SNIP, 10 m-WT, and RHS did not show a significant increase after both 12 months and 36 months of ERT. As reported above, only mean values for FVC and 6-MWT increased after both 12 months (t0 vs t1: FVC, $p=0.001$; 6-MWT, $p=0.044$), and 36 months (t0 vs t3: see above), respectively. Mean values for patient self-reported FSS decreased only at 36 months (t0 vs t3: $p=0.019$), indicating less perceived fatigue, see Fig. 3. Detailed follow-up values between t0 and t3 for individual patients are depicted in Fig. 4.

Discussion

This retrospective study reports in a unique patient cohort, 36 months comprehensive and highly standardized follow-up data of pulmonary function, ability to walk and muscle strength after cessation and resuming ERT in patients with genetically and enzymatically confirmed LOPD. The data were derived from the Swiss Pompe registry. ERT cessation followed a supreme court decision on

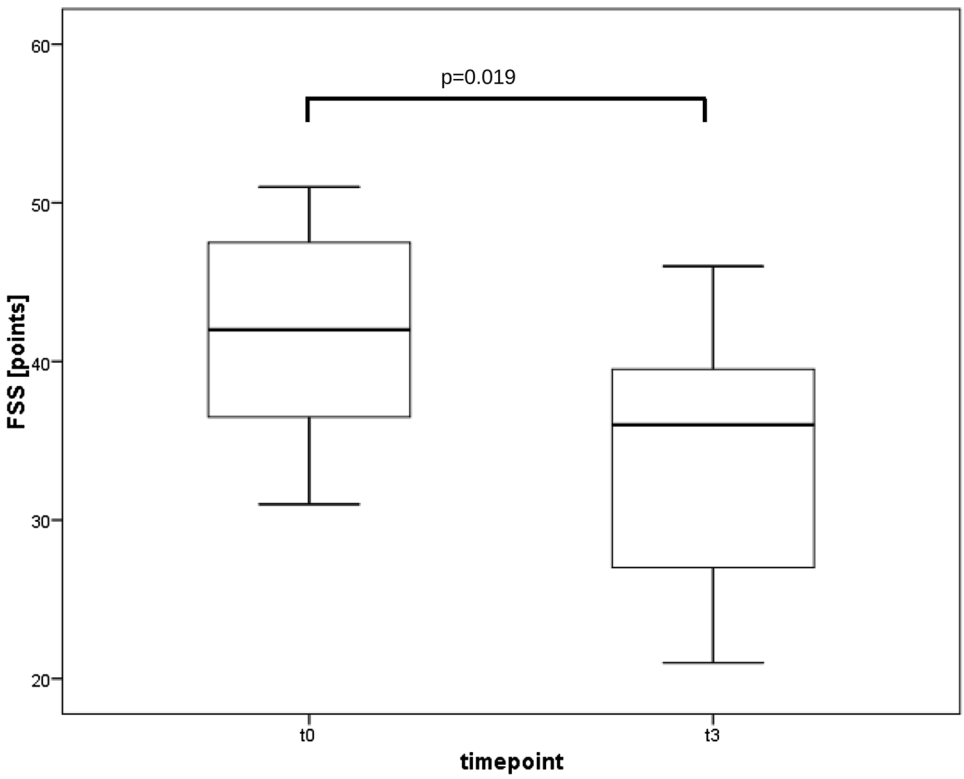

Fig. 3 Follow-up of patient reported fatigue severity scale (FSS) score just after resuming ERT (t0) until the end of the observation period at 36 months (t3). Note that lower values indicate less perceived fatigue. Statistical analysis were performed using the paired t-test. On each box, the central horizontal bar indicates the median, the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively, and the whiskers extend to the interquartile range

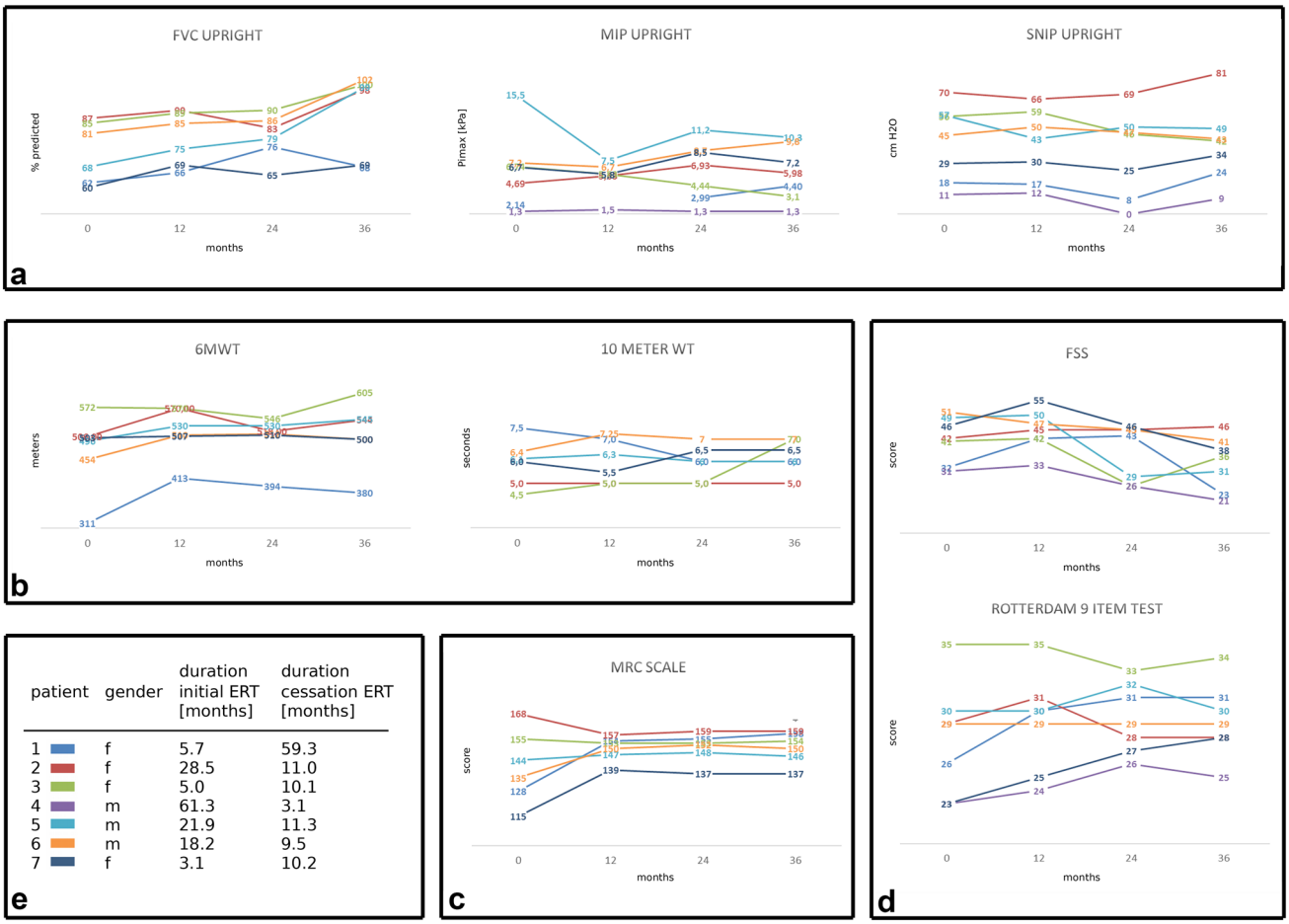

Fig. 4 Comprehensive follow-up of individual patients after resuming ERT until end of observation period at 36 months. **a** Pulmonary function parameters with predicted forced vital capacity (FVC), maximal inspiratory pressure (MIP), and sniff nasal inspiratory pressure (SNIP). **b** Ambulation test with 6 min walk test (6-MWT) and 10 m walk test (10 m-WT). **c** Muscle force tests with sum score on medical research council (MRC) grading scale. **d** Patient reported outcome and daily life activities with the Fatigue Severity Scale (FSS), and the Rotterdam Handicap Scale. **e** Gender, age, and duration of initial ERT and cessation. Note that colors of individual patients match in all figure parts. One patient (no. 4) was wheelchair-bound and could not perform all tests

reimbursement policy of rhGAA in Switzerland. Twelve months follow-up data after resuming ERT of this patient cohort have been reported previously [10]. After resuming ERT, pivotal predicted FVC and 6-MWT increased at 36 months. Predicted FVC regained values similar to before cessation of ERT, whereas 6-MWT remained below values before cessation of ERT. In a comprehensive follow-up analysis, no other functional parameters changed relevantly during the 36 months.

The follow-up study results at 36 months confirm the trend that has been observed at 12 months [10], both FVC and 6-MWT remained increased. Although the small number of patients in our cohort warrants cautious interpretation of the statistical analysis, these results are nevertheless in line with previous reports on ERT outcome of treatment-naïve patients [7, 16–20]. Additionally, patient reported scale values for fatigue (FFS) dropped at 36 months of ERT, reflecting less perceived fatigue. This observation underlines the benefits of long-term ERT from a patient reported outcome measure (i.e. FSS), which is, therefore, not only statistically significant, but also clinically relevant in terms of improved quality of life. Additionally, this finding is in line with the improvement seen in more objective data like FVC and 6-MWT underscoring the global health benefit derived not only from short-term [7] but also from long-term ERT [21] in this patient group. On an individual basis these improvements may counteract the burden of a laborious every other week infusion therapy. Other parameters from pulmonary function (SNIP, MIP), walking ability (10 m-WT), muscle strength (MRC sum score), and other patient-reported outcome (RHS) did not show a relevant change. No treatment adverse effects occurred during this period.

These long-term and comprehensive follow-up data assessed in a standardized way after ERT cessation complement the published literature on treatment effect of ERT in LOPD patients. Especially, the data provided here may help in counselling patients who wish to interrupt ERT (e.g. for travelling, moving, break from treatment burden), or have to interrupt ERT (e.g. due to inter-current diseases, treatment side effects). In our previous study [10], we reported a relevant decline after ERT cessation even after 5.7 and 3.1 months, respectively, in both FVC and the 6-MWT. However, the clinical significance is strongly dependent on the antecedent degree of pulmonary and exercise function. LOPD patients with a significantly altered pulmonary function beforehand may run into ventilation dependency if the FVC only slightly drops on ERT interruption, or they may lose the ability to walk in the worst case. Therefore, even short interruptions of several months may lead to clinical significant decline in moderate or severely affected patients. In contrast, if necessary short or long lasting prolongation of the infusion interval (i.e. from 14 days to 21 or 28 days) of ERT might be an alternative to decrease treatment burden [22]. However, all these data have to be interpreted with great caution as they rely only on single patient reports. Our recommendation is to stick to the every other week ERT treatment and to avoid longer interruptions.

To summarize, our data suggests that long-term interruption of rhGAA treatment in LOPD may lead to deterioration of clinical meaningful parameters and quality of life. In addition, a clinical restoration after ERT cessation is possible for most of the LOPD patients within a 36 months follow-up.

Compliance with ethical standards

Conflicts of interest TH and KMR served as consultants, received funding for travel expenses and received honoraria from serving on a scientific advisory board from Genzyme, Switzerland. OF received travel expenses and honoraria from serving on a scientific advisory board from Genzyme, Switzerland. OS and DL received funding for travel expenses from Genzyme, Switzerland. RS declared no conflict of interest.

Ethical standards The local ethics committee approved this retrospective analysis, and written informed consent was obtained from all participants.

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