Original Article

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Cost-effectiveness analysis of enzyme replacement therapy (ERT) for treatment of infantile-onset Pompe disease (IOPD) in the Iranian pharmaceutical market

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SUMMARY Infantile-onset Pompe disease (IOPD) or acid maltase deficiency is a rare metabolic disorder. It is caused by a deficiency in functioning of the enzyme acid alpha-glucosidase and leads to the accumulation of glycogen in the liver, heart, muscle, and other tissues. Myozyme is an effective drug, but it imposes a heavy financial burden on societies and healthcare systems. Therefore, this study was conducted to analyze the cost-effectiveness of Myozyme compared to conventional therapy for the treatment of IOPD. PubMed, Scopus, Web of Science, and Cochrane library databases were searched on December 2018 to identify the effectiveness of Myozyme versus conventional therapy. Then, a cost-effectiveness and a cost utility study were conducted in patients suffering from IOPD. In this cost effectiveness and cost utility analysis, Markov and decision tree models were used for modeling. Model parameters were obtained from international data, and the perspective of the payer was considered. Every cycle was one year; the model was run for 22 cycles. TreeAge pro 2011 was used for analysis. Finally, one-way and probabilistic sensitivity analyses were performed. Two papers were included and 39 patients were evaluated as the treatment group in both studies. Results revealed the effectiveness of Myozyme. Results also revealed a wide range of adverse reactions. Enzyme replacement therapy (ERT) resulted in 4.21038 quality-adjusted life years (QALY) per $381,852. The incremental cost per QALY was $96,809 and the incremental cost per life years gained (LYG) was 74,429 over a 22-year time horizon. Sensitivity analysis indicated the robustness of the results. Myozyme is effective for IOPD and could increase the life expectancy of patients significantly. However, since the calculated incremental cost per QALY was 17 times higher than the GDP per capita of Iran, Myozyme is not cost effective in Iran.

Keywords Myozyme, enzyme replacement therapy, Pompe disease, cost-effectiveness, Iran

1. Introduction

Pompe disease is an inherited metabolic disorder that is also known as acid-maltase deficiency or glycogen storage disease type 2 (GSD type 2) (*1,2*). The disease is caused by a mutation in the acid alpha-glucosidase gene, which is necessary for degradation of glycogen (*3*). A deficiency of acid-maltase causes the accumulation of glycogen in the lysosomes of the heart, liver, skeletal muscle, and other tissues (*4,5*) and it has destructive effects on muscles (*6*). This stored glycogen first affects skeletal and cardiac muscles (*7*) and then causes feeding abnormalities, cardiac hypertrophy, weakness, respiratory insufficiency, hypotonia, and eventually death (*8*). The incidence of this orphan disease is 1 in 40,000 live births (*9*).

There are two forms of Pompe disease, infantile-onset Pompe disease (IOPD), and late-onset Pompe disease (LOPD) (*10*). IOPD is more severe and appears in the first months of life (*11*). The early symptoms are cardiomegaly, muscle weakness, hepatomegaly, hypotonia, and death in the first year of life (*11*). LOPD (*i.e.* juvenile- and adult-onset) can occur as early as the age of 1 year to as late as the sixth decade of life (*3,11,12*). The age of the onset of symptoms depends on the severity of the deficiency in acid-maltase. The

more severe the deficiency, the faster the symptoms appear (*13*).

Enzyme replacement therapy (ERT) with human acid alpha-glucosidase (Myozyme) has been available since 2006 for both IOPD and LOPD (*14*). Studies have indicated that Myozyme can improve the survival rate, respiratory efficiency, and cardiac and motor function (*13*). However the improvements depend entirely on the age and onset of drug therapy (*8*); the sooner the treatment is started, the outcomes are better. Nonetheless, there are two main problems with Myozyme. First it requires high dosages and it has a low level of effectiveness (*15*). Second, the cost of Myozyme is substantial and imposes a substantial burden on healthcare systems and societies. Two studies have conducted economic evaluations in developed countries (*12,16*) but no study has economically evaluated ERT in a developing country like Iran. Therefore, the aim of this study was to perform a cost-utility analysis of Myozyme versus conventional therapy to treat IOPD in Iran.

2. Materials and Methods

This study was approved by the Tehran University of Medical Sciences ethics committee (approval No. IR.TUMS.SPH.REC.1396.2902).

2.1. Study design

A cost-utility analysis was conducted for ERT in patients with classic IOPD. Currently, ERT is the only treatment available for patients with IOPD. There is no medical comparator for treatment of IOPD and thus conventional therapy was considered as a comparator of Myozyme in this study. Conventional therapy consists of ventilatory care, nutrition, and care in the pediatric intensive care unit (PICU). Quality-adjusted life years (QALY) was the main outcome in the current study. The local cost of treatment was converted to US dollars based on the exchange rate in 2017. A lifetime time horizon was used to model costs and QALYs for different alternatives.

2.2. Measurement of effectiveness

A systematic search of PubMed, Scopus, Web of Science, and Cochrane library databases was conducted prior to December 2018 to identify the best available published evidence on the effectiveness of ERT for IOPD. The details of this systematic review are presented elsewhere (*17*).

2.3. Assessing costs and cost-effectiveness

The perspective of the payer for healthcare was considered when calculating the cost of medication and relevant care. Only direct medical costs were measured when calculating the cost of treatment. In addition to the cost of Myozyme, the cost of injection and the treatment of adverse reactions were calculated in the ERT arm.

The price of Myozyme was obtained from the Iran Food and Drug Administration (IFDA), which is the only organization in charge of approving medicines in Iran. The cost of Myozyme was calculated based on the Myozyme dosage, which was 20 mg/Kg every two weeks. In order to calculate the cost of Myozyme, the average weight of patients was first estimated. As each Myozyme vial contains 50 mg of acid alpha-glucosidase, the number of vials per person was calculated based on the following formula (*18*):

$$\text{Number of vials} = (\text{Average weight} * 20)/50$$

In the no ERT arm, the cost of care in the PICU, as the only cost driver, was estimated based on the number of days hospitalized in the PICU and the per diem price of care in the PICU. The average number of days hospitalized in the PICU and the per diem price of care in the PICU were obtained from the Iranian Book of Medical Fees.

The incremental cost-effectiveness ratio (ICER) was estimated using the following formula (*19*):

$$\text{ICER} = (\text{Cost of ERT} - \text{Cost of no ERT})/(\text{QALYs gained with ERT} - \text{QALYs gained with no ERT})$$

2.4. Modeling and Model parameters

A combination of a decision tree and a Markov model was used to estimate total costs and QALYs in the ERT and no ERT arms by the end of the lives of patients with IOPD. The Markov model was based on the stages of Pompe disease. Although a published model evaluated the costs and effects of ERT in treating Pompe disease (*12*), that model was modified and improved based on the actual condition of patients. That is, a stage of "Alive, symptomatic" was added as the first stage because when patients with IOPD receive ERT they are alive and also have symptoms of the disease. Figure 1 shows all phases of both ERT treatment and conventional therapy. Every Markov cycle was considered to be one year. The model was run using TreeAge pro 2011.

Model parameters including health status, transition probabilities, and utility scores were obtained from literature (Table 1). The utility scores for different health statuses were obtained from two studies (*12,16*). In a study by Castro *et al.*, the utility score was 0.70 for ERT and 0.388 for no ERT (*12*). However, a study by Kanters *et al.* reported that the ERT group had an average utility score of 0.62 (*16*). The utility scores of Castro *et al.* were used in the current model and the utility scores of Kanters *et al.* were used for sensitivity analysis. Discount rates were not used because both costs and effects were incurred during the same period (*20,21*).

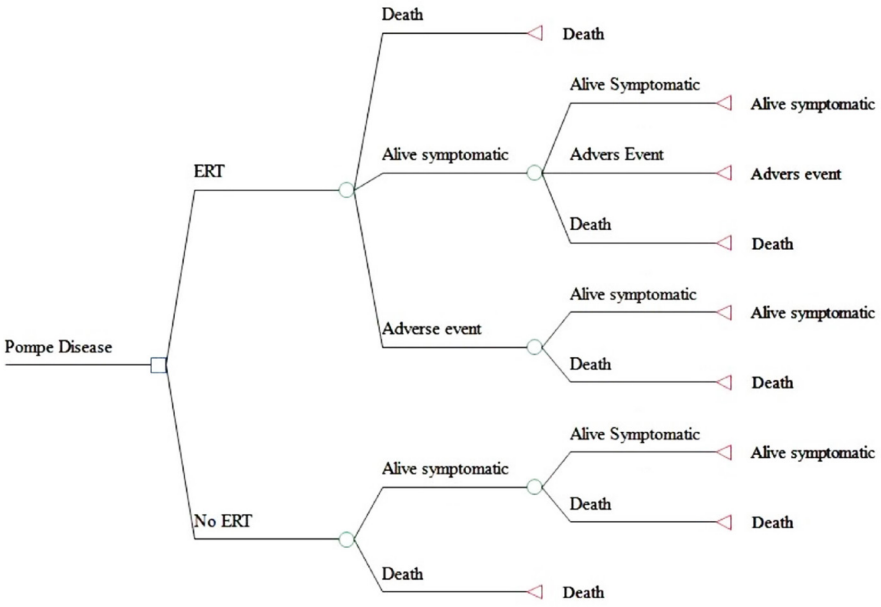

Figure 1. Model designed to analyze treatment of infantile-onset Pompe disease. This figure shows the phases of ERT treatment and Conventional therapy. ERT, enzyme replacement therapy.

Table 1. Transition probabilities for enzyme replacement therapy (ERT) and conventional therapy

Pompe disease	Stages		Probabilities	*Ref.*
	From	To		
ERT	Alive, symptomatic	Alive, symptomatic	0.33	(*12*)
	Alive, symptomatic	Adverse event	0.56	(*29,30*)
	Alive, symptomatic	Death	0.11	(*12*)
	Adverse event	Death	0.259	(*12*)
	Adverse event	Alive, symptomatic	0.741	(*12*)
Conventional therapy	Alive, symptomatic	Alive, symptomatic	0.08	(*12*)
	Alive, symptomatic	Death	0.92	(*12*)

2.5. Model assumptions

The model was designed based on the following assumptions:

i) All patients receiving conventional therapy (no ERT) die at the age of six months (*22*).

ii) The utility score for the treatment group was 0.7 for all stages (*12*). That is, the adverse events of ERT were negligible and ignored in the current model.

iii) After the first symptoms of the disease develop, patients are normally hospitalized due to the severity of the disease (*2*).

iv) In the ERT arm, a fixed rate survival of 75% was used for each cycle (*12*).

v) Patients suffering from classic IOPD do not have a normal growth rate due to feeding problems (*22*). Nonetheless, a 5% weight gain was assumed for the patients' growth rate based on expert opinions.

2.6. Sensitivity analysis

In order to assess the robustness of the model, a one-way deterministic sensitivity analysis and a probabilistic sensitivity analysis were performed. The costs and utility scores were included in the sensitivity analysis.

3. Results

3.1. Effectiveness

The results of a systematic review indicated that only two studies met the inclusion criteria for analysis. Research questions included the population of interest (IOPD), intervention (ERT), comparator (no ERT), and outcome (survival or QALY). The details of the results of that systematic review are presented elsewhere (*17*).

3.2. The cost of Myozyme

In order to calculate the cost of Myozyme, the average weight of patients was first estimated. The average weight of the patients was determined from 12 patient profiles from the IFDA in 2018; patients included eight females and four males. The weight of patients varied from 5 to 15 Kg, with an average of 7.29 Kg. The acceptable dose of Myozyme was 20 mg/Kg every other

week. The number of vials per person was calculated based on the following formula (*18*):

Number of vials = (Average weight * 20)/50

The number of vials consumed per patient was 2.96-3.0 every two weeks and 6 vials per month. Therefore, 72 vials of Myozyme were consumed in the first year of treatment (the first Markov cycle) at a cost of $48,964.3. However, considering the cost of all medications, the total cost of the first cycle was $49,456.94 (Table 2). According to the model's assumption, the weight of patients will increase 5% each year. Thus, the cost of Myozyme was increased by 5% for the following years (cycles).

3.3. Other costs

The results of a literature review indicated that the probability of an adverse event occurring was 56% and that the probability of anaphylactic shock in particular occurring was 1%. The risk of death due to anaphylactic shock has been reported to be 50% (*12*). When patients suffer adverse events, they receive hydrocortisone, hydroxyzine, and an antihistamine. The respective cost of these drugs was $12.24, $13.6, and $13.6 (Table 2).

3.4. Cost-effectiveness

Figure 2 shows the results of modelling. The results of the 22-year model verified that no ERT resulted in 1.087 years (0.422 QALYs) while ERT resulted in 6.015 life years (4.210 QALYs) on average. Based on the calculated costs, the use of ERT increased the cost by $366,777 and increased the life expectancy of patients by 4.93 years (Table 3). That is, no ERT resulted in $15,075 per 0.422 QALY and ERT resulted in $381,852 per 4.210 QALYs. Therefore, the ICER for ERT was $74,852 per LYG (life year gained) and $96,809 per QALY gained (Table 4).

3.5. Deterministic sensitivity analysis

In order to assess the robustness of the results, the effect of the costs on ICER was first examined. The total cost of ERT was reduced by 5, 10, and 20% to ascertain how these changes would affect the results of ICER. Although these changes reduced the value of the ICER to $6,364, the current results were robust up to a 22%

Table 2. The cost of the first cycle

	Drug	Number	Cost ($)
1	Hydrocortisone	24	12.24
2	Hydroxyzine	24	13.6
3	Antihistamine	24	13.6
4	Administration	24	453.2
5	Myozyme	72	48,964.3

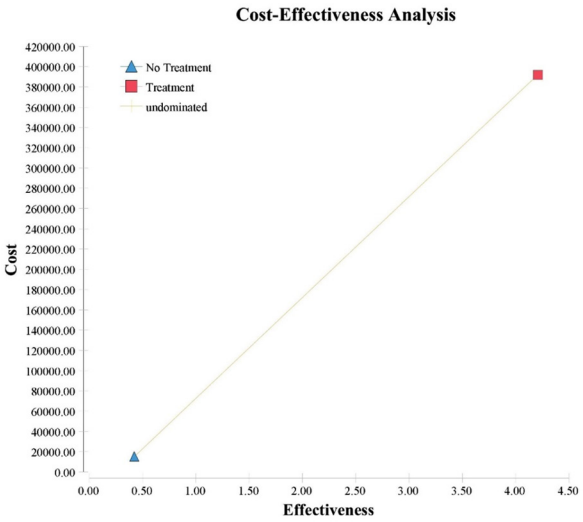

Figure 2. Cost effectiveness graph of treatment in comparison to no treatment. Although ERT resulted in more QALY in comparison to conventional therapy, it was not a cost-effective option due to its high cost. ERT, enzyme replacement therapy; QALY, quality-adjusted life year.

Table 3. Cost-utility analysis results

	Mean cost	QALY	ACER	Incremental cost	Incremental QALY	ICER
No ERT	15,075	0.42174	35,745	366,777	3.78864	96,809
ERT	381,852	4.21038	90,693			

ACER, average cost-effectiveness ratio; ERT, enzyme replacement therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 4. Cost-effectiveness results

	Mean cost	LYG	ACER	Incremental LYG	ICER
No ERT	15,075	1.08696	13,869	4.92787	74,429
ERT	381,852	6.01482	63,485		

ACER, average cost-effectiveness ratio; ERT, enzyme replacement therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained.

reduction in the cost of ERT.

The minimum and maximum value of utilities, which ranged from 0.24 to 0.82, were also used to assess the impact of these changes on the value of the ICER. These changes modified the value of the ICER from $358,945 to $81,318 per QALY, respectively, but none of the scenarios were cost-effective.

3.6. Probabilistic sensitivity analysis

Gamma and a normal distribution were used in order to determine the distribution of the costs and utilities (*23*). Table 5 shows the range of variables used for sensitivity analysis. A Monte-Carlo simulation was run for 1000 trials. The results of probabilistic sensitivity analysis indicated that 100% of the ERT trials were not cost-effective (Figure 3).

4. Discussion

The aim of this study was to assess the cost-effectiveness of ERT (Myozyme) in comparison to conventional therapy in the treatment of IOPD. The model indicated that ERT could increase the life expectancy of patients by 6.01 years, which is equal to 4.21 QALYs based on utility scores.

The past performance of the IFDA indicated that the IFDA has been using a cost-effectiveness threshold equal to the GDP per capita. This is compatible with World Health Organization (WHO) recommendation for developing countries (*24,25*). A report by the Central Bank of Iran indicated that the per capita GDP of Iran was $5,757 in 2018 (*26*). The current results indicated that the ICER was $96,809, which was 16.82 times the GDP per capita of Iran in 2018 (*24,25*). Uncertainties regarding parameters in the current study were addressed through probabilistic sensitivity analysis. This analysis indicated that the ICER was higher than the recommended threshold value in all cases (100 %) (Figure 3) and, therefore, confirmed the robustness of the current findings.

The results of the current study are consistent with the results of studies in many other countries (*12,16*). A cost-effectiveness analysis of ERT compared to no treatment was performed by Castro *et al.* (*12*). The ICER per QALY was £234.308 and £109.991 for England as a

Table 5. Range of variables for sensitivity analysis

	Variable	Base case	Range	Distribution
Utility	Treatment	0.7	0.5-0.9	Normal
	Conventional therapy	0.388	0.2- 0.576	Normal
Cost ($)	Adverse event	89,787	116,794-62,780	Gamma
	Alive, symptomatic	89,654	116,661-62,647	Gamma
	Conventional therapy	402	0-1,017	Gamma

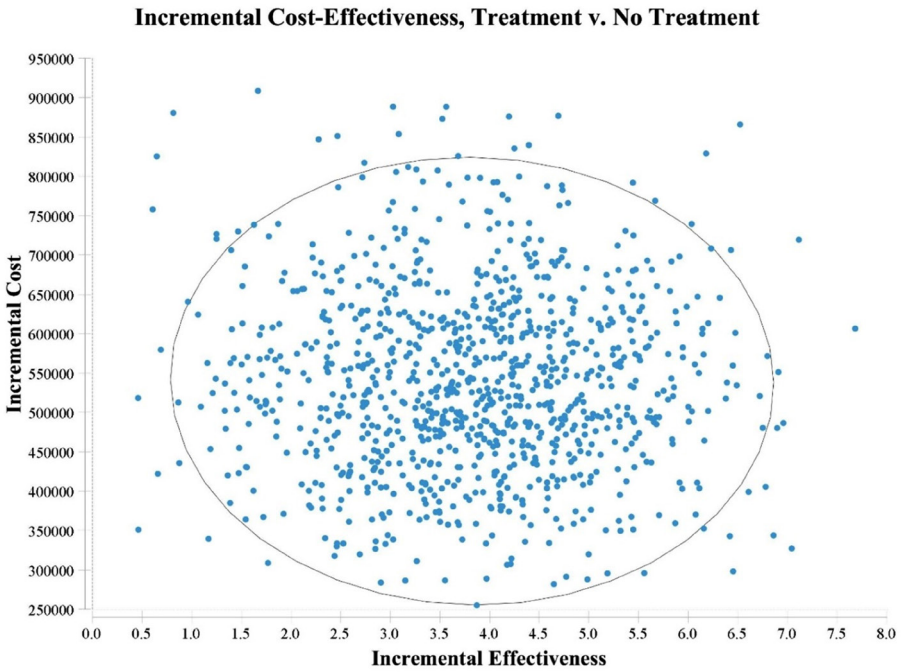

Figure 3. Incremental cost effectiveness scatterplot of ERT versus no ERT. A PSA graph shows that all trials were far from the threshold and that all trials were not cost-effective. ERT, enzyme replacement therapy.

high-income country and Colombia as a middle-income country, respectively. According to the National Institute of Health and Clinical Excellence (NICE), the cost-effectiveness threshold for England was £30,000 (*27*) and that for Columbia was equal to $10,615 USD (*28*). Therefore, the utilization of ERT was not a cost-effective option for treatment of IOPD in either country.

The manufacturer's price for ERT and its monopoly in England and Columbia had a great impact on the final results of previous studies, but in the current study the cost of Myozyme played a large role in the final results of cost-effectiveness analysis. In modelling of England, no treatment resulted in £149.187 per 0.16 QALY and ERT resulted in £1,337.12 per 5.23 QALYs. In modelling of Colombia, no ERT resulted in £49.676 per 0.16 QALY while ERT resulted in £607.329 and 5.23 QALYs. The main difference is due to the price variation in various countries. The difference between those costs might be associated with the different healthcare systems and health insurance. The costs of both ERT and no ERT differ from the costs in Iran. The QALY gained according to the study by Castro *et al.* differed from the findings of the current study. This could be attributed to both different sources of international data and different modeling. For example, the current study used data on an economic evaluation conducted by Castro *et al.* (*12*) and two quasi experimental studies (*29,30*).

The findings of this study are consistent with those of a study by Kanters *et al.* (*16*) who used a patient simulation model to assess the cost-effectiveness of ERT versus supportive therapy. Kanters *et al.* found that life expectancy in patients receiving ERT was 14 years and the incremental cost was £7 million. Likewise, the incremental QALY was 6.8 and thus the incremental cost per QALY gained was £1 million. One of the main causes of variations in the results of different studies could be attributed to the study's perspective. The perspective of society is recommended, but many studies adopt the perspective of the payer (*31*). The perspective of society is a wider one (*32*) and includes all cost and outcomes. The perspective of society was considered in the study by Kanters *et al.*, while the current study considered the perspective of the payer to economically evaluate care; indirect costs like lost productivity and transportation costs were not included in the analysis, so the overall costs may be underestimated. Therefore, different perspectives may result in different costs and outcomes.

This study has several limitations worth mentioning. First, there were few patients. Second, international data over a brief time period were used. And finally, a cost analysis was not performed due to the small number of patients.

In conclusion, Myozyme is effective for IOPD and could increase the life expectancy of patients significantly. Nonetheless, it imposes a heavy burden on the healthcare system and society. The calculated ICER was 17 times higher than per capita GDP of Iran in 2018. These findings suggest that the use of Myozyme for IOPD is not cost-effective in Iran.

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