

Effect of enzyme replacement therapy in late onset Pompe disease: open pilot study of 48 weeks follow-up

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Abstract Late-onset Pompe disease (LOPD) is an autosomal recessive disorder caused by deficiency of the enzyme acid glucosidase alfa (GAA). Recently, enzyme replacement therapy (ERT) using recombinant human GAA (rhGAA) became clinically available, and is expected to modify the clinical course in LOPD of various stages. In this study, we evaluated the efficacy and adverse events of ERT for 48 weeks in Korean LOPD patients. Five Korean LOPD patients were included in the study. At baseline, clinical and laboratory features, including muscular and pulmonary function, were assessed, and rhGAA was infused every 2 weeks. Then, patients were examined at every 12-week interval for evaluation of changes in motor and pulmonary function for 48 weeks along with adverse reactions to ERT. The muscular and pulmonary function of the patients varied depending on the baseline condition of the patient after 48 weeks of ERT. However, the overall function of the patients showed stabilization of the disease rather than the improvement seen in infantile-onset Pompe

disease. This is the first clinical study on ERT of Korean LOPD patients. Results of our study showed stabilization of muscular and pulmonary function in LOPD patients for 48 weeks with a favorable prognosis for patients who received early diagnosis and ambulatory patients. One of our patients developed a serious anaphylactic reaction, which necessitated the cessation of further ERT. Therefore, our study shows that early diagnosis and ERT are important in preventing further deterioration of the disease.

Keywords Late-onset Pompe disease · Korean · Enzyme replacement therapy · Acid glucosidase alfa · Adverse event · Anaphylaxis

Introduction

Pompe disease (PD) is an autosomal recessive lysosomal storage disorder caused by deficiency of the enzyme acid glucosidase alfa (GAA). Accumulation of lysosomal glycogen causes muscle damage that leads to cellular dysfunction and structural disorganization, especially in cardiac and skeletal muscles. The prevalence of PD ranges from 1:14,000 to 1:300,000 depending on geographic region and ethnicity [1].

While infantile onset Pompe disease (IOPD) is always associated with almost complete deficiency of GAA enzyme activity (less than 1 % of normal), LOPD is associated with reduced enzyme activities ranging from 1 to 40 % of normal, and the retained enzyme activities are closely related to the age of onset in patients with LOPD [2]. Clinically, LOPD typically presents with progressive myopathy, predominantly affecting thigh and axial muscles sometimes with an elevated creatine kinase (CK) level. Another predominant feature of LOPD is the early

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development of respiratory failure as a result of diaphragmatic involvement, and 30–40 % of patients develop respiratory failure requiring artificial ventilation before they become wheelchair-bound. In addition, musculoskeletal deformities such as rigid spine syndrome, scapular winging, and scoliosis are also frequently present [3–5].

With the introduction of enzyme replacement therapy (ERT) using recombinant human GAA (rhGAA), many reports have described beneficial effects such as improvement of muscular and respiratory function in LOPD. However, a recent systematic review has suggested an improvement and/or stabilization in at least two-thirds of patients treated by ERT [5]. In Korea, the use of rhGAA in treatment of LOPD was approved by the Ministry of Food and Drug Safety and became available for clinical use in 2012, and most patients are now being treated. The aim of this study was to evaluate the clinical course of Korean patients with LOPD undergoing ERT using rhGAA for 48 weeks in a single center. No previous study regarding the impact of ERT on the clinical course of LOPD among Korean ethnic groups has been reported; therefore, our study would provide a useful reference for clinicians involved in treatment and care of patients with LOPD, particularly in Korea.

Materials and methods

Patients

Five Korean LOPD patients (two males and three females) were included in the study with written informed consent. This study was reviewed and approved by the Institutional Review Board of Pusan National University Yangsan Hospital. Patients enrolled in this study were initially diagnosed at three different hospitals (Pusan National University Yangsan Hospital, Pusan National University Hospital, and Gangnam Severance Hospital) from 1997 to 2011, but all of them had received their first ERT in Pusan National University Yangsan Hospital since 2012. The diagnosis of LOPD was made by reduced GAA enzyme level by enzyme assay using blood or muscle sample, and was confirmed by detection of mutation in each allele of GAA. Three patients enrolled in this study were previously reported [6].

The clinical and familial history was obtained from the patients and their family members. All patients gave informed written consent for DNA analysis at the time of diagnosis. Four of them underwent an open muscle biopsy, and all showed multiple vacuoles in their muscle fibers, which showed intensive staining by periodic acid-Schiff and acid phosphatase stains.

Methods

All patients were evaluated at baseline and every 12 weeks for 48 weeks. The functional outcome after ERT was monitored by different muscular and pulmonary function tests. Muscular function was evaluated by Medical Research Council (MRC) sum score and 6 min walk test (6 MWT). MRC sum score was calculated by summation of MRC scores of six muscle groups (maximum score is 60) [7], including shoulder abduction, elbow flexion, extension of the wrist, hip flexion, extension of the knee, and dorsal flexion of the foot on both sides. These muscle groups can be easily tested against gravity with the patient in sitting posture and/or lying down. This examination was performed by a single experienced neurologist to ensure inter-rater reliability. 6 MWT was performed and the results were measured as described [8]. Testing was conducted and monitored by a well-trained nurse at all times.

Pulmonary function test was evaluated by checking the percentage of the predicted forced vital capacity (%FVC) and forced expiratory volume in one second (%FEV1) in upright position. Pulmonary function test was performed at baseline and every 12 weeks.

At every visit for ERT (2-week interval), patients were asked to report any adverse reactions during or between infusions of rhGAA. To evaluate the patient's medical condition and to monitor the possible side effects of ERT, laboratory tests including complete blood count, liver/kidney function tests, serum creatine kinase (CK), serum glucose, and electrolytes were performed at baseline and every 12 weeks. The electrocardiogram and chest roentgenogram were also acquired at baseline and every 12 weeks. In all patients, echocardiography and spine roentgenography were performed at baseline before ERT.

ERT using rhGAA (Myozyme[®], Genzyme) was started from 2012, and 20 mg/kg of rhGAA was administered by intravenous infusion every other week according to the instructions provided by the pharmaceutical company.

Results

Baseline characteristics

The baseline characteristics and features of the patients are shown in Table 1. Five LOPD patients (two males and three females), with a mean age at onset of 19.6 years (range 6–36 years of age), were included. In all patients, first symptom at onset was running or climbing difficulties caused by proximal leg weakness. The mean time lag to development of respiratory failure after the diagnosis was 12.8 years.

Table 1 Baseline clinical and characteristic features of five patients included in the study

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age of onset	6 years	36 years	35 years	17 years	15 years
Affected family member	Elder brother	Younger brother and younger sister (patient 3)	Elder sister (patient 2) and elder brother	None	None
Initial clinical symptom	Proximal limb weakness	Proximal limb weakness	Proximal limb weakness	Proximal limb weakness	Proximal limb weakness
Age of wheelchair use	Age 22	Not in use	Not in use	Not in use	Not in use
Age of first ventilator use	Age 21	Age 50	Age 49	No symptom	Age 25
respiratory symptoms					
Ambulatory status at baseline	Wheelchair bound	Independent walking	Independent walking	Independent walking	Independent walking
Ventilator use at baseline	Continuous NIV usage	Intermittent NIV usage	Intermittent NIV usage	No ventilatory support	Intermittent NIV usage
Serum CK level at presentation (IU/L)	1,500	463	164	774	1,788
GAA activity at diagnosis ^a	0.3 (ref. 7.3 ± 2.2)	0.3 (ref. 0.5–1.5)	0.36 (ref. 0.5–1.5)	0.17 (ref. 0.5–1.5)	0.42 (ref. 0.5–1.5)
Echocardiogram	MVP	Normal	Normal	Normal	Normal
Electromyographic findings	Myopathic MUPs myotonic discharges	Myopathic MUPs pseudomyotonia	Myopathic MUPs pseudomyotonia	Myopathic MUPs myotonic discharges	Myopathic MUPs myotonic discharges
Muscle pathology	Vacuolar myopathy	Vacuolar myopathy	Not done	Vacuolar myopathy	Vacuolar myopathy
Scoliosis	Yes	Yes	Yes	Yes	No
Genotype	c.1857C>G+c.2015G>A	c.1316T>A+c.2238G>C	c.1316T>A+c.2238G>C	c.546G>T+c.2171C>A	c.1309C>T+c.1316T>A

NIV non-invasive ventilation, CK creatine kinase, GAA acid alpha glucosidase, MVP mitral valve prolapse, MUPs motor unit potentials

^a GAA activities were measured from peripheral leucocytes except for patient 1 in whom it was measured from biopsied skeletal muscle tissue

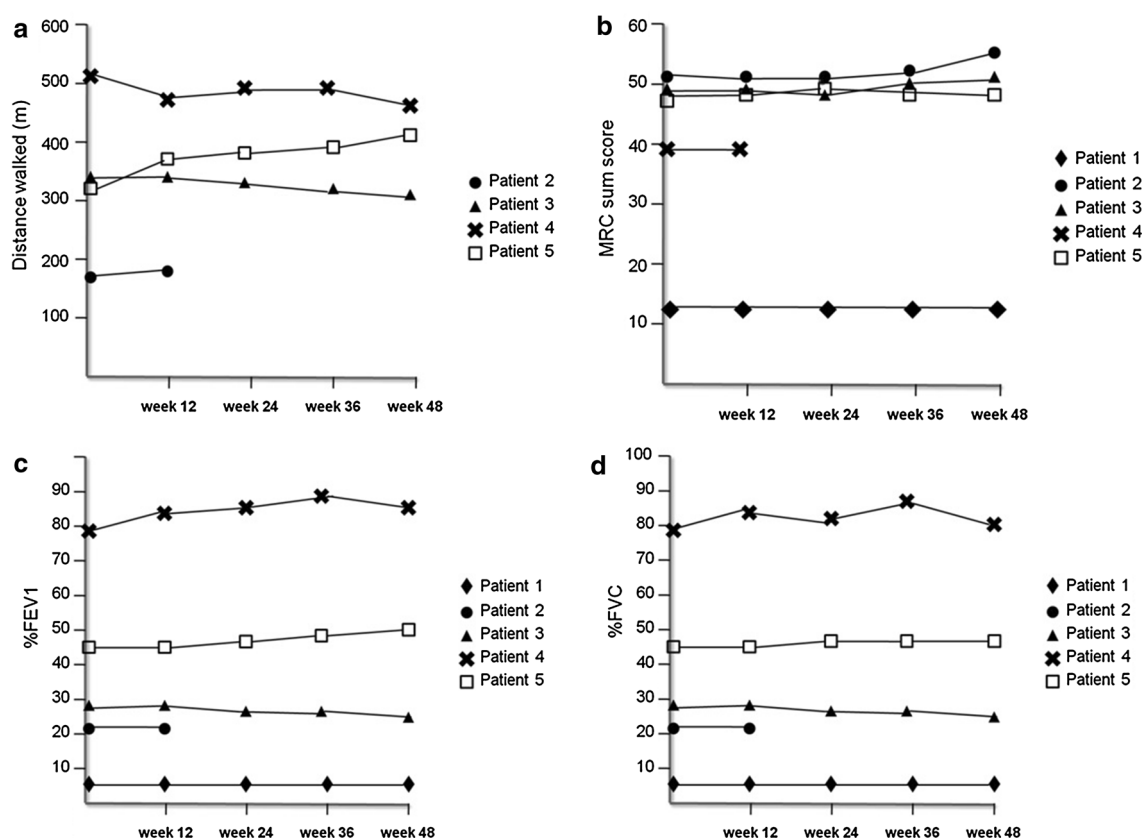


Fig. 1 Serial changes in motor and respiratory function of the patients during the observation period. Results of **a** serial 6-min walk test, **b** Medical Research Council sum score, **c** % predicted value of

forced expiratory volume at one second, and **d** % predicted value of forced vital capacity

The serum CK levels of five patients ranged from 164 to 1,788 IU (mean value 1,048 IU) and were elevated at baseline in four patients, except for one (patient 3 in Table 1). Needle electromyography was performed on at least one distal and two proximal muscles in both upper and lower extremity. Paraspinal muscles were not specifically tested, however, the needle electromyography showed myotonic or complex repetitive discharges in all patients [9].

None of our patients had cardiac abnormalities except for one patient who had mitral valve prolapse (patient 1). Scoliosis was observed in four of our patients, all of whom were under ventilator support.

At baseline, four patients were under ventilator support, except for one (patient 4) whose %FVC at baseline was 79 with waddling gait, but she was able to walk without aid. Patient 1 had become dependent on artificial ventilation 11 years before and was under non-invasive ventilation (NIV) for 24 h per day. He had also been wheelchair-bound for 10 years. Patients 2 and 3 are sisters of the same family. Patient 2 developed respiratory difficulty and aspiration pneumonia, and was tracheostomized 11 years before. At the start of the study, she was using ventilator

support for more than 12 h per day. Although she was able to walk for a short distance of less than 100 m, she needed to take frequent rests. Patient 3 developed respiratory failure 4 years before and had started using NIV since then. She was using NIV less than 12 h per day (only during sleep) and was able to walk more than 500 m with waddling gait. Patient 5 developed progressive respiratory difficulty, which led to the usage of NIV 2 years before. He was using NIV around 12 h per day at the start of the study. He was able to walk a long distance without significant difficulties, but with waddling gait.

Changes in motor and pulmonary function of the patients

The changes in muscular and pulmonary function of the LOPD patients following ERT are shown in Fig. 1. The MRC sum scores remained unchanged, except for patient 4, who showed a slight improvement between 36 and 48 weeks. However, this patient showed a slight decline in 6 MWT at the same time.

The results of 6 MWT varied depending on the patient. Although patient 5 showed progressive improvement in the

distance walked, patients 3 and 4 showed a slight decrement or remained unchanged throughout the study. As patient 1 was wheelchair-bound and patient 2 was unable to continue with the ERT, we were not able to observe the serial changes in the muscular function of these patients.

Pulmonary function was evaluated by %FVC and %FEV1. In patients 4 and 5, who had milder symptoms and longer duration of the disease compared to the other patients, both parameters showed a tendency of stabilization or mild improvement. Patient 3, who showed a slight decline in 6 MWT, also showed a progressive decline in pulmonary function. Pulmonary function of patient 1, which was already extremely compromised before ERT, remained unchanged throughout the study. In patient 2, for whom ERT was soon discontinued because of a severe adverse reaction, the effect of ERT on pulmonary function could not be optimally evaluated. However, none of the patients showed any change in terms of respiratory patterns or duration of artificial ventilation usage.

Thus, it appears that the effect of ERT on muscular and pulmonary function varied depending on the patient during the period of 48 weeks. Only one (patient 5) showed a tendency of mild improvement in both muscular and pulmonary function, another (patient 4) showed stabilization, and the other (patient 3) showed a tendency of progressive decline. The effect of ERT could not be optimally evaluated in patients 1 and 2.

Adverse reaction

During ERT, we encountered adverse reactions from two patients. In patient 3, no significant problem was noted until her second ERT, when she complained of chest tightness and mild dyspnea associated with lowered blood pressure during infusion of rhGAA. At her third ERT, rhGAA infusion was started with a reduced rate (13 mg/kg/h) with full monitoring of the patient's blood pressure, electrocardiogram, and venous oxygen saturation. At an infusion rate below 63 mg/kg/h, the patient did not show significant side reaction except for mild tachycardia up to 90/min. However, whenever escalation of the infusion rate to 88 mg/kg/h was attempted, she developed chest tightness and hypotension. At the fourth ERT, the patient developed dyspnea, tachycardia, and lowered blood pressure even at the start of infusion with a reduced infusion rate (13 mg/kg/h), and ERT was stopped. At the fifth ERT, the patient was premedicated with intravenous injection of 5 mg of dexamethasone and 4 mg of pheniramine maleate before ERT. However, the patient developed dyspnea, tachycardia, and severe hypotension shortly after the start of infusion. Infusion of rhGAA was stopped immediately and 1 mg of epinephrine was injected intravenously, along with inhalation of a ventolin nebulizer. The patient showed

progressive recovery after treatment, and no further ERT was attempted.

Patient 5 developed an urticaria associated with itching sensation after the sixth ERT. She was seen by a dermatologist and treated with oral corticosteroids and antihistamine. Although her symptoms showed a tendency of progressive improvement with repeated ERT, she still has a mild itching sensation for a few days following ERT. Fortunately, her symptom is easily controlled by oral antihistamines.

Discussion

With the recent introduction of ERT as a disease modifying therapy, the significance of early diagnosis of LOPD has become more important. However, the diagnosis of LOPD is frequently delayed because of its similarities in clinical features and laboratory findings with other neuromuscular diseases, and by the lack of awareness of clinicians [10]. Our cohort also showed a significant delay in diagnosis from symptom onset (average 10.9 years), as previously reported [11].

The baseline clinical features of our patients showed no significant cardiac abnormality, except for patient 1, who showed mitral valve prolapse on the echocardiogram. This finding is in accordance with the previous literatures that reported only a small number of LOPD patients are associated with cardiac abnormality, while cardiomegaly and heart failure are the most prominent features of IOPD [12, 13]. On the other hand, it is remarkable that four out of five patients in our cohort had scoliosis, while a recent multi-center Pompe registry reported a lower prevalence rate of scoliosis (24.8 %) in LOPD [14].

Previous studies suggested a favorable effect of ERT in patients with LOPD. A large placebo-controlled double blind clinical trial of rhGAA in patients with LOPD (LOTS) showed stabilization of the muscular and respiratory function over 78 weeks [15]. A systematic review on ERT outcomes in LOPD patients also suggested a stabilization or improvement in more than two-thirds of patients [5]. Another recent paper on LOTS extension study reported a strong tendency of stabilization in LOPD patients undergoing ERT over a period of 104 weeks, although it also suggested that some patients might show slow deterioration after achievement of maximal clinical improvement after approximately 1–2 years of ERT [16].

This is an uncontrolled study involving a relatively small number of enrolled patients with quite variable clinical severity, and a short observation period; therefore, it is clearly limited to clarifying the effect of ERT on LOPD. However, the results of our study provide a few suggestions on the therapeutic efficacy of ERT in LOPD.

Previous observations suggested that, up to a third of patients with LOPD do not show improvement and show progressive deterioration despite ERT, but the factors determining the responsiveness are still unclear [5]. One of the most important factors determining the responsiveness might be the disease severity of the individual patients. Because the disease severity is closely related to the duration of disease, progressive build-up of the autophagic process, leading to irreversible muscle fiber damage could significantly limit the efficacy of ERT [17, 18]. While two of our patients (patients 4 and 5) with relatively shorter duration of the disease (11 and 15 years, respectively) showed stabilization or slight improvement, patient 2, who had a disease duration of 20 years, showed a tendency of decline. Another point is in regard to the question of whether or not to treat the patient with extremely advanced stage of disease. Patient 1, who had disease duration of 27 years, was already in the extreme stage of the disease at the start of ERT. He had been wheelchair-bound for 10 years and dependent on NIV for 9 years with marked muscle atrophy. He was completely dependent on others in all of his daily activities and could not tolerate more than 2 min without NIV in sitting position. His baseline MRC sum score was 12 and %FVC was 7, and showed no sign of improvement. Despite continuous ERT, he was recently tracheostomized because of intolerable aerophagia. Thus, in this particular patient with far advanced stage of the disease, it is obvious that ERT provided no benefit at all. Although one paper describing a favorable response to ERT in advanced stage of LOPD has been reported [19], none of the patients were as severely affected as patient 1 of our study. Considering the cost and time consumed for ERT, a treatment guidelines for advanced stage of LOPD will be needed.

As observed in our study and also in previous studies, ERT provides a stabilization of the disease in LOPD rather than a dramatic improvement, which is usually achieved in IOPD. The limited effect of ERT in LOPD can be explained, at least in part, by the advanced pathological changes in LOPD patients. Recent studies showed that the prominent autophagic process observed in skeletal muscle fibers of LOPD patients causes dysfunction of the endocytic process and formation of numerous autophagic vacuoles, which in turn leads to mistargeting of infused rhGAA, eventually leading to irreversible muscle fiber damage [20].

ERT can be associated with many adverse events. According to clinical trials and post-marketing safety studies, allergic or anaphylactic reactions occur in 14 % of LOPD patients receiving ERT [21]. Although most of them are mild and transient, as in our patient 5, serious anaphylactic reaction may occur in some patients, as observed in our patient 2. The main cause of allergic or anaphylactic

reactions remains elusive, although there is evidence that it may be related to formation of IgG antibody against rhGAA [22–24]. However, the anti-GAA IgG antibody was negative in our patient 2 who experienced a severe adverse event. This may suggest the formation of other anti-idiotypic antibodies against rhGAA or antibodies against the additives included in the drug.

Conclusions

The therapeutic effect of ERT appears to be limited, probably because of the abnormally enhanced autophagic process in skeletal muscles of LOPD. Thus, earlier diagnosis and prompt implementation of ERT is very important to prevention of further deterioration in LOPD.

Although our study is limited by the small number of patients and relatively short duration of observation, this is the first Korean study to report on the clinical experience of ERT on LOPD patients achieving stabilization of the disease.

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