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Cardiac outcome in classic infantile Pompe disease after 13 years of treatment with recombinant human acid alpha-glucosidase

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ABSTRACT

Background: Cardiac failure is the main cause of death in untreated classic infantile Pompe disease, an inheritable metabolic myopathy characterized by progressive hypertrophic cardiomyopathy. Since the introduction of enzyme replacement therapy (ERT), survival has increased significantly due to reduced cardiac hypertrophy and improved cardiac function. However, little is known about ERT's long-term effects on the heart.
Methods: Fourteen patients were included in this prospective study. Cardiac dimensions, function, conduction and rhythm disturbances were evaluated at baseline and at regular intervals thereafter.
Results: Treatment duration ranged from 1.1 to 13.9 years (median 4.8 years). At baseline, all patients had increased left ventricular mass index (LVMI) (median LVMI 226 g/m^2, range 98 to 599 g/m^2, Z-score median 7, range 2.4–12.4). During the first four weeks, LVMI continued to increase in six patients. Normalization of LVMI was observed in 13 patients (median 30 weeks; range 3 to 660 weeks). After clinical deterioration, LVMI increased again slightly in one patient. At baseline, PR interval was shortened in all patients; it normalized in only three. A delta-wave pattern on ECG was seen in six patients and resulted in documented periods of supraventricular tachycardias (SVTs) in three patients, two of whom required medication and/or ablation. One patient had severe bradycardia (35 beats/min).
Conclusion: This study shows that ERT significantly reduced LVMI, and sustained this effect over a period of 13.9 years. The risk for rhythm disturbances remains. Regular cardiac evaluations should be continued, also after initially good response to ERT.

1. Introduction

Before the introduction of enzyme replacement therapy (ERT), cardiac failure was the main cause of death in patients with the classic infantile form of Pompe disease (OMIM 232300), a lysosomal storage disorder caused by deficiency of the enzyme acid alpha-glucosidase (EC 3.2.1.20). A hallmark of the disease is the progressive accumulation of glycogen, predominantly in skeletal and cardiac muscle, but also in various other tissues throughout the body. Pompe disease presents as a spectrum of clinical phenotypes, with the severest classic-infantile form leading to complete deficiency of alpha-glucosidase. Patients present with progressive generalized myopathy and cardiac hypertrophy. Motor milestones are not achieved, and patients rarely survive beyond one year of age. Cardiac failure is the main cause of death [1–4].

Since the introduction of ERT with recombinant human alpha-glucosidase (rhGAA, alglucosidase alfa), survival has improved significantly, due mainly to reduced cardiac hypertrophy and improved cardiac function [5–9]. However, little is known about the long-term effects of ERT on the heart. The present report describes the effects of ERT on cardiac size, cardiac function, and conduction pattern in fourteen classic-infantile Pompe patients over a treatment period up of 13.9 years.

2. Material and methods

2.1. Patients

This study is part of an ongoing prospective clinical study investigating the safety and efficacy of ERT in classic-infantile Pompe patients. Classic-infantile Pompe disease was confirmed by profound deficiency of α-glucosidase in fibroblasts (<1%), mutation analysis, and the presence of hypertrophic cardiomyopathy. For this study of long-term effects,

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we only included patients who had been receiving ERT for at least 12 months. ERT doses ranged from 20 mg/kg every other week to 40 mg/kg weekly.

During the study period five additional patients were diagnosed. Four did not start ERT because of poor respiratory and/or motor condition or because parents decided not to start ERT. The ages of these patients at time of diagnosis ranged from 2.6–4.6 months. LVMI ranged from 171 to 523 g/m^2 at time of diagnosis, and were in the same range as the study cohort, none of these patients was ventilator dependent. All untreated patients died before the age of one year.

2.2. Study design

The study was performed at Erasmus MC University Medical Center - Sophia Children's Hospital Rotterdam (Netherlands), and was approved by the Institutional Review Board. Written informed consent was obtained from parents or legal guardians. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institutional Review Board. Standardized assessments were performed before the start of ERT and every three months thereafter.

2.3. Echocardiography

Conventional echocardiography with trans-thoracic M-Mode, two-dimensional echocardiography and conventional echo-Doppler measurements was performed by an experienced sonographer (JP) using a Philips iE33 Echocardiography System (Philips Medical Systems, Andover, MA, USA). Recordings were made at baseline and at regular intervals thereafter according to the recommendations of the American Society of Echocardiography [10]. The following parameters were documented: left ventricular internal cavity dimension in diastole (LVIDd), inter-ventricular septum thickness in diastole (IVSd), left ventricular posterior wall thickness in diastole (LVPWd), and left and right ventricular pre-ejection periods (LVPEP and RVPEP). These values were compared with normal values according to the Boston Z-scores [11]. Left ventricular mass index (LVMI) was calculated using the Devereux formula and indexed by body surface area [12]. Left ventricular hypertrophy was considered to be present if the LVMI Z-scores were >+2SD [11].

Systolic function was examined by calculating the shortening fraction (SF). Values between 28 and 44% were considered normal [13]. To assess diastolic function, we used conventional Doppler imaging to examine the E/A ratio. The resulting measurements of the peak early (E) and late (A) transmitral filling velocities were then compared with published reference values [14]. In January 2007, to optimize the assessment of diastolic function, pulsed wave Tissue Doppler Imaging (PWTDI) was added to the study protocol as an evaluation method. PWTDI velocities from the standard apical four-chamber views were acquired as described [10] and compared with corresponding measurements in age and sex-matched healthy controls.

Relative wall thickness (RWT) was calculated as RWT = ((IVSd + LVPWd)/LVIDd). A cut-off value of 0.42 was used to divide left ventricular (LV) hypertrophy into concentric (RWT > 0.42) and eccentric hypertrophy (RWT < 0.42) [15]. Patients without LV hypertrophy were classified as normal (RWT < 0.42) or concentric remodeling (RWT > 0.42).

2.4. Electrocardiography

Standardized 12 lead electrocardiograms (ECGs) were made using a Mortara ELI 350 ECG machine (Mortara Instrument Inc., Milwaukee, USA.) At regular intervals, we obtained ECGs for all patients in order to determine the PR interval, the QT interval corrected for heart rate, the LV voltages, and any rhythm or conduction disturbances. The QT interval was measured in lead II, V5, or V6. The corrected QT interval was determined by dividing the measured QT interval by the square root of the RR interval (Bazett's formula). LV voltages were calculated using the sum of the R wave in lead V6 and the S wave in lead V1. Pediatric reference values were obtained from Rijnbeek et al.; these consisted of a Dutch cohort from Rotterdam and were corrected for age and heart rate [16]. Two investigators examined all ECGs (CvC, IF).

2.5. Statistical analysis

For mitral valve E/A ratio, Z-scores were calculated as the difference between the measured value and the mean reference value divided by the standard deviation from the reference value. Z-scores >2 or <−2 were considered abnormal. Measurements of PWTDI velocities and mitral valve E and A velocities at each patient's last assessment were compared with corresponding measurements in age and sex-matched healthy controls who have participated in an echocardiographic normal value study of our institute [17]. Variables were summarized using descriptive statistics comprising median and range. Differences in cardiac dimensions over time were evaluated using the Wilcoxon rank signed test. P-values < .05 were considered statistically significant. Statistical analyses were performed using SPSS version 21.0.

3. Results

3.1. Patients

Fourteen patients were treated for >12 months and included in this study; their baseline characteristics are summarized in Table 1. Age at start of treatment ranged from 3 days to 8.3 months (median age 2.7 months). At study end, the duration of ERT ranged from 1.1 to 13.9 years (median 4.8 years). All patients had fully deleterious variations in the GAA gene, and profound deficiency of alpha-glucosidase activity. The commonest variations were c.2481 +102_2646+31del, which leads to an in-frame deletion of exon 18, and c.del525T, which leads to an unstable messenger with no GAA-protein production. Together they accounted for 15 of the 24 variations found in the GAA gene. Two patients were cross-reactive immunologic material (CRIM) negative, which implies that the variants on both alleles did not result in any GAA protein production.

At start of therapy, all patients had concentric LV hypertrophy (Table 2). Two patients had LV outflow-tract obstruction, and two others had accelerated mid-ventricular velocities of the left ventricle. Four patients (patients 2, 3, 4 and 12) experienced symptoms of congestive heart failure. At start, ten used cardiac medication (Table 1), at study end five still needed medication. Systemic blood pressures and renal function were within normal limits. All patients were hypotonic and most showed clearly reduced scores on the Alberta Infant Motor Scale (Table 1). Two patients were in an end-stage condition of the disease (patients 2 and 4). Four patients required oxygen via nasal prong/cannula (patients 4, 7, 8 and 13); one other patient was ventilator dependent (patient 2). During follow-up, four other patients became ventilator dependent. Later, two of these patients (both CRIM negative) died, at 4.4 and 4.3 years. Neither patient died due to cardiac complications. Patient 3 died after a period of unexplained hyperthermia, possibly due to brainstem dysfunction. Patient 5 died due to respiratory failure during a viral infection.

3.2. Echocardiography

3.2.1. LV morphology

At baseline, LVMI was profoundly elevated in all patients (median LVMI 226 g/m^2, range 98 to 599 g/m^2; median Z-score 7, range 2.4–12.4; Table 2). The LVPWd was elevated at baseline in 13 patients. Fig. 1 shows the effect of ERT on LVMI and LVPWd over time, both show similar effects during follow-up. In eight patients, LVMI decreased immediately after start of ERT. In the remaining six patients it continued to increase for the first four weeks (median increase 79.0 g/m^2 (range 12.4–149 g/m^2)), and then declined. At the last assessment, the median LVMI was 70.8 g/m^2 (range 48.2 to 119.6 g/m^2, median; Z-score, 0.3 range −0.9 to +2.4); in 13 patients it had normalized (Fig. 2).

Median time to normalization was 30 weeks (range 3 to 660 weeks). LVMI also normalized in patient 12, who had had dilated hypertrophic cardiomyopathy at start. One patient who never reached fully normal values died at the age of 4.3 years.

3.2.2. Cardiac systolic and diastolic function

At baseline, four patients had decreased left ventricular SF (Table 2). SF normalized during treatment. At baseline diastolic function of the LV as measured by E/A ratio was normal in all patients. At follow-up, two patients had abnormalities in diastolic function: patient 3 showed a decline in diastolic function before she died; patient 2, who had end-stage disease, had abnormal E/A ratios in most measurements.

3.3. Diastolic function measured by TDI

At last assessment, we obtained TDI values for 10 patients. The results are shown in Table 3. The early mitral inflow velocities (E') were significantly lower and the tricuspid A' velocities were significantly higher than in healthy age-matched controls. In the patient group, MV E/E' ratios were slightly increased.

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Table 1
Clinical features.

Pt	Gender	Age at diagnosis (months)	Age at start ERT (months)	Weight (kg)/height (cm) at start ERT	Age at study end in months (years)	Survival[b]	Weight (kg)/height (cm) at study end	Mutations	CRIM status	Baseline cardiac medication[d]	Start invasive ventilation (years)	AIMS at baseline (P-value)	Maximal motor milestone
1	M	0.7	3.8	7.8/76	171 (14.2)	Alive	51/175	c.2481+102_2646+31del c.1799G>A	+	None	–	10 (22)	Persistent walker
2	F	3.6	7.2	8.3/73	174 (14.5)	Alive	55/165	c.1115A>T c.525delT	+	Diuretics	0.6[a]	5 (0)	Tetraplegic
3	F	0.6	3.0	5.8/60	51 (4.3)	Deceased	18.9/110	c.525delT c.525delT	–	Diuretics	2.2	4 (1)	Sitting
4	F	6.2	8.3	5.7/62	174 (14.5)	Alive	33.6/146	c.1913G>T c.1548G>A	+	Diuretics, ACE-inhibitor and Digoxin	0.9	5 (0)	Tetraplegic
5	M	0.2	1.9	4.0/52	53 (4.4)	Deceased	16.7/107	c.2741delinsCAG c.2741delinsCAG	–	Diuretics	2.0	6 (25)	Walking[c]
6	M	0.7	1.2	3.6/52	103 (8.6)	Alive	40/132	c.del525T c.1933G>T	+	Beta-blocker	–	3 (1)	Persistent walker
7	F	0.2	0.5	4.0/50	98 (8.2)	Alive	32/134	c.2481+102_2646+31del c.2481+102_2646+31del	+	ACE-inhibitor	–	4 (36)	Persistent walker
8	M	0.1	0.1	3.2/46	69 (5.8)	Alive	19.6/113	c.1460T>C c.1460T>C	+	None	2.7	2 (3)	Walking[c]
9	M	2.0	2.2	4.8/59	64 (5.3)	Alive	21.7/115	c.525delT c.2481+102_2646+31del	+	None	–	7 (12)	Bum scoots
10	F	2.3	2.4	6.3/66	52 (4.3)	Alive	23.4/114	c.2481+102_2646+31del c.2481+102_2646+31del	+	Beta-blocker	–	1 (0)	Persistent walker
11	F	0.1	0.3	4.2/52	27 (2.2)	Alive	13/88	c.525delT c.1933G>A	+	None	–	2 (3)	Persistent walker
12	F	4.4	4.6	5.8/65	26 (2.2)	Alive	13/91	c.2104C>T c.379_380del	+	Diuretics and ACE-inhibitor	–	6 (0)	Persistent walker
13	M	3.8	3.8	61/67	24 (2.0)	Alive	13.4/88	c.2481+102_2646+31del c.525delT	+	Diuretics and beta-blocker	–	4 (0)	Persistent walker
14	M	2.9	3.0	5.4/62	17 (1.4)	Alive	10.2/82	c.2104C>T c.2481+102_2646+31del	+	Diuretics	–	7 (5)	Pulls to stand

[a] Invasive ventilation started before start of ERT.
[b] Two patients died; their deaths were not related to cardiac events.
[c] Lost the ability to walk after becoming ventilator dependent.
[d] Baseline cardiac medication. Patients 2, 3, 4 and 12 experienced symptoms of congestive heart failure, in the other patients medication was started as standard treatment for hypertrophic cardiomyopathy.

Table 2
Cardiological parameters.

Pt	Baseline								Study end							
	LVM	LVM vs BSA	SF	IVSd	LVPWd	LVIDd	RWT	PR interval	LVM	LVM vs BSA	SF	IVSd	LVPWd	LVIDd	RWT	PR interval
1	**65.2**	**171 (5.4)**	45	**0.9 (5.5)**	**1.0 (8)**	2.7	**0.7**	0.1	112.7	70.4 (−0.9)	41	0.8 (−0.7)	0.8 (−0.3)	4.6	0.3	0.08
2	**83.3**	**203 (6.4)**	42	**1.1 (8)**	**1.0 (7.7)**	2.7	**0.8**	0.08	191.3	119.6 (1.5)[b]	49	1.1 (1.5)	1.0 (1.4)	1.0	0.4	**0.1**[c]
3	**96.2**	**308 (8.7)**	**25**	**1.4 (13.8)**	**1.1 (10.5)**	2.4	**1.0**	0.07	**82.8**	**109 (2.4)**[a]	46	**1.0 (4)**	**1.0 (5)**	3.0	**0.7**	**0.08**
4	**188.4**	**599 (12.4)**	**10**	**1.8 (19.6)**	**1.6 (18.4)**	**3.7**	**0.9**	0.1	129	111.3 (1.7)	41	**0.9 (2.9)**	0.8 (1.9)	NA	**0.7**	**0.08**[c]
5	**77.0**	**296 (8.7)**	64	**1.4 (15.1)**	**1.2 (13.2)**	1.2	**2.2**	**0.1**	49.14	78 (0.8)[a]	57	0.6 (0)	0.6 (0.8)	3.0	**0.5**	0.12
6	**42.0**	**191 (6.1)**	35	**0.9 (7.3)**	**0.9 (8.2)**	2.1	**0.9**	0.09	81.4	67.8 (−0.9)	37	0.7 (−0.6)	0.6 (−1.4)	0.8	0.4	0.25[d]
7	**50.8**	**231 (6.9)**	44	**0.95 (7.9)**	**1.30 (14.9)**	1.7	**1.3**	**0.08**	78.2	71.1 (−0.3)	32	0.1 (0.6)	0.8 (0.6)	3.7	0.4	**0.05**[d]
8	**19.8**	**98 (2.4)**	39	**0.75 (5.1)**	0.38 (−0.5)	**1.2**	**0.9**	0.08	44.4	57.6 (−0.9)	46	0.5 (−1.2)	0.6 (−0.5)	3.4	0.3	**0.08**
9	**37.8**	**140 (4.4)**	55	**1.1 (9.7)**	**0.79 (5.8)**	1.9	**1.0**	0.08	61.7	74.3 (0.3)	37	0.7 (0)	0.6 (0.1)	3.7	0.4	0.12[d]
10	**78.2**	**237 (7.2)**	37	**1.4 (13.3)**	**0.82 (5.7)**	2.6	**0.9**	**0.08**	85.8	63.3 (1.8)	38	0.9 (1.9)	0.6 (−0.4)	4.1	0.4	**0.08**[d]
11	**27.5**	**110 (3.2)**	38	**0.85 (6.2)**	**0.75 (5.5)**	1.6	**1.0**	0.06	32.0	48.2 (−0.8)	36	0.5 (−0.4)	0.4 (−1.3)	3.1	0.3	0.09
12	**81.5**	**263 (7.6)**	**25**	**0.89 (6)**	**0.71 (4.1)**	**3.7**	**0.43**	**0.07**	41.5	74.1 (0.5)	35	0.5 (−0.6)	0.5 (−1.2)	3.6	0.3	0.08
13	**74.6**	**220 (7.0)**	32	**1.1 (8.9)**	**0.85 (6.2)**	**2.2**	**0.9**	**0.08**	36.1	64.5 (−0.2)	39	0.6 (−0.5)	0.47 (−1)	3.1	0.4	**0.08**
14	**73.8**	**238 (7.5)**	**20**	**0.97 (7.4)**	**1.2 (12.1)**	**2.5**	**0.9**	0.08	30.9	65.7 (−0.03)	32	0.7 (1.6)	0.5 (−0.2)	2.6	**0.5**	**0.08**
Median	74.6	225.5 (7)	37.5	1.0 (8.0)	0.95 (7.9)	2.3	0.9	0.08	49.1	70.8 (0.3)	38.5	0.7 (0.0)	0.6 (−0.3)	3.1	0.4	0.08
Range	19.8–188.4	98–599	10–64	0.8–1.8	0.4–1.6	1.2–3.7	0.4–3.1	0.06–0.1	30.9–191.3	48.2–120	32–57	0.5–1.1	0.4–1.0	0.8–4.6	0.3–0.7	0.05–0.3

IVSd: inter-ventricular septum thickness in diastole in centimeters; LVIDd: left ventricular internal cavity dimension in diastole in centimeters; LVM vs BSA: Left ventricular mass indexed for BSA; LVPWd: left ventricular posterior wall thickness in diastole in centimeters; SF: Shortening fraction in percentage; RWT: Relative wall thickness.
Abnormal values are marked in bold; NA = not available; Z-score between brackets.

[a] Deceased.
[b] This patient had abnormal values in most measurements, but last two measurements were normal.
[c] confirmed WPW.
[d] Deltawaves on ECG.

3.4. Electrocardiography

During follow-up, we evaluated a total of 118 ambulant ECGs from 14 patients. At baseline, PR interval had been normal in nine patients and shortened in five (median PR interval 80 ms, range 60 to 100 ms; Table 2). At study end, the PR interval was within normal limits in six patients and was shortened in eight.

At baseline, LV voltages had been substantially increased (median 4.8 mV, range 2.2 to 8.6 mV); after start of ERT they declined (median 3.9 mV, range 1.7 to 6.2 mV). All patients had also had repolarization disturbances (strain). This normalized in all patients, except in patients 2, 3 and 5, in whom LVMI was slightly increased at last assessment or who showed increased value(s) of LVMI in the measurement (s) before the final one. Four patients (patient 1, 9, 10 and 13) had an incomplete right-bundle-branch block.

At baseline, the corrected QT-interval was normal in ten patients (median: 390 ms range 340 to 430 ms), and shortened in four (patients 1, 4, 13 and 14). At study end, corrected QT-interval was normal in ten patients, shortened in three (patients 4, 5 and 11), and increased in one (patient 2).

Delta waves, suggestive for Wolff-Parkinson-White (WPW) pattern, were found in six patients (patients 2, 4, 6, 7, 9 and 10). In the years after start of therapy, arrhythmias had been documented in three patients (patients 2, 4 and 5). Holter ECGs were performed in four patients (patients 2, 4, 7 and 12). Multiple episodes of supraventricular tachycardia (SVT) were documented in patients 2 and 4. Patient 5 had one episode of SVT, in the days before he died. The tachyarrhythmia were successfully converted by adenosine; in patient 2, rhythm control was established by Sotalol, and in patient 4 it was established by Atenolol and Flecainide. Due to frequent relapses, patient 4 underwent ablation of three aberrant pathways. In patient 2, the most recent Holter ECG revealed severe sinus bradycardia (range of 35 bpm to 97 bpm) and over 6000 pauses were recorded over 24 h, with a maximum duration of 3.5 s. Due to the patient's poor clinical condition, it was decided not to implant a pacemaker.

4. Discussion

Due to a positive effect of ERT on cardiac hypertrophy, many patients with classic-infantile Pompe disease treated with ERT have now survived far beyond their first year of life [5–8,18–20]. Studies particularly focusing on the long-term consequences on cardiac structure, rhythm and function have not been performed, which was the reason for this study.

4.1. Effect of ERT on left ventricular mass and systolic function

At start of ERT, all patients in our study had prominent hypertrophic cardiomyopathy, with LVMIs of up to 599 g/m^2 (Z-scores of up to +12.4). As hypertrophy was already present in patients who had been diagnosed shortly after birth, it may – as noted by others [21,22] – have developed during pregnancy. Earlier we found in untreated patients that the extent of hypertrophy was related to age [2]. Extraordinary one of our patients had severe dilated cardiomyopathy as well as hypertrophy.

Our study showed that ERT led to a significant effect on LVMI, LVPWd and systolic function in all patients (Fig. 1). Reduction of LVMI and LVPWd were seen in previous studies with a shorter follow-up [8,23,24], new is that this effect is preserved for almost 14 years of ERT. LVMI normalized in 13 patients. Those in whom it did not fully normalize (n = 2), or in whom it increased slightly (n = 1), either died, or were in the end stage of disease at the start of ERT with a very high baseline LVMI. In none of these patients was cardiac failure the cause of death.

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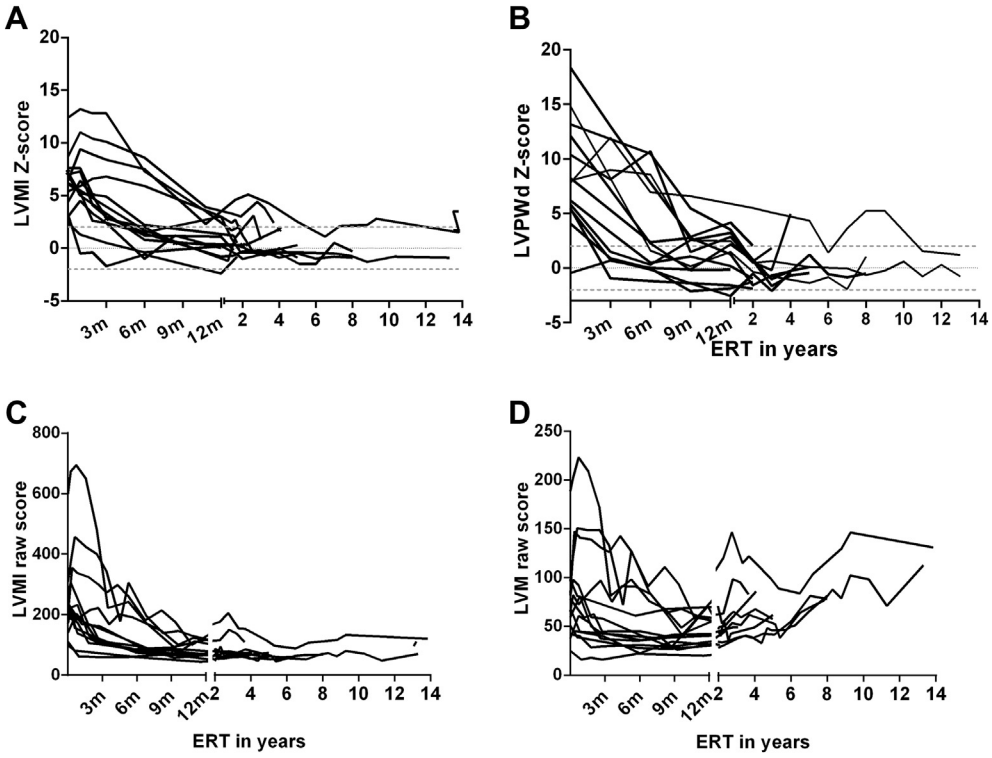

Fig. 1. Left ventricular cardiac dimensions over time. A) LVMI Z-scores B) LVPWd Z-scores C) LVMI raw scores D) LVM raw scores. Each of the 14 patients is represented by a different line. The dashed grey lines represent the upper and lower limit of normal (Z-score of +2 and −2) and normal value (Z-score of 0).

At study end, systolic LV function was normal in all patients. A study by Chen et al. limited to 12 months of ERT also showed that LV function improved [25].

4.2. Effect of ERT on diastolic function

Using conventional echocardiography, we found no diastolic dysfunction at baseline. However, pseudo-normalization of E/A ratio cannot be ruled out. As PWTDI appears to be more sensitive than conventional echocardiography in detecting abnormalities in diastolic function, we added this measurement to our follow-up protocol. At the end of the follow-up period, patients had significantly lower E' velocities and a trend to higher E/E' ratios at the level of the mitral valve compared to controls. This was also observed by Chen et al. after one year of ERT [25]. This suggests that patients with Pompe disease who receive ERT have abnormal relaxation of the left ventricle, and also increased filling pressures. However, these data are difficult to interpret, since, in healthy young children, E' values and E/E' ratios also change significantly. In future studies, new imaging techniques such as speckle tracking might help to detect diastolic dysfunction at an early stage [26].

4.3. Effect of ERT on ECG parameters and cardiac rhythm

In line with the effect of ERT on LVMI, we found a reduction in LV voltages. Repolarization disturbances also disappeared. Importantly, despite treatment with ERT, the short PR and WPW pattern remained present. At start of ERT, 36% of patients had had a short PR interval; at the end of the study, 57% did. At end of study, six patients had a WPW pattern.

A short PR interval is often found in patients with classic infantile Pompe disease [27,28], it is also found in other storage diseases affecting the heart such as Fabry disease and Danon disease, and in patients with PRKAG2 mutations [29,30].

The mechanism underlying this short PR interval is not completely understood; an interesting hypothesis was raised in 1982 by Bharati et al., who correlated electrophysiological abnormalities with pathological postmortem findings in the conduction system of untreated patients with classic-infantile Pompe disease. They found marked glycogen infiltration and vacuolization and an increase in cell size of the Purkinje cells and suggesting that the short PR interval reflected an enhancement of conduction caused by the deposition of glycogen [31]. The electrophysiological finding that the atrium-His interval was shortened and the His-ventricular interval was normal, while enlarged cells filled with glycogen were found in all parts of the conduction system including the bundle of His, challenges this hypothesis. Another theory was proposed by Arad et al. [32], who studied a mouse model with a human PRKAG2 mutation, a disease that leads to glycogen accumulation in the cytoplasm of cardiomyocytes. They observed that the annulus fibrosis was disrupted by glycogen-filled cardiomyocytes, allowing atrioventricular activation by bypassing the AV node. This disruption might also explain the short PR interval and the WPW pattern, and the fact that patients were prone to developing SVTs or severe bradycardia.

Various publications report that arrhythmias, including fatal arrhythmia such as SVT and ventricular fibrillation (VF), may occur in patients with classic-infantile Pompe disease [9,28,33,34]. Three of our patients developed spontaneous periods of SVTs, which required medical intervention. These findings may relate to the observed WPW pattern. While our patients with recurrent SVTs were already severely affected at start of therapy, we cannot rule out that patients who respond well may also develop SVTs or other rhythm disturbances. We therefore advise regular monitoring of all patients receiving long-term ERT.

5. Limitations of the study

This study has several limitations. Due to the rarity and severity of the disease, research in Pompe disease is restricted to cohort studies with relatively small sample sizes.

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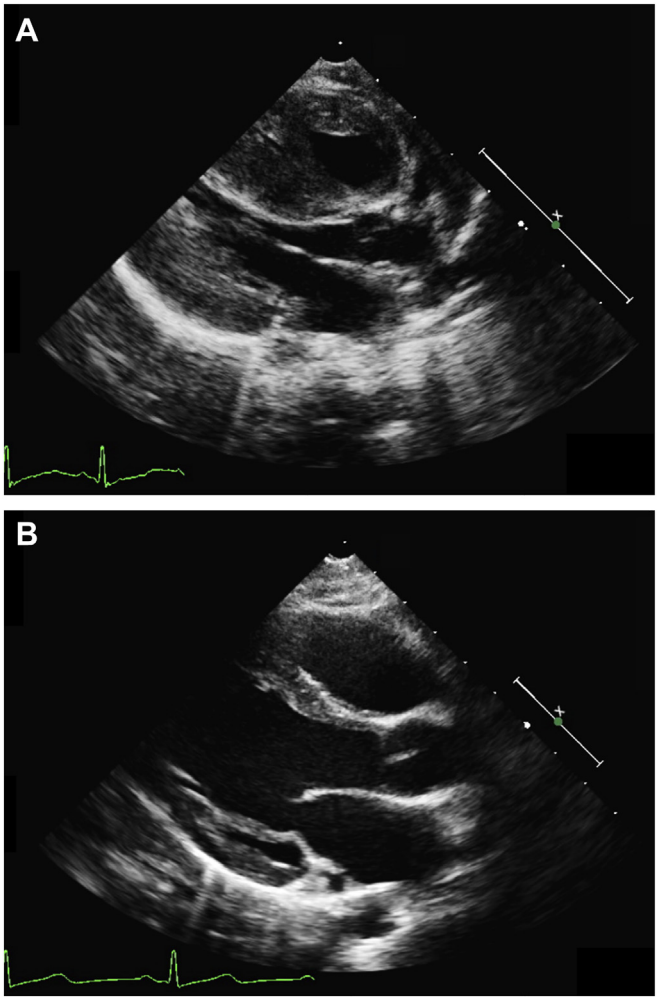

Fig. 2. Echocardiographic parasternal long axis view of patient 9. Echocardiographic parasternal long axis view of patient 9 at A) baseline and B) after 5 years of treatment. Note the major difference in both septal and posterior wall thickness.

In addition, increasing insight into the treatment of Pompe disease has led to adaptations in dosage regimens specifically because of skeletal muscle weakness. With respect to cardiac hypertrophy we observed a good response in all patients in our group regardless of the dose. This does not rule out that a higher dose may have had additional benefit in some patients. For several reasons some patients did not receive ERT, this may have influenced our data in part, it should be noted however that patients included in the study and treated with ERT represented the entire spectrum of disease severity of classic infantile Pompe disease. Because PWTDI was not yet available at the start of the study, our follow-up of diastolic function is limited and should be interpreted with caution.

6. Conclusion

This study shows that ERT has a significant effect on cardiac dimensions, which was maintained for almost 14 years. During the first weeks of treatment, before it starts to decline and eventually reaches normal values, LVMI may continue to increase. The time to normalization differs between patients: in some patients LVMI remained slightly elevated or showed a secondary increase. Two patients died, but not because of cardiac failure. In most patients, the effect decrease in LVMI was reflected in reductions of LV voltages and the disappearance of repolarization disturbances. Patients remained at risk of rhythm disturbances. At study end, 57% of patients had a short PR interval, 43% had a WPW pattern and 21% had SVTs, indicating that regulatory cardiac monitoring of patients remains warranted.

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Conflict of interest

AvdP and JvdH have provided consulting services for various industries in the field of Pompe disease under an agreement between these industries and Erasmus MC, Rotterdam, the Netherlands. LR has, in the past, received a speaker's grant and traveling fee from Shire and Genzyme. The other authors declare that they have no conflict of interest.

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Table 3
Pulsed Doppler and Pulsed-wave Tissue Doppler velocities at final assessment.

	Patients			Controls[a]			P[b]
	n	Median	Range	n	Median	Range	
Age (years)	10	5.0	1.0–14.0	14	5.7	1.7–7.5	.9
Pulsed Doppler velocities							
Mitral valve E velocity (cm/s)	10	98.8	74.8–127.8	14	100.4	78.8–120.9	1.0
Mitral valve A velocity (cm/s)	10	58.2	31.8–81.1	14	54.9	36.5–67.1	.3
Mitral valve E/A ratio	10	1.7	1.0–4.0	14	1.8	1.4–3.1	.2
Pulsed-wave tissue Doppler velocities							
Mitral valve lateral E' velocity (cm/s)	10	14.2	7.9–17.9	13	18.7	16.5–24.0	***.00***
Mitral valve lateral A' velocity (cm/s)	10	5.5	3.2–7.0	13	5.3	3.8–12.5	.7
Mitral valve E/E' ratio	10	6.9	5.3–11.5	13	5.2	3.9–6.6	***.01***
Tricuspid valve lateral E' velocity (cm/s)	8	12.7	10.7–19.9	13	12.9	10.6–15.2	.9
Tricuspid valve lateral A' velocity (cm/s)	9	9.7	3.6–13.4	13	6.8	4.9–9.8	.02

Statistically significant values are marked in bold/italics.
[a] Institutional reference values.
[b] Wilcoxon rank singed test.

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