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ORIGINAL ARTICLE

Effectiveness of enzyme replacement therapy in adults with late-onset Pompe disease: results from the NCS-LSD cohort study

L. J. Anderson · W. Henley · K. M. Wyatt · V. Nikolaou · S. Waldek · D. A. Hughes · R. H. Lachmann · S. Logan

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Abstract
Objectives To determine the effectiveness of enzyme replacement therapy (ERT) for adults with late-onset Pompe disease.
Design A longitudinal cohort study including prospective and retrospective clinical outcome data. Age- and gender-adjusted treatment effects were estimated using generalised linear mixed models. Treated patients contributed data before and during treatment. Untreated patients contributed natural history data.
Participants Consenting adults (N=62) with a diagnosis of late-onset Pompe disease who attended a specialist treatment centre in England. This cohort represented 83 % of all patients in the UK with a confirmed diagnosis of this rare condition. At study entry, all but three patients were receiving ERT (range of treatment duration, 0 to 3.1 years).
Outcome measures Percent predicted forced vital capacity (%FVC); ventilation dependency; mobility; 6 min walk test (6MWT); muscle strength and body mass index (BMI).
Results An association was found between time on ERT and significant increases in the distance walked in the 6MWT ($p<0.001$) and muscle strength scores ($p<0.001$). Improvements in both these measures were seen over the first 2 years of treatment with ERT. No statistically significant relationship was found between time on ERT and respiratory function or in BMI.
Conclusions These data provide some further evidence of the effectiveness of ERT in adults with late-onset Pompe disease.
Synopsis The results of this longitudinal cohort study of 62 adults with late-onset Pompe disease, provide further evidence on the effectiveness of ERT in this rare condition.

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L. J. Anderson (✉) · W. Henley · K. M. Wyatt · V. Nikolaou · S. Logan
Institute of Health Research, University of Exeter Medical School, Veysey Building, Salmon Pool Lane, Exeter, Devon EX2 4SG, UK
e-mail: l.j.anderson@exeter.ac.uk

R. H. Lachmann
University College London Hospitals, London, UK

S. Waldek
Salford Royal NHS Foundation Trust, Salford, UK

D. A. Hughes
Department of Haematology, University College, Royal Free Campus, London, UK

Introduction

Pompe disease (glycogen storage disease type II or acid maltase deficiency; OMIM 232300) is a rare autosomal recessive disorder caused by a deficiency in the lysosomal enzyme acid alfa glucosidase (GAA). This leads to a lysosomal accumulation of glycogen in different tissues, particularly striated muscle, resulting in progressive debilitation, organ failure and/or death.

Traditionally the disease is classified according to age of onset (Hirschhorn and Reuser 2001), with severity ranging from a rapidly fatal infantile-onset phenotype, to slowly progressive late-onset phenotypes (Slonim et al 2000; Kishnani et al 2006b).

Infants with the classic form of infantile-onset Pompe disease typically present within the first month or two of life, with muscle weakness, hypotonia, hepatomegaly, massive cardiac enlargement due to hypertrophic cardiomyopathy, cardiac failure and respiratory failure. If untreated, infants usually die from cardiorespiratory failure by 6–9 months (van den Hout et al 2003; Kishnani et al 2006b). Late-onset Pompe disease may present at any age and comprises non-classical infantile, juvenile, and adult Pompe phenotypes (Engel et al 1973; Wokke et al 1995; Slonim et al 2000).

In all late-onset phenotypes, the main characteristics are a symmetrical proximal myopathy and respiratory compromise. Clinical presentation may be with predominant proximal myopathy or with predominant respiratory failure, but the disease is progressive and eventually all patients will require mobility aids and some form of non-invasive ventilation (Hagemans et al 2005). In addition, kyphoscoliosis is common and there is an increased incidence of reduced bone density (van den Berg et al 2010; Papadimas et al 2011). More rarely ptosis, dysphagia and deafness have been reported.

Human recombinant alfa glucosidase (Myozyme®, Genzyme Corporation, MA, USA) was licensed in Europe and the USA in 2006. Early studies focussed on infantile Pompe disease (Van den Hout et al 2000, 2001) and ERT in this patient group has been reported to improve survival as well as cardiac, respiratory and motor functions (Kishnani et al 2006a, 2007, 2009). There have also been reports of the use of ERT in late-onset patients (van Capelle et al 2008; Bembi et al 2010; Strothotte et al 2010; Angelini et al 2012; Regnery et al 2012) but only one placebo controlled clinical trial has been published to date (van der Ploeg et al 2010). The authors of this multicentre study reported significant differences between the alfa glucosidase and placebo groups in distance walked in the 6MWT and %FVC at 78 weeks.

We conducted a longitudinal cohort study, collecting prospective and historical data from patients with Pompe disease to estimate the effectiveness of ERT. Treated patients contributed data before and during treatment and untreated patients contributed natural history data. This paper reports the clinical findings for adults with late-onset Pompe disease.

Methods

The data used in this study were collected as part of the National Collaborative Study for Lysosomal Storage Disorders (NCS-LSD), a longitudinal cohort study funded by the Health Technology Assessment (HTA) programme, part of the National Institute for Health Research. This study aimed to determine the natural history of six lysosomal storage disorders (LSDs) (Gaucher disease, Fabry disease, Pompe disease, mucopolysaccharidosis type I and type II and Niemann Pick type C), and to try to measure the effectiveness and cost of treatment strategies (Wyatt et al 2012).

Outcome measures

Forced vital capacity was spirometrically assessed and expressed as a percent of predicted value (%FVC); motor function of ambulatory patients was assessed using the 6 min walk test (6MWT); muscle strength of upper and lower limb muscles was tested manually using the limited Medical Research Council (MRC) grading scale (range 0–5; summary score range 0–120). Ventilation dependency (intermittent or continuous), mobility status and body mass index (BMI) were also recorded.

Power

Simulated power calculations [see (Henley et al 2014) for details of the approach] showed that a sample size of 62 adults provides 80 % power to detect an effect of time on treatment of at least 0.11 standard deviations (SD) per year based on cross-sectional data sampled from a mean of 1 year follow-up. The minimum detectable effect size reduced to 0.064 SD per year if three data points were available for each patient, sampled from across the expected treatment history.

For full details of study procedures and analysis methods, please refer to our general methods paper (Henley et al 2014).

Results

Patient demographics

Of the 75 patients with a confirmed diagnosis of late-onset Pompe disease in the UK, two were deemed ineligible for inclusion by their clinician (i.e. they may have become distressed by participating in the study). Sixty eight patients were approached and invited to participate during their clinical appointment and written, informed consent was obtained from 65 patients (87 % of diagnosed population). Sixty two patients were adults, aged 16 and over, with a mean age at study entry of 46.5 (range, 16.3 to 76.7) years. The families of three children with late-onset Pompe disease also consented to their participation. However, data from these children were excluded from this analysis due to the anticipated differences in severity at baseline, given the very early onset of symptoms in these children.

At the time of study entry, 59 patients were receiving alglucosidase alfa and the mean duration of treatment was 1.3 (range, 0 to 3.1) years. Patient demographic characteristics are presented in Table 1.

Data was collected at the time of entry to the study, and follow up data was available from all patients. A third data point was available for 52 patients. The number of retrospective data points per patient ranged from 1 to 4.

Clinical outcomes

Results showing the effect of time on ERT on continuous outcome measures are summarised in Table 2, where the estimate of change gives an indication of the effect size for continuous variables. For full details of gender-, age- and

Table 1 Patient demography characteristics

	N=62
Gender	
Male, *n*	37
Female, *n*	25
Age at recruitment (years)	
Mean (SD)	46.5 (13.8)
Median (range)	45.6 (16.3 to 76.7)
Age at diagnosis (years)	
Mean (SD)	39.7 (15.2)
Median (range)	37.7 (1.5 to 67.7)
Treatment at recruitment	
Not on ERT, *n*	3
ERT (alglucosidase alfa), *n*	59
Age of first infusion (years)	
Mean (SD)	45.5 (14.1)
Median (range)	44.6 (16.4 to 74.7)
Time on ERT at recruitment (years)	
Mean (SD)	1.3 (0.8)
Median (range)	1.3 (0 to 3.1)
Physical characteristics at recruitment	
Requires no ventilation, *n*	32
Requires nocturnal ventilation, *n*	19
Requires intermittent daytime ventilation, *n*	5
Missing data, *n*	6
Can walk/stand unaided, *n*	34
Can walk aided one stick, *n*	12
Can walk aided more than one stick, *n*	5
Wheelchair bound, *n*	10
Bed-bound (i.e. can't get into wheelchair), *n*	0
Missing data, *n*	1

centre-effects on outcome measures, please refer to (Wyatt et al 2012).

Ventilation

We have historical ventilation data on 57 people. Patients were categorised as being ventilator-free or ventilator-dependent. By the age of 30, seven patients were reported as being ventilator-dependent (six on ERT and one not on treatment at this time). By 50 years of age, a further ten patients were ventilator-dependent (all on ERT) and a further 13 patients became ventilator-dependent after the age of 50 (all on ERT). Thirty-one patients (29 on ERT and two not on treatment) remained ventilator-free.

Percent of predicted forced vital capacity (%FVC)

A longitudinal model was fitted to assess the linear relationship between %FVC and time on ERT. After adjusting for age, time on ERT was not significantly associated with change in %FVC when time was categorised as "not treated", <12 months, 12–36 months and >36 months (Table 2; p=0.14) with mean changes of 1.77 % (95 % CI −0.75 to 4.29) in patients treated <12 months, −0.21 % (95 % CI −2.55 to 2.14) in patients treated for 12–36 months, and −2.11 % (95 % CI −5.68 to 1.46) in patients treated for >36 months. Further analysis explored the shape of the relationship between %FVC and time on ERT treated as a continuous variable, but provided no evidence for a non-linear association between FVC and time on ERT (Fig. 1a; edf=1.44, p=0.15).

Mobility

We have historical mobility data on 59 patients. Patients were categorised as being mobile if they could walk for 5 m or stand for 6 min unaided, as having restricted mobility if they could walk aided, or as being wheelchair dependent (i.e. immobile).

Thirty two patients reported having no mobility problems at any point during data collection. Of the 27 patients with mobility problems, four reported having restricted mobility by the age of 30. By the age of 35, one additional patient reported having restricted mobility. By 60 years of age, 15 additional patients reported having restricted mobility, with a further seven patients reporting restricted mobility after the age of 60. Nine of the 27 patients with mobility problems were reported as being wheelchair-dependent by 60 years of age.

Table 2 The association between time on ERT and continuous outcomes in adults with late-onset Pompe disease (linear mixed effects models)

Outcome	*N*	Range	Mean at start of ERT	Estimate of *change* in outcome with time on ERT (95 % CI)			*p*-value
				<12 months	12–36 months	>36 months	
%FVC	57	10 to 130	59.6	1.77 (−0.75 to 4.29)	−0.21 (−2.55 to 2.14)	−2.11 (−5.68 to 1.46)	0.14
6MWT (m)	20	88 to 560	246	43.7 (13.8 to 73.6)	51.3 (29.1 to 73.5)	16.1 (−21.4 to 53.6)	<0.001
Muscle Test Score	53	62 to 120	98.4	3.53 (1.39 to 5.66)	4.04 (2.26 to 5.83)	1.30 (−1.92 to 4.52)	<0.001
BMI (kg/m^2)	60	10 to 46.2	24.5	0.36 (−0.24 to 0.97)	0.14 (−0.39 to 0.68)	0.46 (−0.62 to 1.54)	0.62

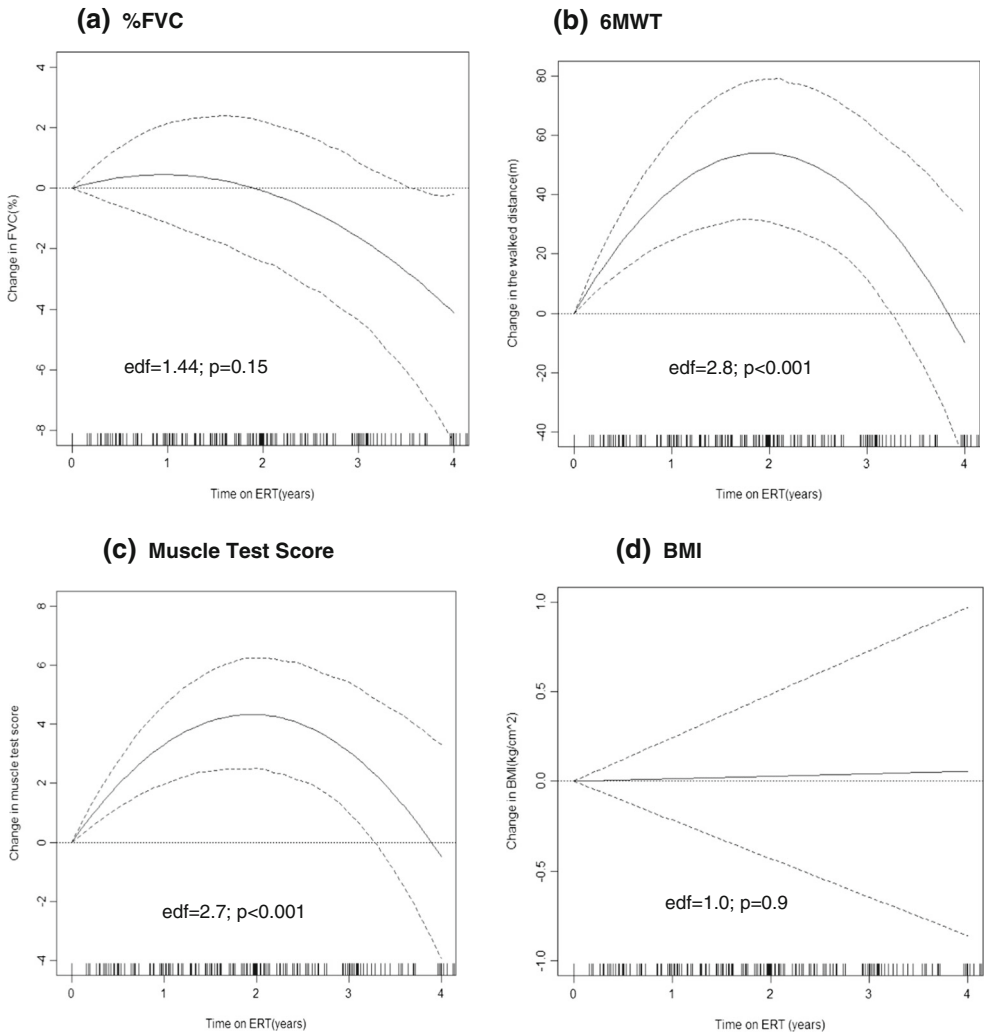

Fig. 1 Association between time on ERT and outcomes in adults with late-onset Pompe disease, adjusted for age. These *plots* illustrate the shape of the relationship between outcome and time on ERT after adjustment for age and gender (based on the best fitting linear or quadratic model). The *vertical axis* measures the expected change in outcome as patients accumulate time spent on ERT, relative to the point at which patients start on ERT (expressed as an absolute difference). The *solid line* provides estimates of mean change in outcome and the *dashed lines* provide a 95 % confidence interval around the model estimates. This effect is incremental to the underlying age-related change in outcome. The extent to which the estimated relationship departs from linearity can be assessed by considering the estimated degrees of freedom (labeled on the plot as "edf"). Values of the edf close to 1 indicate that the relationship is linear or close to linear. The "rug plot" provides a visual representation of the frequency distribution for time on ERT. Each individual data point is represented by a *single vertical mark* at the appropriate location on the chosen time scale (years)

Six minute walk test (6MWT)

The distance walked in six minutes by participants with Pompe disease was significantly, negatively associated with age (data not shown, $p<0.001$). After adjusting for age, time on ERT was associated with a significant increase in the distance walked in this test (Table 2; $p<0.001$) when time was categorised, with mean increases of 43.7 m (95 % CI 1.8 to 73.6) in patients treated <12 months, 51.3 m (95 % CI 29.1 to 73.5) in patients treated for 12–36 months, and 16.1 m (95 % CI −21.4 to 53.6) in patients treated for >36 months. Further analysis treating time as a continuous variable suggested a significant non-linear effect of time on ERT, with the distance walked improving over the first two years after commencing ERT, when the treatment effect peaks before appearing to decline (Fig. 1b; edf =2.8, $p<0.001$). However, the low number of patients on treatment for more than 2 years, mean that this result should be interpreted with caution.

Muscle strength test

Muscle strength score was not significantly associated with age in adult onset patients (data not shown, $p=0.56$). After adjusting for age, time on ERT was associated with a

significant improvement in muscle test score (Table 2; $p<0.001$) when time was categorised, with mean increases of 3.53 (95 % CI −1.39 to 5.66) in patients treated <12 months, 4.04 (95 % CI 2.26 to 5.83) in patients treated for 12–36 months, and 1.3 (95 % CI −1.92 to 4.52) in patients treated >36 months. Further analysis suggested a significant non-linear association between muscle test score and time on ERT. Again, this analysis suggests muscle strength improves for the first 2 years of treatment and then declines (Fig. 1c; edf=2.7, $p<0.001$). Again this result beyond two years should be treated with caution.

Body mass index (BMI)

We found a significant increase in BMI with age (data not shown; $p<0.001$). However, after adjusting for age there was no significant association between BMI and time on ERT when time on ERT was categorised (Table 2; $p=0.62$) or treated as a continuous variable (Fig. 1d; edf=1.0, $p=0.90$).

Safety and complications

Of the 62 adults with late-onset Pompe disease in this study, one patient experienced anaphylactic reactions, two patients required pre-medication due to infusion-associated reactions and no patients were reported as experiencing febrile reactions. No patients died during the course of the study.

Discussion

These data provide longitudinal follow-up of adults with late-onset Pompe disease treated with ERT. They demonstrate improvement, or stabilisation in most outcomes measured, and support other studies which have reported that the effect of ERT is sustained for up to 2 years (van der Ploeg et al 2010, 2012; Regnery et al 2012).

Our cohort comprised a heterogeneous group of 62 adults (aged 16 or over) with late-onset Pompe disease. Their mean age at study entry was 46.5 years (range, 16.3 to 76.7 years) and mean age at diagnosis was 39.7 years (range, 1.5 to 67.7). All but three were receiving alglucosidase alfa and the mean duration of treatment at recruitment was 16 months. At study entry more than a third of our cohort (for whom we had data) required ventilation and almost half had restricted mobility.

A systematic review of the effectiveness of ERT in late-onset Pompe disease recently descriptively analysed 21 studies containing clinical data from 368 late-onset Pompe disease patients (Toscano and Schoser 2012). They concluded that treatment with alglucosidase alfa is effective and attenuates progression of late-onset Pompe disease in most patients. The central trial involved 90 patients aged 8 years or more, who were ambulatory and free of invasive ventilation (van der Ploeg et al 2010). Sixty patients were randomised to receive alglucosidase alfa and 30 to placebo for 78 weeks. Compared to placebo, the treated group showed a statistically significant improvement in 6MWT and %FVC. There were no significant differences reported in muscle test score or SF-36 physical component score. Other notable studies include a multicentre, open label, observational study which evaluated the clinical effectiveness of ERT in 74 late-onset Pompe patients in Italy (Angelini et al 2012) and a 36 month observational study of 38 adults with late-onset Pompe disease (Regnery et al 2012). Similar to our cohort, the Angelini and Regnery studies both included patients who are wheelchair-bound (7/74 and 11/38 respectively).

After adjusting for age, we found no statistically significant association between time on ERT and %FVC. However, small increases were observed in %FVC in the first 24 months of treatment with ERT, followed by a small decrease in this outcome in patients who had been on treatment for 36 months or more. Respiratory failure is the leading cause of death in patients with late-onset Pompe disease (Hirschhorn and Reuser 2001; Gungor et al 2011). In natural history studies, pulmonary function has been reported to decline by up to 1.6 % per year (Van der Beek et al 2009; van der Beek et al 2012), while the likelihood of needing either non-invasive or invasive ventilation has been reported to increase by an average of 8 % each year following diagnosis (Hagemans et al 2005). Therefore the small increases in %FVC observed over the first 2 years of treatment in this study could be interpreted as stabilisation of pulmonary function in this cohort. Furthermore, a recent observational study looking at the impact of ERT on survival in adults with Pompe disease reported that ERT was positively associated with survival (hazard ratio, 0.41; 95 % CI, 0.19 to 0.87) (Gungor et al 2013). The authors of this study concluded that the beneficial effect of ERT on survival is likely to be related to its positive effect on pulmonary function and suggested that the effect of ERT on survival may be greater if treatment is initiated earlier.

Our results reflect those reported by Regnery et al who described small levels of decline in %FVC and no reduction of hours of ventilation over the three years of treatment with ERT (Regnery et al 2012). Similarly, Angelini et al observed an increase or stabilisation of %FVC in 65 % of their patients, and a reduction in 35 % of patients, although there were no significant changes compared to baseline in any treatment group. Conversely, Van der Ploeg et al reported an absolute increase of 3.4 % in FVC ($p=0.006$) in patients treated for 78 weeks with alglucosidase alfa, compared with the placebo group. However, that study excluded patients at the severe end of the spectrum who had a %FVC outside the range of 30–80 %, while our cohort included some patients outside these parameters (range %FVC, 10–130 %). Respiratory function is clearly sensitive to the method of measurement. While it is

recognised that %FVC is not the most sensitive of measurements, for this multi-centre study, it was important to choose a measure which was routinely recorded, and could be readily compared with other published trials.

6MWT data was available for only 20 patients. Nonetheless, our results reinforce findings reported elsewhere, which show a significant decline in distance walked with age and a statistically significant association between duration of treatment with ERT and an increase in distance walked. Our analysis suggests that the distance walked increased for the first two years before plateauing and then declining, although given the large range at baseline and the small number of patients involved, this result should be treated with caution. Regnery et al reported an increase of 32 m after 12 months and a further increase of 12 m after 24 months on treatment, followed by a decline after 36 months treatment (Regnery et al 2012). Similar observations were made in the Italian cohort, although results were not significantly associated with therapy duration (p=0.91), while Van der Ploeg et al reported a 25.1 m increase in distance walked in the group who had received ERT for 78 weeks, compared to controls whose distance walked decreased by an estimated 3 m (van der Ploeg et al 2010).

We also found a statistically significant association between time on ERT and improved muscle strength. As with the 6MWT, the treatment effect appears to plateau after about two years of treatment before declining again. The progressive deterioration in proximal arm and leg strength is one of the defining features of late-onset Pompe. Previous studies have provided only inconclusive evidence of an effect of ERT on muscle strength. The van der Ploeg trial reported an improvement in proximal arm and leg muscle strength which was not statistically significant (van der Ploeg et al 2010), while Regnery et al reported no improvement in muscle strength compared to baseline after three years of treatment with ERT (Regnery et al 2012).

No statistically significant association between ERT and changes in BMI was seen. Similarly, no significant changes from baseline were reported in the Italian cohort, although the findings of a series of three cases of late-onset Pompe disease treated for six months were reported to gain weight (Bernstein et al 2010).

One of the striking features of our results is the suggestion of a decline in the effectiveness of ERT after 2 years. It is possible that within our cohort, individual responses were variable and only the most severe cases were on treatment for long enough to demonstrate statistically significant degrees of improvement. It is increasingly recognised that late-onset Pompe disease is multi-systemic with numerous different phenotypes and it is possible that patients presenting with different symptom patterns might respond differently to ERT (Regnery et al 2012; Schuller et al 2012). Alternatively, this decline may simply be due to the natural history trajectory outstripping the treatment effect, and it is likely that antibody development resulting in reduced enzyme activity could contribute to this. This observational study did not record antibody response or genotype results for all participants, and additional investigation is necessary to consider this phenomenon further.

There are inevitable weaknesses in the use of observational data to assess treatment efficacy. Key amongst these is the difficulty in controlling for confounding by variables related to the intrinsic severity of the conditions. This is a particular issue in conditions such as Pompe disease that are heterogeneous in their manifestations. Differential attendance at participating centres, related to condition severity will also impact on the analyses and may be further complicated by the lack of completeness in recording of key outcomes amongst those who did attend. Similarly, dose and frequency of administration of ERT is physician-dependent and will vary from centre to centre, and will influence the rate at which measured outcomes change. Finally, although the collection of historical data allowed us to examine the natural history of treated and untreated conditions, it is likely that there have been changes over time in which tests are carried out and how they are performed. These limitations are discussed in more detail in our companion general methods paper (Henley et al 2014).

Conclusion

Our data support the conclusions of previous research that ERT is effective in improving outcomes in adults with late-onset Pompe disease, as demonstrated by stabilisation of respiratory function and improved mobility and muscle strength.

We recognise the difficulties in mounting large randomised placebo-controlled trials, powered on clinical outcomes for rare conditions such as Pompe disease. We have shown that observational data from a cohort study which collects both retrospective and prospective data can be used to provide estimates of treatment effectiveness. However, the slowly progressive nature of this condition and the fact that ERT has been available to these patients for only a short period of time means that further longitudinal data is required to consider the long-term prognosis for patients on this therapy, particularly for parameters such as ventilation-dependency.

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Compliance with Ethics Guidelines

Informed consent All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients before being included in the study.

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Competing interest Lindsey Anderson, Katrina Wyatt, Stuart Logan, Vasilis Nikolaou and William Henley declare that they have no conflicts of interest.

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