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Research Article

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Effects of Enzyme Replacement Therapy on the Respiratory and Motor Functions Among Patients with Late-Onset Pompe Disease for Long-Term

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Abstract

Background: Pompe is a congenital metabolic disorder and muscles involvement that is the most common presentation of it. The late-onset Pompe disease (LOPD) is a type of Pompe according to the age of clinical presentation. In LOPD, the muscles of the trunk and proximal lower extremity have not normal function, and the repertory failure can be happening for these patients. Enzyme replacement therapy (ERT) is a new method for treatment of these patients, but the efficacy and safety of this method are challenging for long-term so that in this pilot study efficacy and safety were evaluated for two years.

Methods: In this prospective study, the patients with LOPD included this study, and they received rhGAA every two weeks for two years. In this period the motor and respiratory function of them were evaluated, and the serology makers such as CPK and LDH were measured every six months. This study was registered as a trial with ID: IRCT2017111120981N2 and approved by the ethics committee of Tehran medical sciences branch, Islamic Azad University.

Results: Two adults who were suffering LOPD for 17 and 12 years were investigated in this study. Both of them did not show any side event also the motor function of them had better, and one of them can be walked for more distance, on the other hand, the respiratory function was slightly improved and the CPK levels dramatically reduced.

Conclusion: The results of this study showed the ERT was safe and effective for treatment or control the disease activity of patients with LOPD and help them, but this method is so expensive special for long- term. This is a small pilot study and needs more investigation for efficacy and safety of ERT or other available methods.

Keywords: Enzyme replacement therapy; Late-onset pompe disease; Motor functions; CPK levels

Introduction

Glycogen storage disease type II as known as Pompe is a rare autosomal recessive and metabolic disease caused by the deficiency of acid alpha-glucosidase (GAA). In this disease, glycogen doesn't convert to glucose in lysosomes so that glycogen increasing in lysosomes of cell especially in muscle cells then this intercalary of glycogen make irreversible damage on muscles, so that heart, skeletal and respiratory muscles are weakening [1-3]. The incidence of this disease depending on race and geographic region and it is varying from 1:33,000 to 300,000 also estimated the prevalence of it is 1: 40,000 [4]. The effect of the disorder has the range of clinical signs and symptoms such as hypotonia, cardiomyopathy, repository failure, and death [5,6].

According to the age of clinical presentation of this disease categorized into infantile and late-onset phenotypes. Infantile Pompe shows the clinical features in the first two years of life and the most common presentation of this form associate with cardiorespiratory and muscle hypotonia. The late-onset Pompe disease (LOPD) has the different of clinical presentation. Usually, the muscles of the trunk and proximal lower extremity are weakening so that the patients of LOPD have the disorder in walking, climbing stairs, and other gross motor activity [5,7]. In advanced stages of LOPD upper extremity and respiratory muscles have been involvement and the respiratory failure is the cause of death in these patients [8-10].

Variables	Patient 1	Patient 2
Age, y	31	31
Sex	Female	Male
Age of onset, y	11	14
Age of diagnosis, y	31	24
Initial clinical symptom	Proximal limb weakness, orthopnea	Proximal limb weakness
Walking aids/ wheelchair	No	No
Ventilator assistance	No	No

Table1: Baseline characteristics and features of the patients.

In recent years, enzyme replacement therapy (ERT) was presented to the treatment of Pompe. This method improved the progression of the two forms of Pompe, and it was approved by the US and the European Union, but there are few studies about safety and efficacy of ERT [11-15]. Also, there is no any evidence that showed the effect of ERT among Iranian LOPD patients. Hence, the aim of this study was the evaluation of effects of ERT on respiratory and motor functions in the Iranian patients with LOPD.

Variables	Patient 1					Patient 2				
	Baseline	At 6 months	At 12 months	At 18 months	At 24 months	Bassline	At 6 months	At 12 months	At 18 months	At 24 months
CPK (IU/L)	1040	876	899	687	717	1505	1592	1512	1623	1911
LDH (IU/L)	1225	860	660	808	685	870	914	904	791	831
Aldolase (U/L)	0.5	9.3	8.4	13.1	12	12	10.1	15.2	8	16

Table 2: Some routine laboratory parameters.

Materials and Methods

Two Iranian LOPD patients (one male and one female) who referred to neurology clinic of Buali- Hospital, a teaching center affiliated with Tehran medical sciences branch, Islamic Azad University, Tehran, Iran, were included in the study. The diagnosis of LOPD was made by reduced GAA enzyme level by an enzyme assay using blood or muscle sample and was confirmed by detection of mutation in each allele of GAA. This study was reviewed and approved by the ethics committee of Tehran medical sciences branch, Islamic Azad University (Code: IR.IAU.TMU.REC.1394.70) and written informed consent was taken prior to enrollment. Also, this study was registered at Iranian Registry of Clinical Trials (ID: IRCT2017111120981N2).

Treatment protocol

ERT using rhGAA (Myozyme, Genzyme, USA) was applied for a 24 months period, and 20 mg/kg of rhGAA was administered by intravenous infusion every other week according to the instructions provided by the pharmaceutical company. 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-phospho-kinase (CPK), serum aldolase, lactate dehydrogenase (LDH), and electrolytes were performed at baseline and every six months. In all patients, electrocardiogram (ECG) and echocardiography were carried out at baseline, 6, 11, 18 and 24 months after ERT.

Motor function evaluation

Manual muscle testing (MMT): A neurologist assessed muscle strength of upper and lower limb muscles. Moreover, the grades were assigned using the Medical Research Council (MRC) scores grading scale (50=full strengths; 0=no muscle activity) [15]. All the examination was done at the baseline, 6, 12, 18 and 24 months.

The 6-minute walk test (6-MWT): The 6-MWT was performed in accordance with American Thoracic Society Guidelines [16], and the distance walked in 6 minutes was recorded in meters. As the same time of MMT, the 6-MWT were evaluated for our patients.

Respiratory function test: Predicted forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) in the upright and supine position were measured by spirometric test at the baseline, 6, 12, 18 and 24 months.

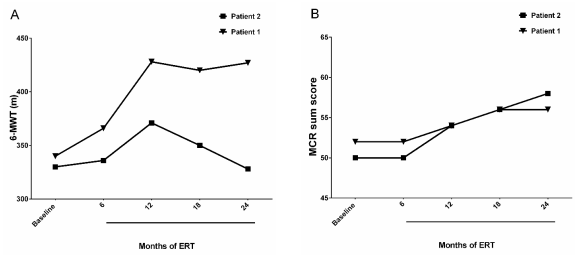

Figure 1: The muscular function of patients after 24 months ERT. A: Relative change in combined isokinetic muscle strength including major muscle groups at the shoulder, elbow, wrist, hip, knee, and ankle based MCR sum score; B: 6-MWT.

Results

Baseline characteristics

As the show in the Table 1, in the patient 1 (female) and 2 (male), the first symptom at onset was running or climbing difficulties caused by proximal leg weakness. Also, the patient 1 suffered from occasional orthopnea. Also, none of the patients needs to wheelchair and/or ventilator use. The age of onset disease in patient 1 and 2 was 11 and 14 years, respectively (Table1).

Safety assessments

All the patients were followed by research visits for safety and efficacy and contacted by telephone to inquire regarding the incidence of any adverse effects during the study period. Over the 24-months follow-up, patient's symptoms remained stable, and none of them did not require any walking device or mechanical ventilation. Also, ECG and echocardiography revealed no any abnormalities in our patients.

Muscular function

Regarding Figure 1a, although 6-MWT performance was lower than expected for healthy people [17], it improved by 87 m (patient 1) during ERT. Indeed, patient 1 showed progressive improvement distance walked, however; patients 2 showed a slight decrement or remained unchanged throughout the study. Also, the MCR score showed the ERT leads to relative improvement in patients compared to

the baseline (Figure 1b). In other words, ERT attenuates the reduction of muscular function during 24 months treatment.

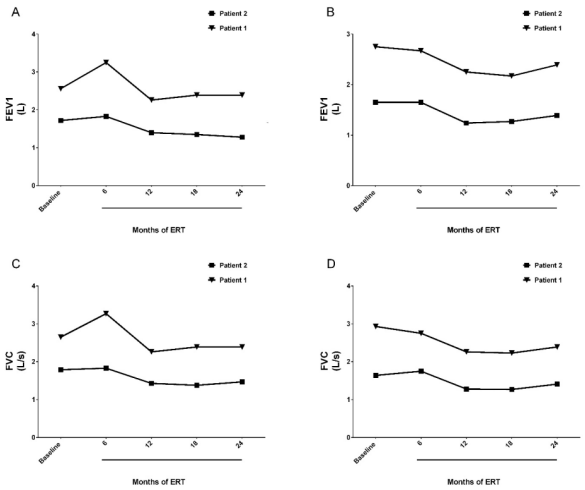

Figure 2: The respiratory function of the patients evaluated by spirometry. Predicted the value of forced expiratory volume at one second (FEV1) in upright (A) and supine (B) position; Predicted value of forced vital capacity (FVC) in upright (C) and supine (D) position.

Respiratory function

As the show in Figure 2A and B, FEV1changes in both upright and supine position showed a tendency of stabilization or mild decline after 24 months. In the same way, FCV in upright position at the baseline was 2.65 L (patient 1) and 1.79 L (patient 2) that it showed slight decrement to 2.39 L and 1.47 L in patient 1 and 2 at 24 months, respectively (Figure 2c). The favorable change of the FVC was noted for the first 6 months, but it was mildly decreased during remained ERT sessions. However, none of the patients showed any change in terms of respiratory patterns or duration of artificial ventilation usage.

Routine laboratory results

The CPK levels of patient 1 decreased during treatment (from 1040 to 717, Table 2), however; in the patient 2 it was markedly elevated. Other biochemical parameters measured for safety reasons did not change during the treatment.

Discussions

In this prospective pilot study, the efficacy and safety of ERT in patients with LOPD were evaluated for two years and the clinical finding or adverse effect of ERT monitoring in this period. Also, the evaluation of the patients did not stop anyway in follow-up. LOPD is the rare disease so that few patients were included in this study also there are not many studies about ERT in patients with LOPD in the literature on the other side almost of studies investigated a small size of patients, and the evidence for efficacy and safety of ERT is not strong. Based on our results, like several previously published papers, none of the patients have any adverse effect following ERT. On the other hand, some studies showed some adverse effects of ERT such as facial erythema, flu-like symptoms, bronchospasm, and tongue edema [11,12, 18-27]. Also, some life-threatening adverse effects such as fatal tracheal hemorrhage, emphysema, pneumothorax were reported in few studies [19,22,24].

The LOPD disorders the muscles function so that the determination of changes in motor performance is the main outcome measurement efficacy of ERT. In last trials, the 6-MWT of most patients were improved, and some of them can walk for more distance after ERT, and in someone, the progress of the disease was stopped. However, there is not the clear correlation between duration of ERT and improvement of disease activity [12,18, 22-28]. In our study, patients were under ERT for two years, and the results were showed the ERT has an effective role in improving 6-MWT. Also, the respiratory function was stable, and it was without any significant changes in this investigation, but in some studies with more patients approximately half of patients had better and others had stable [12,19,21, 23-26]. The CPK levels as a useful marker for diagnosis of LOPD and them are decreased when it response to treatment. In most of the studies the same of this paper, the CPK levels were reduced due to ERT, but in some studies, the CPK levels did not have changes [21,29,30]. The sample size is the most important limitation of this investigation also the ERT is very expensive and follow-up the patients is so difficult. The more researchers need to the evaluation of the efficacy of ERT to help patients with LOPD.

Conclusion

The ERT is a safe way to treatment of patients with LOPD, and also it seems this method is improving muscles function in this patients and help them to back a normal life, but ERT is so expensive and uses this method for a long duration not possible for most patients. On the other hand, the researchers about this treatment are limited, and it is needed to do multicenter clinical trials researchers with a large population.

Conflicts of Interest

The authors declared no conflicts of interest.

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