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Effect of enzyme replacement therapy with alglucosidase alfa (Myozyme®) in 12 patients with advanced late-onset Pompe disease

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Abbreviations: GAA, acid alpha-glycosidase; ERT, enzyme replacement therapy; FVC, forced vital capacity; MIP, maximum inspiratory pressure; MEP, maximum expiratory pressure; MFM, Motor Measure Function scale.

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ABSTRACT

Background: The efficacy of enzyme replacement therapy (ERT) in patients at an advanced stage of Pompe disease has only been addressed in a few studies. Our objective was to assess the long term effects of ERT in a cohort of patients with severe Pompe disease.
Methods: We identified patients from the French Pompe Registry with severe respiratory failure and permanent wheelchair use (assisted walk for a few meters was allowed) when starting ERT. Patients' medical records were collected and reviewed and respiratory and motor functions, before ERT initiation and upon last evaluation were compared.
Results: Twelve patients (7 males) were identified. Median age at symptom onset was 24 years [IQR = 15.5; 36.0]. At baseline ventilation was invasive in 11 patients and noninvasive in one, with a median ventilation time of 24 h [IQR = 21.88; 24.00] (min 20; max 24). ERT was initiated at a median age of 52.5 years [IQR = 35.75; 66.50]. Median treatment duration was 55 months [IQR = 39.5; 81.0]. During observational period no adverse reaction to ERT was recorded, five patients (41.67%) died, three decreased their ventilation time by 30, 60 and 90 min and two increased their assisted walking distance, by 80 and 20 m.
Conclusion: Some patients at a very advanced stage of Pompe disease may show a mild benefit from ERT, in terms of increased time of autonomous ventilation and of enlarged distance in assisted walk. ERT can be initiated in these patients in order to retain their current level of independence and ability to perform daily life activities.

1. Introduction

Pompe disease is a rare recessive metabolic disorder caused by deficiency of the lysosomal enzyme acid alpha-glycosidase (GAA). The late onset form of the disease has a variable age of onset and is characterized by a spectrum of symptoms dominated by a slowly progressive myopathy and respiratory muscle involvement [1,2]. To date, one randomized placebo-control study [3] and several other reports [4–7] showed improvement in walking distance and stabilisation of respiratory function in late-onset Pompe disease under enzyme replacement therapy (ERT) with recombinant human GAA (rhGAA, Myozyme®), at least during the first two years of treatment [8–11]. However, the efficacy of ERT in patients at an advanced stage of the disease, confined in a wheelchair and ventilator dependent, has not been proven in a randomized trial [12], and this issue has been only addressed in a few studies of severely affected patients, mainly focusing on respiratory function [13–15]. Moreover, these studies assessed the benefit of ERT over a short period of time, generally not exceeding two years. Therefore, the objective of this study was to assess the long term effects of ERT in a cohort of patients with severe, very advanced, Pompe disease.

2. Materials and methods

Since 2004, a nationwide registry on Pompe disease was established in France (French Pompe Registry); all patients diagnosed with Pompe disease who signed a specific informed consent were included. Among the patients included in the French Pompe Registry, we identified all patients that were severely affected when starting the enzyme replacement therapy. Inclusion criteria were: (i) severe respiratory failure requiring ventilatory support for >12 h/day; and (ii) permanent wheelchair use (assisted walk for a few meters was allowed). All patients were treated with intravenous infusions of alglucosidase alfa (Genzyme

Table 1
Demographic characteristics of patients.

	Sex/age at last evaluation	Age of symptoms onset	Age at diagnosis	Age at loss of ambulation	Age at ventilation/type	Age at ERT initiation	ERT duration (months)	Anti-rhGAA antibodies (peak)	Anti-rhGAA antibodies (last evaluation)	Mutation 1	Mutation 2
1	F/38	16	18	25	25/invasive	29	110	1:51,200	0	c.482_483del	c.482_483del
2	M/71[a]	46	46	66	47/invasive	66	54	1:51,200	1:6400	c.-32-13T>G	c.1293_1326+57del
3	M/69[a]	28	30	58	28/invasive	68	11	1:1600	1:1600	c.-32-13T>G	c.525delT
4	F/57	20	48	42	32/invasive	50	87	1:25,600	1:6400	c.-32-13T>G	c.2041-1G>A
5	M/42[a]	14	17	33	19/invasive	41	11	1:25,600	1:25,600	c.1551+1G>A	c.1551+1G>A
6	M/68[a]	36	45	54	52/invasive	63	56	1:51,200	1:200	c.-32-13T>G	c.655G>A
7	F/27	3	3	11	11/invasive	18	114	1:102,400	1:3200	c.1933G>A	c.2584G>A
8	F/60	36	43	51	53/invasive	55	63	1:12,800	1:6400	c.-32-13T>G	c.655G>A
9	M/74	40	45	50	67/invasive	70	43	1:409,600	1:204,800	p.Arg725Trp	c.2481+102_2646+31del
10	F/40[a]	20	22	28	22/invasive	38	29	0	0	n.a.[b]	n.a.[b]
11	M/32	6	11	11	16/non-invasive	26	80	1:3200	1:800	n.a.[c]	n.a.[c]
12	M/61	35	50	48	35/invasive	56	49	1:1600	1:1600	c.-32-13T>G	c.525delT

n.a.: not available.
[a] Deceased patient.
[b] Acid maltase activity in muscle homogenate (U/mg of protein) = 0.
[c] Acid maltase activity in blood lymphocytes (μkat/kg) = 0.5 (5.2–15.6).