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Effect of enzyme therapy in juvenile patients with Pompe disease: A three-year open-label study

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ABSTRACT

Pompe disease is a rare neuromuscular disorder caused by deficiency of acid α-glucosidase. Treatment with recombinant human α-glucosidase recently received marketing approval based on prolonged survival of affected infants. The current open-label study was performed to evaluate the response in older children (age 5.9–15.2 years). The five patients that we studied had limb-girdle muscle weakness and three of them also had decreased pulmonary function in upright and supine position. They received 20-mg/kg recombinant human α-glucosidase every two weeks over a 3-year period.

No infusion-associated reactions were observed. Pulmonary function remained stable ($n = 4$) or improved slightly ($n = 1$). Muscle strength increased. Only one patient approached the normal range. Patients obtained higher scores on the Quick Motor Function Test. None of the patients deteriorated. Follow-up data of two unmatched historical cohorts of adults and children with Pompe disease were used for comparison. They showed an average decline in pulmonary function of 1.6% and 5% per year. Data on muscle strength and function of untreated children were not available. Further studies are required.

1. Introduction

Pompe disease (glycogenosis type II, acid maltase deficiency) (OMIM 232300) is a rare neuromuscular disorder caused by deficiency of the lysosomal enzyme acid α-glucosidase. As a result, glycogen accumulates in lysosomes of many cell types, but predominantly in skeletal muscle fibers. The process is progressive and finally destroys the muscle architecture and function [1–4]. The disease encompasses a clinical spectrum [5–8]. The classic infantile form is characterized by progressive cardiac hypertrophy and rapid loss of muscle function. Symptoms manifest shortly after birth and patients usually die within the first year of life [1,2,7,8]. Childhood, juvenile and adult phenotypes may present any time from infancy to late adulthood. The disease course is less progressive and cardiomyopathy is usually absent. Patients eventually become wheelchair and ventilator dependent. Respiratory failure is the major cause of early demise [9–11]. An intermediate non-typical infantile variant with cardiac hypertrophy and respiratory failure in early childhood has been described as well [12]. The nature of the acid alpha-glucosidase gene mutations is largely decisive for the degree of enzyme deficiency and clinical severity [1,13].

Until recently there was no therapy for patients with Pompe disease other than supportive care. This has changed with the introduction of Enzyme Replacement Therapy. So far clinical trials with recombinant human acid α-glucosidase have mainly focused on infants and there have been incidental reports on effects in adults [14–22]. Treatment of infants was shown to increase survival, to diminish cardiac hypertrophy and to improve motor

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outcome. Based on positive results recorded in these trials, enzyme therapy with recombinant human acid α-glucosidase was approved for all patients, but it was explicitly stated that the safety and efficacy of the therapy still had to be proven across the clinical spectrum. The present study was designed to test the safety and efficacy of enzyme therapy in juvenile patients over a three-year treatment period.

2. Materials and methods

2.1. Study design

This study was conducted as an 18-month single center, open-label, phase II study followed by an 18-month extension period and was approved by the Institutional Review Board of the Erasmus MC-Sophia Children's Hospital. Informed consent was obtained from patients and parents.

The endpoints of the study were exploratory and included safety, and the effect of treatment on pulmonary function, muscle strength and function. All assessments were performed at baseline and every three months thereafter.

2.2. Inclusion and exclusion criteria

Inclusion criteria were:

- Confirmed diagnosis of Pompe disease documented by deficient α-glucosidase activity in fibroblasts and/or DNA analysis
- Age between 5 and 18 years
- Demonstrable muscle weakness by manual muscle testing
- Able to provide 3 reproducible FVC measurements in sitting position (within 5% of one another)
- Able to walk 10 m

Patients were excluded if they required invasive ventilation or non-invasive ventilation whilst awake or in upright position. None of the patients had previously received enzyme therapy. Patient characteristics are described in Table 1.

2.3. Treatment

Patients received every other week, intravenously, 20-mg/kg recombinant human α-glucosidase from Chinese hamster ovary cells (Genzyme Corporation, Cambridge) in a step-wise manner: 0.2, 0.8, and 3.5 mg/kg/h each for 30 min and 10 mg/kg/h for the remainder of the infusion. Total duration of the infusion was approximately 3.5 h.

2.4. Safety variables

Physical examination, vital signs, and adverse event recording were performed at every visit. Echocardiograms and standard 12 lead electrocardiograms (ECG) were performed at baseline and at regular intervals thereafter along with safety laboratory measurements (complete blood count with differential, blood urea nitrogen, creatinine, glucose, uric acid, calcium, phosphorus, albumin, total protein, sodium, potassium, chloride, serum glutamic oxaloacetic transaminase/aspartate transaminase (SGOT/AST), serum glutamic pyruvic transaminase/alanine transaminase (SGPT/ALT), alkaline phosphatase, total bilirubin, creatine kinase (CK), creatine kinase with MB fraction (CK-MB), and urinalysis). Anti-recombinant human α-glucosidase IgG antibodies were measured from week 0 through week 74.

2.5. Pulmonary function

Pulmonary function (Forced vital capacity (FVC)) was assessed by spirometry [23] in the upright and supine position. The maximum value of three reproducible tests was used for analysis. The effect of therapy on pulmonary function in patients with an FVC <80% predicted at baseline was compared with two cohorts of untreated patients. Historical cohort 1 comprised 8 untreated children with Pompe disease that had an FVC <80% predicted at their first visit to our hospital. Historical cohort 2 consisted of 16 adult patients that were followed for a mean duration of 16 ± 7 years (published in part by [24]).

2.6. Muscle strength

Muscle strength was assessed by Manual Muscle Testing (MMT) [25] and Hand-Held Dynamometry (HHD) [26–28]. MMT was scored by an 11-point modified version of the Medical Research Council (MRC) scale [29]. HHD was conducted using a hand-held dynamometer (CT3001, C.I.T. Technics, Groningen, the Netherlands). Muscle groups tested by HHD and MMT were: neck flexors, shoulder abductors, elbow flexors, wrist extensors, hip flexors, hip abductors, knee extensors, knee flexors, foot dorsal flexors. Individual scores for each muscle group were summed to calculate a total score for MMT (maximum score 45) and for HHD (Newton). The

Table 1
Diagnostic and baseline characteristics of the study patients.

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at diagnosis (y)	3.5	11.6	1.1	3	2
Age at first symptoms (y)	2.7	6.5	0.8	2.5	1
First symptoms	Episodes with falling and not able to take support on the legs	Difficulties with running during sports and while climbing stairs	Delayed motor milestones and hypotonia	Frequent episodes of falling	Floppy child, delayed motor milestones
Age at start therapy (y)	5.9	12.7	8.9	12.9	15.2
Respiratory support at baseline	None	None	None	None	BIPAP at night
Genotype[a]	del exon 18 (s) 1634C> T (i)	525delT (s) unknown	c.-32-13T> G (m) 923A> C (s)	c.-32-13T> G (m) 2331 + 2T> A (s)	c.-32-13T> G (m) 525delT (s)
α-Glucosidase activity in fibroblasts (nmol/h/mg) Normal range: 45–160	2.8	8.4	13.3	8.6	17.9

[a] Effect of the mutations: severe (s), intermediate-severe (i), and mild (m) (see for details www.pompecenter.nl).

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HHD sum score was compared with reference values of age related peers [27].

2.7. Muscle function

A 6-min walk test (6MWT) was performed according to the guidelines of the American Thoracic Society [30]. The maximum walking distance achieved in 6 min was measured at comfortable pace and at fast speed. Functional activity assessments included two timed tests: 10 meter running and rising from supine position to standing position [29]. The Quick Motor Function Test, a test that was specifically designed and validated for Pompe patients, was performed on regular intervals [31]. The scale consists of 16 specific motor function items. A total score is achieved by summing the scores for each item.

2.8. Patient and parent reports

All patients and their parents were interviewed at baseline and every three months thereafter. The interviews were scheduled before the different assessments and consisted of relevant issues such as mobility, fatigue, muscle pain, and self-reported changes from baseline.

2.9. Statistical analysis

The individual relationships between various outcomes and treatment duration for the different patients were evaluated using least-squares regression. In case of non-linear relations, Spearman's correlation coefficients' were used. For each patient, HHD% predicted values were estimated by linear interpolation of the reference data. Mean values of FVC% predicted according to age in an untreated historical control group was calculated by repeated measures ANOVA. On group level the various repeated measurements were analyzed by mixed model ANOVA (random coefficients models) (SAS PROC MIXED 8.2). p-values <0.05 were considered significant.

3. Results

3.1. Patient characteristics study group

Five juvenile patients, three males and two females, were enrolled in the study (Table 1). They ranged in age from 5.9 to 15.2 years. All presented with mobility problems early in life (0.8–6.5 years). They were diagnosed between 1.1 and 11.6 years of age. The diagnosis was confirmed by mutation analysis (see Table 1 for details), and deficient α-glucosidase activity in cultured fibroblasts (range 2.8–17.9 nmol/mg/h). The α-glucosidase activity was clearly below the normal range (45–160 nmol/mg/h).

3.2. Safety

Patients were treated with 20-mg/kg alpha-glucosidase every two weeks. The three years of treatment were well tolerated. No infusion-associated reactions occurred during 390 infusions in total. None of the patients received premedication with antihistamines or corticosteroids. All patients developed IgG antibodies against the recombinant human enzyme between week 8 and week 38. The highest titers were observed between week 38 and week 74 and ranged from 800 to 6400 units (Fig. 1). Lab safety parameters remained stable. There were no apparent changes in the condition of the patients in the two weeks between sequential infusions.

3.3. Pulmonary function

At baseline, two of the five patients (patient 1 and 3) had normal pulmonary function in both sitting and supine position (Fig. 2). Their 'postural drop', defined as the difference between the forced vital capacity in sitting and supine position (ΔFVC), was 4% and 3%.

The other three patients (patient 2, 4 and 5) had a decreased pulmonary function (Forced Vital Capacity (FVC) of <80% predicted) at baseline (Fig. 2), with a postural drop of 9.9%, 18.0%, and 33.3%. According to the ATS/ERS guidelines a postural drop of >25% is indicative for weakness of the diaphragm [32,33]. Patient 5 required nocturnal non-invasive ventilation (Bi-level Positive Airway Pressure).

During treatment, pulmonary function of patients 1 and 3 remained within normal limits (Fig. 2A and B). The FVC predicted remained stable in patients 2 and 4 and increased significantly in patient 5 ($p = 0.01$, sitting and $p < 0.01$, supine, Fig. 2A and B). The postural drop remained unchanged.

3.4. Muscle strength

At baseline, muscle weakness was more pronounced in the proximal muscles than the distal muscles and more in the lower extremities than the upper extremities. Hip muscles (flexors, extensors and abductors) and neck flexors were most affected.

Table 2 shows the results of the individual patients obtained over three years therapy. On a group level, both muscle strength assessed by MMT and HHD increased significantly (MMT 0.07% (= 0.08 MMT point)/week ($p = 0.007$), HHD 3.0 Newton/week ($p = 0.01$)).

However, whilst all patients reached near-normal sum scores applying MMT, muscle strength measured with HHD remained below that of healthy peers. One patient showed significant catch-up growth towards normal values (Fig. 3), the other patients did not but did not deteriorate either.

3.5. Muscle function

Walking at comfortable pace appeared insufficiently challenging for the children and the results did not show any consistency over the different assessment days. This was different for the 6MWT at fast pace. At baseline the patients ran with an average speed of 3.4 to 5.5 km/h (see Table 2 for individual data). At the end of the study they managed to increase their distance with 64–184 m (mean increase 120 m). This increase was significant on group level (0.7 m/week ($p = 0.045$)).

Unfortunately there are very few data available to compare with. One study reported healthy children between 12 and 14 years of age to run with mean velocities of 11.8 km/hour (range 10.3–13.4 km/h) [34] during a 6 min test. Three of our patients were in or above this age category.

At baseline, rising from supine to standing position took on average 4.4 times longer for the patients compared to healthy peers (see [35] for reference values age 5–12 years and Table 2 for individual data). On a group level, the results showed a trend towards significance ($p = 0.07$ for rising and 0.096 for running).

3.6. Quick motor function test (QMFT)

Patients were regularly tested on 16 motor items that were specifically difficult for patients with Pompe disease.

Before start of treatment, patients had difficulty with most motor items tested, except for reaching hands over midline in supine position and stretching both arms simultaneously upward in sitting position.

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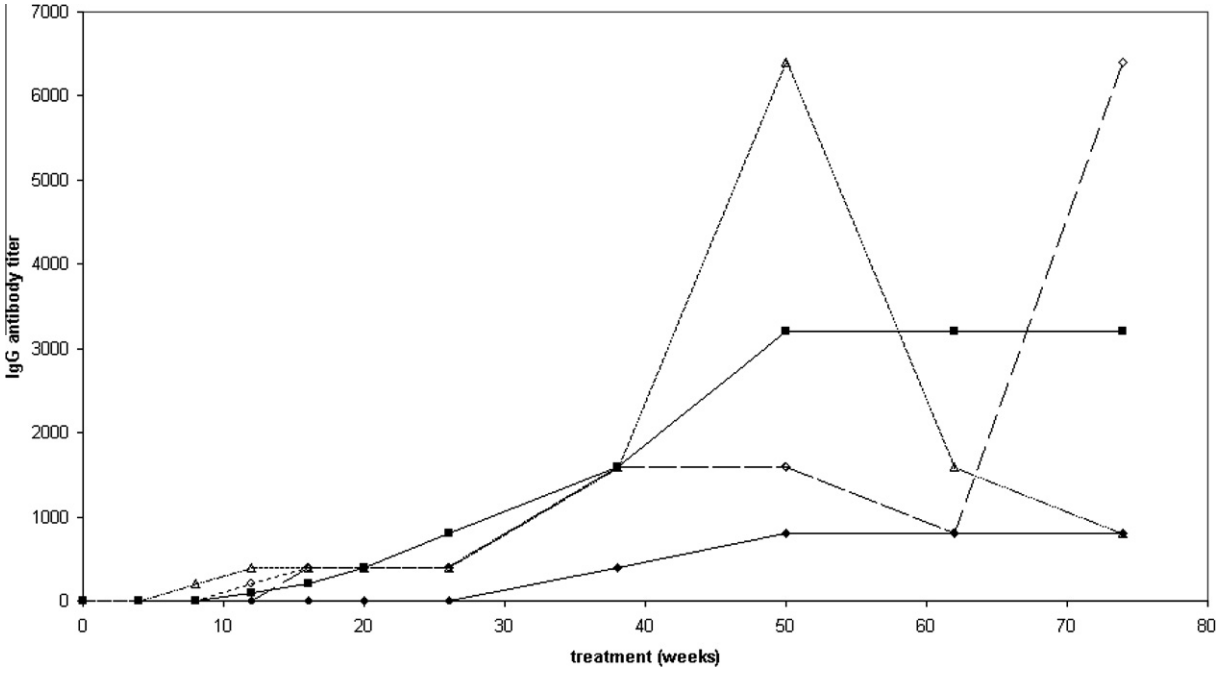

Fig. 1. Anti-recombinant human α-glucosidase IgG antibody titers over 74 weeks of treatment. ◇ = patient 1, ■ = patient 2, ♦ = patient 3, Δ = patient 4, o = patient 5.

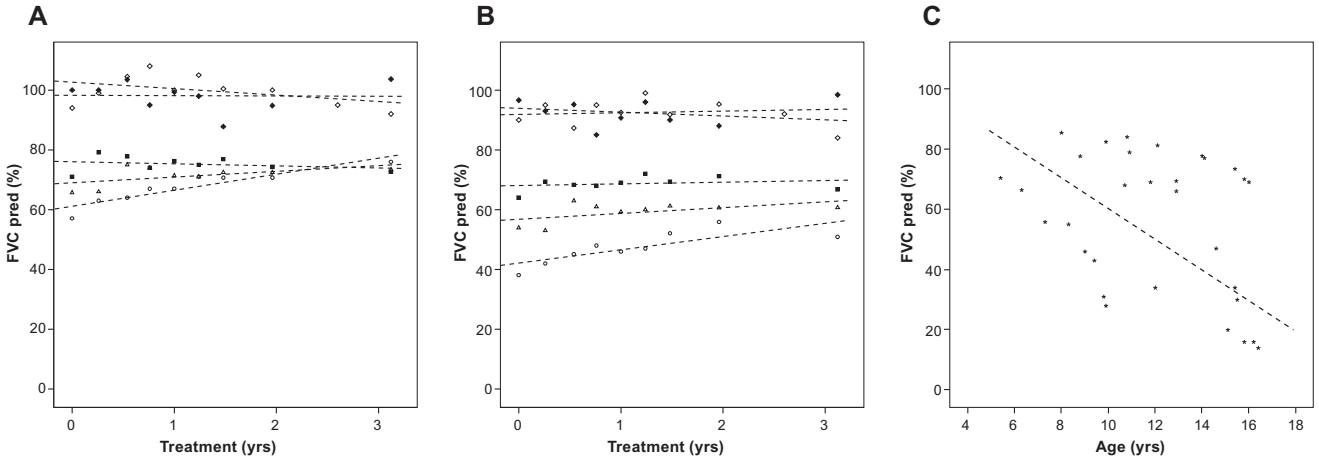

Fig. 2. Effects of enzyme therapy on pulmonary function. (A) Predicted forced vital capacity (FVC) during treatment in sitting position. (B) Predicted forced vital capacity (FVC) during treatment in supine position. ◇ = Patient 1, ■ = patient 2, ♦ = patient 3, Δ = patient 4, o = patient 5. (C) Mean predicted FVC in sitting position of historical cohort 1 comprising 8 untreated patients.

Over three years of therapy, there was a significant increase in QMFT score on a group level ($p = 0.04$, Table 2). Improvements were predominantly found in lifting head 45° in supine position (patients 1, 2, and 4), flexing hips through full range in supine position (all patients), doing a sit-up from supine position (patients 1, 2, 3, and 4), attaining standing position through half knee on the other knee (patients 1, 2, 4, and 5) and climbing four steps (patients 1, 2, 4, and 5).

3.7. Cardiac evaluation

Cardiac evaluation showed no signs of hypertrophic cardiomyopathy. Cardiac dimensions and diastolic and systolic function were normal. Cardiac ultrasound revealed a quadricuspid aortic valve in one patient. A second patient showed minor deformations of the tricuspid valve with a slight prolapse of the anterior leaflet, leading to minimal tricuspid regurgitation. A third patient showed the following ECG abnormalities: an intermittent sinus and atrial rhythm, a delta wave and a non-specific interventricular conduction block. These findings did not change during the study.

3.8. Patient and parent reports

Parents reported that their children had become more active during the day. They were able to participate more easily in activities such as running, playing sports, playing outdoors and cycling and had more energy left in the evening. Regular headaches, muscle pain and fatigue present at start of therapy subsided. Two patients reported that frequent loose stools no longer occurred.

3.9. Surgical interventions

During the study, two patients (patient 2 and 4) received a unilateral Achilles tendon release. For patient 4, this was performed

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Table 2
Results of the individual patients at baseline and after three years of treatment.

		Baseline	3 year ERT	
Patient 1	HHD sumscore (Newton)	521.5	750	$p = 0.008$
	MMT sumscore (%)	86	92	$p = 0.015$
	6MWT (km/hr)	3.4	5.3	$p = 0.006$
	Rising (sec)	4.4	3.94	n.s.
	Running (sec)	4.1	4.0	n.s.
	QMFT (%)	70.3	95.3	$p = 0.001$
Patient 2	HHD sumscore (Newton)	521	865	$p = 0.004$
	MMT sumscore (%)	79	93	$p = 0.07$
	6MWT (km/hr)	4.7	5.8	$p = 0.07$
	Rising (sec)	5.1	4.13	n.s.
	Running (sec)	4.2	4.0	n.s.
	QMFT (%)	73.4	92.2	$p = 0.002$
Patient 3	HHD sumscore (Newton)	605	1202	$p = 0.002$
	MMT sumscore (%)	87	100	$p = 0.001$
	6MWT (km/hr)	5.2	5.9	n.s.
	Rising (sec)	4.4	3.0	$p = 0.06$
	Running (sec)	3.9	3.0	$p = 0.005$
	QMFT (%)	89.1	100	$p = 0.006$
Patient 4	HHD sumscore (Newton)	608	1158	$p = 0.006$
	MMT sumscore (%)	79	100	$p = 0.06$
	6MWT (km/hr)	4.0	5.7	$p = 0.06$
	Rising (sec)	6.2	3.2	$p = 0.01$
	Running (sec)	4.5	3.8	$p = 0.037$
	QMFT (%)	67.2	92.2	$p < 0.001$
Patient 5	HHD sumscore (Newton)	992	1505	$p = 0.01$
	MMT sumscore (%)	83	96	$p = 0.016$
	6MWT (km/hr)	5.5	6.5	n.s.
	Rising (sec)	3.91	2.8	$p = 0.011$
	Running (sec)	3.59	2.9	$p = 0.024$
	QMFT (%)	79.7	92.2	$p < 0.001$

All assessments were performed at baseline and at three months intervals thereafter. The individual changes over the three-year treatment period were evaluated using least-squares regression. All data points gathered every three months over three years time were used in this analysis. ERT = enzyme replacement therapy; HHD = Hand-Held Dynamometry; MMT = Manual Muscle Testing; 6MWT = Six Minute Walk Test; QMFT = Quick Motor Function Test.

6 months after start of treatment and for patient 2, 1.5 years after start of treatment. They recovered well without sequelae.

To judge the significance of our findings we compared the FVC data of the study cohort with those of two untreated historical cohorts. Follow-up data on muscle strength and function of untreated children with Pompe disease were insufficiently available.

3.10. Patient characteristics historical cohort 1

Eight patients with Pompe disease, six males and two females, who did not receive treatment comprised historical cohort 1 (Table 3). All patients in this cohort had a decreased FVC (less than 80%) when first seen in our hospital. Age range of the patients at their first pulmonary function test was 5.4 to 14.1 years. In total 30 FVC measurements were performed in sitting position. Patients were ambulant and presented with mobility problems between 0.8 and 13 years (mean 5.8). They were diagnosed between 1.1 and 14 years. Two of the patients required respiratory support at night. Mutations and alpha-glucosidase activities are shown in Table 3.

3.11. Patient characteristics historical cohort 2

Sixteen untreated patients with Pompe disease, ten females and 6 males comprised historical cohort 2. Full details of this cohort have been published in [24]. Fifteen of these patients were compound heterozygotes (c.-32-13-T- >G in combination with a severe mutation (c.525delT ($n = 8$), c.1548G> A ($n = 2$), c.1115A> T ($n = 2$), c.172C> T ($n = 2$), c.925G> A ($n = 1$))). The genotype of the remaining patient was c.1634C> T (intermediate) /c.525del (severe) functionally comparable to genotype c.1634C> T/del exon18 of patient 1 of the study group. Cohort 2 included patients with normal and decreased pulmonary function at first assessment. Mean age at first symptoms was 24 ± 11 years (range 1–40 years); mean age at diagnosis was 27 ± 12 years. All were ambulant at their first visit, and one patient required respiratory support at night. Four patients were diagnosed before they were 18 years old. Age range at the first pulmonary function test was 11–57 years. In total 95 measurements of vital capacity (VC) in sitting position were performed. Mean follow-up duration of pulmonary function was 9 years (range 2–15 years).

For only one patient pulmonary function measurements were available before the age of 18 years. The first test was performed when the patient was 11 years old. VC at that time was 70% of predicted. Over the next 5 years, his VC decreased to 32%. The patient with genotype c.1634C> T/c.525del, had a VC of 24% predicted at the first available measurement when she was 22 years old. These patients became ventilator dependent at the age of 15, and 20 years.

3.12. Comparison of pulmonary function

The average decline of FVC predicted was 5% per year for historical cohort 1 (Fig. 1C) and 1.6% per year for cohort 2. This was significantly different from the study group.

4. Discussion

The present study assessed safety and efficacy of three years treatment with recombinant human α-glucosidase in five juvenile Pompe patients. All patients were ambulant and free of ventilator support during the day.

Treatment with recombinant human α-glucosidase was well tolerated. In a recent study on enzyme therapy in 18 patients with classic infantile Pompe disease, infusion-associated reactions were reported to occur in approximately 60% of the cases [21]. In the present study none of the patients experienced infusion-associated reactions, even though all five patients developed antibodies. The antibody titers did not reach the high levels that were observed in some infants. These differences might be explained by residual α-glucosidase activity expressed in juvenile patients, as opposed to the virtual absence of enzyme activity in classic infantile patients. The presence of residual activity also explains the more slowly progressive disease course of the study patients prior to start of therapy.

Insight in the natural course of Pompe disease is essential to evaluate effects of treatment. There are several reports on pulmonary function in untreated adults with Pompe disease. They all indicate that pulmonary function declines with disease duration [10,36–38]. Limited data have been published on children. For that reason we compared the pulmonary function of the patients in this study with two historical cohorts. Both cohorts were unmatched. Historical cohort 1 consisted of eight children who all had an FVC predicted of <80% at their first visit. Mean age at first symptoms, age at diagnosis, time lag between diagnosis and age at first assessment were comparable with the study cohort. Five of 8 patients in cohort 1 compared to 3 of 5 patients in the study group had the common c.-32-13-T- >G/null genotype, that is found in 53% of children over 1 year of age and 77% of adults [39,40]. The other genotypes of patients in cohort 1 and the study group are more severe and clinical effects difficult to compare. It can therefore not be ruled out that the 5% predicted FVC decline per year in untreated children is slightly overestimated. On the other hand, historical cohort 2, which consisted of 15 patients with the milder

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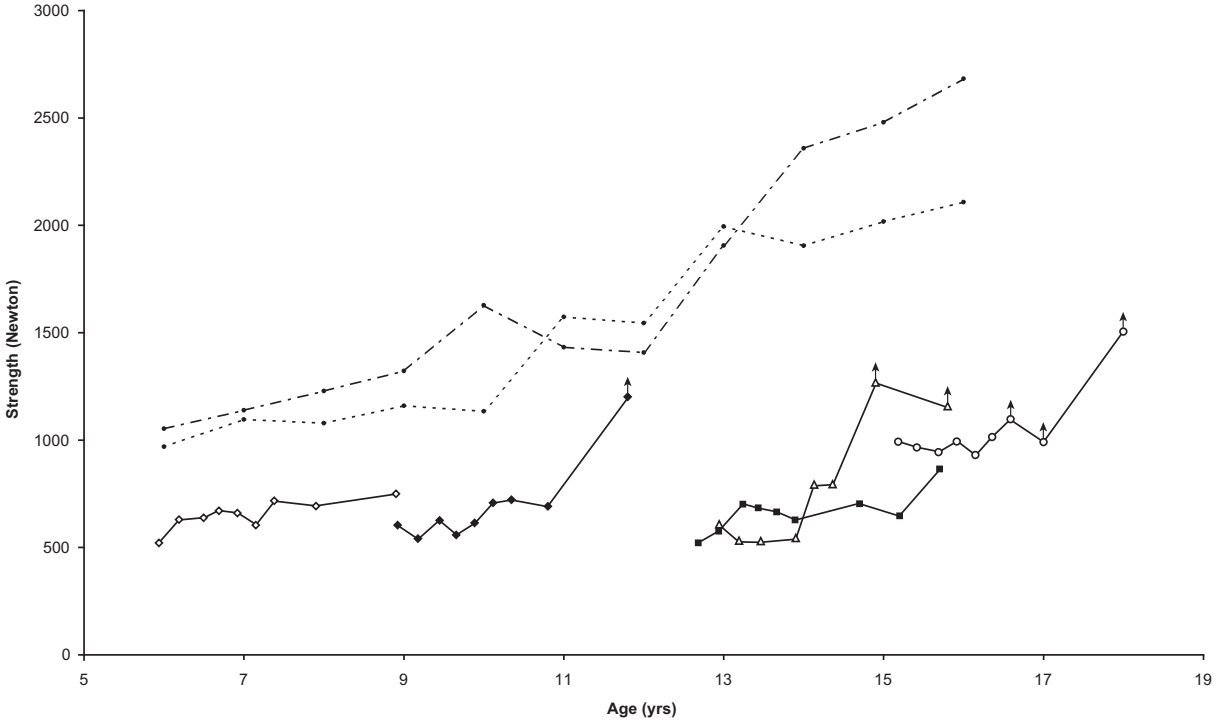

Fig. 3. Effects of enzyme therapy on muscle strength measured by Hand-Held Dynamometry. Results of nine muscles were grouped together to calculate a total sum score. The sum score was plotted for all patients: ◇ = patient 1 (boy), ■ = patient 2 (girl), ♦ = patient 3 (girl), Δ = patient 4 (boy), o = patient 5 (boy). Age related reference values are plotted for -comparison [27]. Reference values boys: –·–·–·–·–. Reference values girls - - - - - - - - -. Patients' muscle strength was measured with an upper limit of testing of 180 Newton per muscle group. The resulting outcomes for these patients therefore underestimate the true outcome (right-censored values). Data points representing right-censored values are represented by arrows.

Table 3
Diagnostic characteristics of the patients of historical cohort 2.

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age at diagnosis (y)	11	7	1	4
Age at first symptoms (y)	10	6	0.5	8
First symptoms	Difficulty climbing stairs	Difficulty running	Delayed motor milestones	Difficulty performing sports
Age at first assessment (y)	12	9.4	9	8
Respiratory support at first assessment	BIPAP at night	BIPAP at night	None	None
Genotype[a]	c.-32-3C> A (s/i) c.877G> S + c.271G> A (s)	c.1829C> T (i) c.1912G> T (s)	c.1798C> T (i) c.525delT (s)	c.-32-13T> G (m) c.1441T> S (s)
α-Glucosidase activity in fibroblasts (nmol/h/mg) Normal range: 45–160	3.4	0.3	1.7	7.8
Characteristics	Patient 5	Patient 6	Patient 7	Patient 8
Age at diagnosis (y)	3	2	10	14
Age at first symptoms (y)	2.5	1	7	13
First symptoms	Frequent falling	Delayed motor milestones	Difficulty lifting head supine pos.	Severe fatigue
Age at first assessment (y)	10.8	5.4	10.7	14.1
Respiratory support at first assessment	None	None	None	None
Genotype[a]	c.-32-13T> G (m) c.2332 + 2T> A (s)	c.-32-13T> G (m) c.1051delG (s)	c.-32-13T> G (m) c.1548G > A (s)	c.-32-13T> G (m) c.1933G> A (s)
α-Glucosidase activity in fibroblasts (nmol/h/mg) Normal range: 45–160	8.6	4.2	9.1	6.2

[a] Effect of the mutations: severe (s), intermediate-severe (i), and mild (m) (see for details www.pompecenter.nl).

c.-32-13-T- >G/null genotype and only one patient with a combination of a severe and intermediate mutation, showed an average decline of 1.6% predicted FVC per year. Also this course was significantly different from the study cohort.

All five patients in our study group had moderate muscle weakness at baseline. During treatment, improvements in strength were recorded with MMT and HHD. All children reached near-normal scores on MMT. Muscle strength assessed with HHD remained below the strength of healthy peers and confirms that MMT is less reliable and sensitive than HHD to give full information about the strength of muscles [41], [42–44]. In particular this is the case for MMT grade 4 that covers a wide range of forces (10–250 New-

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ton) [42]. Applying HHD, one child significantly caught up with healthy peers, while the others did not. Earlier we found that a moderately affected 11-year-old patient needed five years of enzyme therapy before he reached normal strength [45]. This may indicate that long-term treatment may be required to obtain full effects.

Despite the fact that muscle strength remained below normal values, several functional improvements were observed in the patients. They were able to run longer distances in 6 min, or were able to rise faster from the floor. In addition, all patients performed significantly better according to QMFT scores. Part of these improvements may be explained by growth or by the Achilles tendon release operation that was performed in two patients. The fact that several patients learned to lift their head from the surface or to do a sit-up without use of hands, skills particularly difficult for untreated Pompe patients [5], cannot be explained by growth or surgery.

The results of the present study extend previously reported effects of treatment in classic infantile patients [14,16–21], but should be interpreted with caution.

Limitations of our study are the small number of patients and the fact that our study was not placebo controlled. To overcome the latter problem we used two historical cohorts that only partly matched the treated patients. Cohort 2 mainly comprised adults. Historical data of untreated children with Pompe disease were only available for pulmonary function and not for muscle strength and function. We could therefore not fully rule out that untreated children might also have shown improvements of muscle strength and function over a certain period of time, for example with onset of puberty.

We found it encouraging, that none of the patients deteriorated over a three-year period. Some patients showed moderate improvements. All patients tolerated the enzyme infusions well. Long term follow-up studies with more patients are required.

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