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Original Article (Pages: 14988-14996)

Medication Cost of Enzyme Replacement Therapy for Mucopolysaccharidoses in Iran

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Abstract

Background: The mucopolysaccharidoses (MPSs) are a group of rare inherited metabolic disorders caused by lack or insufficient activity of lysosomal enzymes. Although no cure has been identified until now, Enzyme Replacement Therapy (ERT) can reduce symptoms of some types of MPSs. providing ERT for patients is a challenge for health systems due to expensivity of the medicines. In this study, we aimed to examine the average annual cost of medicines used for ERT per patient in Iran healthcare system.

Methods: Data on patients were consolidated from different sources of Iran Food and Drug Administration's (IFDA). After collecting data, patients with MPS I, IV, and VI were categorized into five age groups (5-years interval). The number of vials distributed monthly was used for the estimation of the annual medication cost for each patient and compared against the Gross Domestic Product (GDP) per capita.

Results: Data on 185 patients with MPS was analyzed. The frequency of patients with MPS I, IV, and VI was 27, 40.6, and 32.4%, respectively. The average annual expenditure on ERT medications per patient was estimated at 206.07 United States Dollars. The average annual cost has shown to be about 38 times the current GDP per capita of the country.

Conclusions: The medication cost of ERT for MPS disease is substantial to the health system. To ensure the best clinical effectiveness and efficient use of financial resources, it is highly recommended that healthcare policymakers use an evidence-based clinical practice guideline and improve the data quality in rare diseases registry.

Key Words: Cost of Care, Healthcare System Expenditure, Enzyme replacement therapy, Iran, MPS.

*Please cite this article as: Nabizadeh A, Kheirandish M, GHaribnaseri Z, Oloomi N, Azizi F, Moradi N. Medication Cost of Enzyme Replacement Therapy for Mucopolysaccharidoses in Iran. Int J Pediatr 2021; 9 (12):14988-14996. DOI: **10.22038/IJP.2021.57147.4483**

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Received date: Apr.18,2021; Accepted date:May.20,2021

1- INTRODUCTION

The mucopolysaccharidoses (MPSs) are a group of metabolic disorders caused by an inherent deficiency in the activity of specific lysosomal hydrolase enzymes that involve in the degradation of Glycosaminoglycans (GAGs) (1). Seven distinct types of MPS (type I, II, III, IV, VI, VII, and IX) have been recognized as caused by eleven identified enzyme defects (2). The clinical features associated with MPSs are varied depending on the type and severity of this disease. These include cardiac involvement, obstructive pulmonary disease, hearing loss, ophthalmic disorders, and musculoskeletal dysfunctions. The accumulation of GAGs and gangliosides are responsible for the associated symptoms and complications. These symptoms vary by severity of the disease based upon the type of mutation, age of onset, and the level of residual enzyme activity (3, 4).

Before two decades ago, the primary goal of treatment had been providing supportive care for MPSs patients. This was the case until Enzyme Replacement Therapy (ERT) received approval for treating the somatic symptoms in several types of MPS. Although ERT is not known as a cure for MPS, it is effective in improvement of health-related quality of life (5, 6). Other treatment strategies such as hematopoietic stem-cell transplantation (HSCT), substrate reduction therapy, and gene therapy are currently under investigation as treatment options in MPSs (7). At present, ERT has been approved for four types of MPSs (Laronidase: MPS I, Idursulfase: MPS II, Elosulfase-α: IVA, and Galsulfase: MPS VI). All except for Idursulfase have obtained market authorization in Iran. Furthermore, these medicines are fully subsidized as part of rare disease policies in Iran, making medical treatment available for patients with types I, IV, and VI of MPS.

Just like many orphan drugs, these medicines belong to a category often called Expensive Drugs for Rare Diseases (EDRD). Thus, although a limited number of patients are designated to receive these medicines, the overall economic burden is proportionally high, posing undeniable challenges for the health system.

Such supportive policies might come at a significant opportunity cost. For instance, in times of economic hardship, the financial resources allocated to rare diseases can decrease the government's capacity to reimburse great groups of patients with controllable conditions such as diabetes mellitus. Therefore, policymakers should think about both equity and efficiency in allocating the national health budget. One of the primary steps for making informed decisions is precise awareness of the cost magnitude of the alternatives being considered. The aim of this study was to analyze the cost of ERT for MPS I, IV, and VI patients.

2- METHODS

2-1. Study design and population

This was a retrospective study with a perspective on the healthcare system. MPS I, IV, and VI patients' records during October 2017- October 2018 were obtained from the two databases with routinely collected data.

2-2. Data Sources and Methods

Two administration databases were used to identify all registered patients suffering from MPS I, IV, and VI as well as the medicine consumption of those patients.

HAMI database: Iran Drug and Food Administration (IFDA) has established a registry system named HAMI for MPS patients since 2015. This system records patients' characteristics such as date of birth, gender, residential area, type of MPS, insurance coverage, and status of parental consanguinity.

Medicine consumption dataset: IFDA keeps track of the number of vials of medicines distributed to MPS patients.

Medicine prices were acquired from the latest update of prices on the IFDA website in September 2018. The currency exchange rate was retrieved from the official website of central bank of Iran (1 United States Dollars (USD) =42,000 IRR) (8).

International Monetary Fund database was used to obtain Gross Domestic Product (GDP) per capita for 2018 (5,491 USD) (9).

For data cleansing, several steps were performed. Firstly, two datasets were linked. Pooled datasets were checked for duplicated records and duplications were removed. Next, we considered the data collected from HAMI for cases in which different information had been designated for the same individuals. Finally, pooled datasets were searched for missing values. After detecting a random pattern of missing values, listwise deletion was used to deal with the problem. Data analysis was performed by Excel version 2016.

2-3. Cost calculation

In each type of MPS I, IV, and VI, the patients were categorized into five age groups (with 5-year intervals). The number of vials distributed monthly was used to estimate the annual medication cost for each patient.

In the next step, the average annual number of vials of ERT medications distributed to patients in each age category was determined. This was used to calculate the weighted average of per capita consumption for all three types of MPS patients.

In order to compare the estimated cost between countries, the medication cost was divided by the GDP per capita.

Ethical consideration

Since the big data on patients was consolidated from IFDA, the confidentiality of the information was maintained, and the patient's name did not appear in any results.

3- RESULTS

The frequency of patients with MPS I, IV, and VI were 27, 40.6, and 32.4%, respectively. The age of MPS patients in Iran ranges from 1 year to 28 years. The gender, average age, and the rate of consanguineous marriage among parents in each group of patients are presented in **table 1**. Medicine consumption for the five age groups is displayed in **Table 2**. Medicine expenditure for the age groups is shown in **Fig. 1**.

According to the annual consumption records, the average annual expenditure on ERT medications per patient was estimated at 207,185 USD. The result is depicted in **Fig. 2**.

The average annual cost has shown to be about 38 times higher than the current GDP per capita of the country. **Fig. 3** shows the annual cost-to-GDP ratio in three types of MPS.

Table-1: MPS patients' characteristics

Disease type	Gender		Total	Average age (years)(Mean ± SD)	Rate of parental consanguinity (percentage)
	Male	Female			
MPS I	28	22	50	6.97 ± 3.51	70
MPS IV	41	34	75	10 ± 4.94	84
MPS VI	27	33	60	8.16± 3.95	87

Table-2: Average annual consumption of ERT medicines per patient in different age groups

Age group(years)	MPS I	MPS IV	MPS VI
	NO. consumption (Mean ± SD)	NO Consumption (Mean ± SD)	NO consumption (Mean ± SD)
0 to 5	(18) 132± 50.75	(16) 282.75 ±73.47	(13) 112.61 ± 27.26
5 to 10	(26) 165.23± 61.13	(32) 305.5 ± 68.48	(32) 141.75 ± 33.60
10 to 15	(4) 192 ± 0	(17) 394.59 ± 100.98	(12) 196 ± 53.52
15 to 20	(2) 504 ± 216	(8) 367.25 ± 150.73	(2) 168 ± 24
>20	0	(2) 520 ± 104	(1) 192 ± 0
Age-weighted Average of medicine consumption	168.96	333.15	148

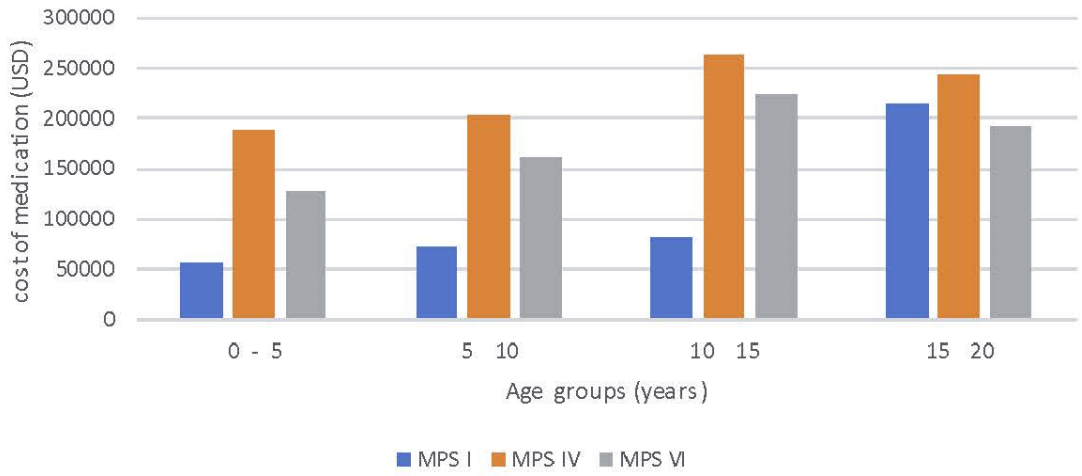

Fig. 1: Average annual medication cost in different age group in MPS for each patient.

4- DISCUSSION

This study aimed to estimate the annual cost of ERT medications of MPS patients in Iran from a health care perspective. The results showed that despite being a rare disease, the medication cost of ERT for MPSs disease is substantial to the healthcare system. The economic burden is even more significant in cases such as MPS IV where the annual cost of ERT is almost 60 times higher than the GDP per capita. This figure is strikingly higher than medication cost in more prevalent and controllable diseases such as diabetes mellitus with less than 0.02 times the GDP per capita (10). This is a challenge in organizing an equitable and efficient healthcare system (11).

Different countries use various strategies for managing MPS patients. A study comparing costs and HRQoL of MPS patients in Bulgaria, France, Germany, Hungary, Italy, Spain, and Sweden showed that Germany has the highest medication cost for MPS patients due to the higher unit costs of disease specific medicines

(€121,665 per patient). While France and Hungary had the lowest costs. This study showed that in children and adults, the main component of cost belonged to medication cost (12). This conclusion is consistent with the study of Davari et al. which estimated that 96.9% of the cost of treatment for MPS-I patients was related to medication (13). By comparing these two studies, it became apparent that cost components in European countries are significantly more than those in Iran. This suggests that MPS patients in Iran do not receive social support services, effective in improving the quality of life of the patients and their parents.

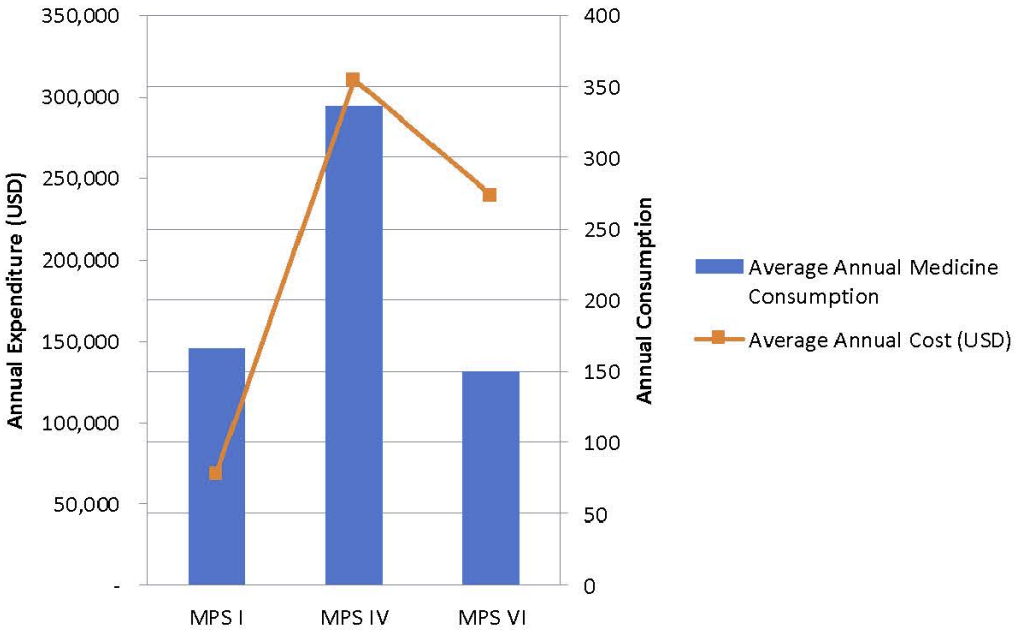

Fig. 2: The average annual medicine cinsumption and cost in MPS patients

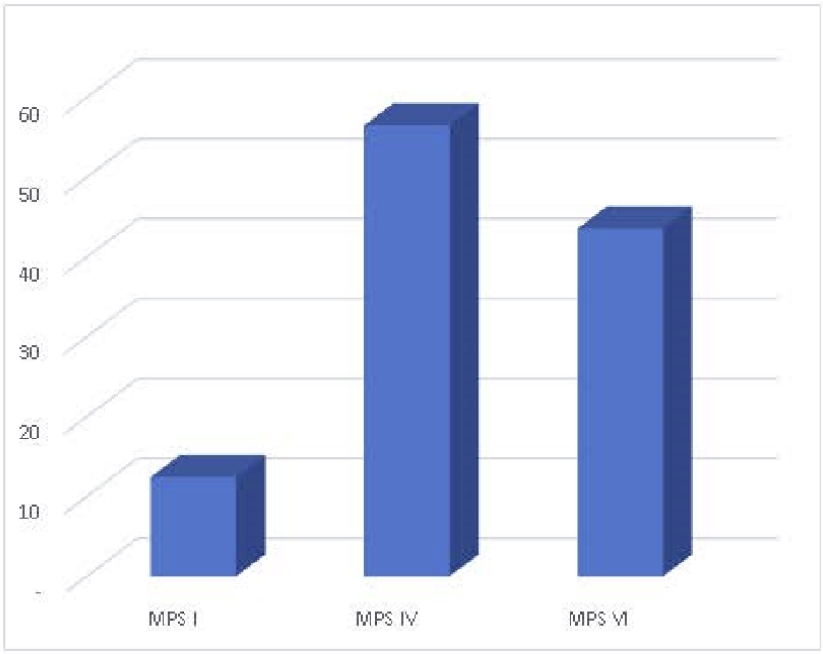

Fig. 3: The average annual cost-to-GDP ratio in MPS patients

The study of Wyatt consisted of a retrospective assessment of 68 patients with MPS-I, and 39 patients with MPS-II, recruited from several UK centers. Wyatt estimated the annual cost of laronidase to the National Health Service (NHS) and publicly funded social-care service to be £ 258,201 for an adult versus £139,563 for a child. A comparison between the cost drivers of MPS patients in Iran and the UK showed that the medication costs in UK with a unit cost of £444.7 are considerably higher than those in Iran (14). Nonetheless, it is important to note that comparing the net costs between the countries may cause misunderstanding and does not show the significance of the cost for each country. Therefore, to standardize the expenditures, it is better to express the costs based on the GDP per capita of the countries. Thus, while the average annual cost of MPS patients in Germany, as the highest cost per patient among European countries, was 5.7 times higher than their GDP per capita in 2012, it was 38 times higher than that in Iran in 2018 (12, 13)

The study performed by Fernando et al. showed that access to medicine for 195 patients with MPS I, II, and VI during 2006-2010 in Brazil has resulted in €57,112,763.76 government spending. During the mentioned years the medical cost for a MPS I and IV patient has been €100,348.9 and €311,535.6, which is equal to 10 and 31 times more than the GDP per capita. These costs are not reimbursed by the health system. Therefore, access to ERT medicine in Brazil is limited (15). Nevertheless, even though the annual cost of MPS I and VI patients in Iran is higher and equals to 12.5 and 44 times more than the GDP per capita, respectively, patients have full access to ERT medicines and the cost is fully covered by the health system. Although reimbursing these medicines is done based on humanitarian and ethical principles, it is necessary to consider the outcome of the therapy to ensure efficient use of resources. A local evidence-based clinical practice guideline could help the IFDA to improve the efficient use of financial recourses.

Results show a high rate of paternal consanguinity (over 80 percent) among MPS patients with the highest rate belonging to MPS VI. This finding is not the same as some other countries such as Brazil that have reported a 20.6 percent rate of paternal consanguinity among MPS patients. This could be due to cultural and societal differences and is of great importance in terms of choosing appropriate policies when dealing with MPS disease at a national level. Premarital health counseling and screening in couples especially those with a positive family history can have an impressive impact on the rate of children being born with MPSs. Furthermore, including MPSs in neonatal screening programs is strongly recommended. This has already started in some countries (16, 17) leading to improved treating results due to earlier detection of patients.

Going through databases to extract patients' records, it became obvious that there is a crucial need to improve the data registry for MPS patients. The review of the patient's profiles demonstrated that patients are registered based on the type of MSP and there are no subgroup classifications. Thus, even though treatment protocols for the different subgroups of MPSs vary significantly, all patients are registered in a single group and are treated equally. For instance, Hurler syndrome which is the most severe MPS I subtypes is characterized by the presence of neurological involvement (18, 19). On the other hand, many studies have shown that laronidase does not cross the blood-brain barrier, and thus has no medical indication in this subtype (20, 23). In both databases that we used, all patients with Hurler syndrome were registered in

MPS-I group, and received laronidase with no medical indication.

In addition, a noticeable share of data was detected as missing, both in the age segment and medical consumption. Out of 313 patient records, we found that 185 patient data was eligible for further analysis. Moreover, contradictory information had been recorded for unique patients in different databases. Therefore, it is recommended to improve the quality of the data registry to prevent such incidences.

Since all information about patients like the weight of patients and type of disease was not recorded, we couldn't perform statistical analysis to reveal the association between the characteristics of patients and incurred costs.

5- CONCLUSION

The average annual cost of treatment for MPS patients is as high as 38 times above the GDP per capita in Iran. The highest share of the cost belongs to MPS IV. This suggests that the IFDA should critically revise its policy and use an evidence-based clinical practice guideline to ensure the best clinical effectiveness and efficient use of financial resources.

Selecting appropriate strategies for reducing the birth of a child with MPS, could also support allocative efficiency of the limited resources effectively.

6- ACKNOWLEDGEMENTS

The authors would like to thank the IFDA staff, particularly Dr. Zolfaghar Taghaviyan, and Zahra Anbari who have helped us in collecting data from the organization database.

7- COMPETING INTERESTS

M. KH. and A. N. hold a position as director-general for assessment and control on prescribing and use of medicines and head of the department of Health Technology Assessment (HTA). None of the authors have any financial or other competing interests.

8- ABBREVIATIONS

ERT= Enzyme Replacement Therapy

GDP= Gross Domestic Product

MPSs= Mucopolysaccharidoses

USD= United States Dollars

GAGs= Glycosaminoglycan

HSCT= Hematopoietic Stem-Cell Transplantation

EDRD= Expensive Drugs for Rare Diseases

IFDA= Iran Food and Drug Administration

HRQoL= Health-Related Quality of Life

UK= United Kingdom

NHS= National Health Service

HTA= Health Technology Assessment

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