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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).