

Cost-utility of new film-coated tablet formulation of deferasirox vs deferoxamine among major beta-thalassemia patients in Iran

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Abstract

Objectives: Thalassemia is a hereditary disease, which caused economic burden in developing countries. This study evaluated the cost utility of new formulation of deferasirox (Jadenu) vs deferoxamine (Desferal) among B-Thalassemia-major patients from payer perspective in Iran.

Methods: An economic-evaluation through Markov model was performed. A systematic review was conducted in order to evaluate the clinical effectiveness of comparators. Because of chelating therapy is weight-dependent, patients were assumed to be 2 years-old at initiation in first and 18 years-old in second scenario, and model was estimated lifetime costs and utilities. Costs were calculated to the Iran healthcare system through payer perspective and measured effectiveness using quality-adjusted life years (QALYs). One-way sensitivity analysis and budget impact analysis was also employed.

Results: The 381 studies were retrieved from systematic searching through databases. After eliminating duplicate and irrelevant studies, 2 studies selected for evaluating the effectiveness. Jadenu was associated with an incremental cost-effectiveness ratio (ICER) of 1470.6 and 2544.7 US\$ vs Desferal in first and second scenario respectively. The estimated ICER for Jadenu compared to generic deferoxamine was 2837.0 and 6924.1 US\$ for first and second scenario respectively. For all scenarios Jadenu is presumed as cost-effective option based on calculated ICER which was lower than 1 gross domestic product per capita in Iran. Sensitivity analysis showed that different parameters except discount rate and indirect cost did not have impact on results. Based on budget impact analysis the estimated cost for patients using Desferal (based on the market share of brand) was 44,021,478 US\$ in 3 years vs 42,452,606 US\$ in replacing 33% of brand market share with Jadenu. This replacement corresponded to the cost saving of almost 1,568,872 US\$ for the payers in 3 years. The calculated cost of using generic deferoxamine in all patients was 68,948,392 US\$. The increase in the cost of using Jadenu for 10% of all patients in this scenario would be 934,427 US\$ (1.36%) US\$ at the first year.

Conclusions: Based on this analysis, film-coated deferasirox appeared to be cost-effective treatment in comparison with Desferal for managing child and adult chronic iron overload in B-thalassemia major patients of Iran.

Abbreviations: BTM = beta-thalassemia major, CC = cardiovascular complications, GDP = gross domestic product, ICER = incremental cost effectiveness ratio, IRR = Iranian Rial, QALYs = quality adjusted life years, RCT = randomize controlled trial, WCC = without cardiovascular complications.

Keywords: beta-thalassemia, cost-utility analysis, deferasirox, deferoxamine, economic evaluation

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1. Introduction

Beta-Thalassemia major (BTM) is the most commonly inherited hemolytic anemia that has the highest prevalence among blood disorders globally, especially in Asia.^[1,2] BTM leads to 50,000 to 100,000 deaths in children under 5 years of age in developing countries.^[3] Studies show that nearly 80% of live births with different forms of thalassaemia occur in low and middle income countries.^[4] Iran is one of the major centers for the prevalence of thalassemia.^[5] Despite the many efforts made to prevent the birth of newborns with BTM, there are currently more than 20,000 individuals registered in the country and each year new cases are added to this community. Statistics show that the overall prevalence of this disease in the provinces is between 3 and 100 case per 100 thousand individual.^[5,6]

Thalassemia management programs impose various direct and indirect costs to the community, including the cost of medication, blood transfusion, physicians appointment, and laboratory tests. Some interventions are fully covered by the government.^[7] Other expenses are provided by the patients or other institutions. Although these costs are not categorized as catastrophic cost, it is vital to propose cost regulatory programs as BTM is a chronic lifelong condition.

The Mainstay of treatment in severe cases is blood transfusion which may lead to iron overload and its accumulation in tissues and organs. As a result, it is necessary to add iron chelators to patients regiments. Chelation therapy aims to balance the rate of iron accumulation from blood transfusion by increasing iron excretion in urine and or faces with chelators.^[8]

The first medication of this category is Desferal (deferioxamine)^[9] which is administrated via injection using a pump. Low Patients adherence to this formulation results in complications and problems associated with the accumulation of iron, after the introduction of this medication were not completely eliminated. Low acceptance and low efficacy of the medication in the removal of iron deposition in the organs led to the introduction of oral formulation of another chelator, deferasirox. Jadenu is a new formulation of deferasirox which has been introduced since 2015 and is characterized by its film-coating which increases the bioavailability of the medicine and, on the other hand, improves the compliance and consistency of use in patients.^[9]

The present study aims to assess the cost-effectiveness and budget impact analysis of using deferasirox (Jadenu, Novartis) in comparison with deferioxamine (Desferal, Novartis and generic form) in patients with BTM in Islamic Republic of Iran health care system.

2. Methods

2.1. Study design

This study was conducted in 2 phases. At the first phase, a systematic review of literature was performed in order to compare the effectiveness Desferal with Jadenu. The search was conducted in PubMed, Scopus and Embase databases for the published articles from 2014 to March 26, 2019. This timeframe was chosen for the fact that Jadenu has entered the market since 2014. Search key words included: deferioxamine, deferasirox, controlled clinical trial, and randomized controlled trial. For each database, a specific and appropriate search strategy was applied using MeSH and other related keywords. Two reviewers independently screened the titles and abstracts of all records.

After that, the full text was screened. Two reviewers extracted the data and assessed the quality of the included trials. Randomized controlled trial (RCT) and systematic reviews of RCT studies were included with the inclusion criteria of the patients with BTM as population; Jadenu as intervention; Desferal as Comparator; and severe bleeding events observed in patients receiving each medicine, is considered as outcome.

2.2. Model description

The second phase is an economic evaluation conducted from the payers perspective. A Markov model has been developed to determine the cost utility of using Jadenu compared with deferioxamine (both generic form and Desferal) in patients with BTM. We used the Markov model to calculate life-time costs and quality-adjusted life-years (QALYs) of each therapy. The incremental cost-effectiveness of different strategies was calculated. The expected costs and outcomes of strategies were compared using a lifelong time horizon. Because of chelating therapy is weight-dependent, patients were assumed to be 2 years of age at initiation in first scenario and 18 years old in second scenario, and model was estimated lifetime costs and utilities To discount future costs and QALYs, 5% and 3% annual discount rate were used respectively. Cardiac disease is a major cause of deaths in patients with BTM,^[7] so, our Markov model has tree health status: BTM without cardiovascular complications (WCC), BTM patients who have cardiovascular complications (CC), and death. According to the World Health Organization guideline, ICER less than 3 times gross domestic product (GDP) per capita considered to be cost-effective.^[10] Univariate (one-way) sensitivity analyses were conducted on selected input parameters that included transition probabilities, utility weights and medicine costs.

2.3. Transitions probability

To calculate the probability of patient transition between WCC and CC states to Death, life expectancy table is used with incremental factor due to BTM and cardiac complications. In order to calculate the probability of transition between states, the compliance with medication in 2 groups, was multiplied in the incidence rate of iron overload-related cardiac complications due to poor compliance. Probabilities were estimated using data from published studies.^[11,12]

The probabilities used in this study are estimated considering the different states the patient can accommodate (according to the Markov model).

In order to calculate the probability of transition from the status of receiving iron chelators therapy without cardiovascular complications (WCC) to the status of confronting cardiovascular complications (CC), the rate of drug adherence and the incidence of cardiac events due to lack of compliance to regimen were used 64% and 7.3% respectively.^[12,13] For Jadenu, medication adherence was 92.9%.^[14]

For determining the probability of transition WCC-Death, the probability of natural death in the country and also the risk ratio for BTM patients (3.9) were used.^[12] To calculate the probability of transition CC-Death, the conversion formula was used to transfer the probability to the death rate of patients with BTM caused by cardiac complications.^[12] Transition probabilities between different stages were presented in Table 1. As Jadenu and Deferioxamine do not cause mortality some probabilities in 2 arms are the same.

Table 1
The probability of transitions between health states, depending on the type of medication.

Medicine names	States	Transition probability
Desferal	WCC—WCC	0.9659
	WCC—CC	0.0262
	WCC—Death	0.0078
	CC—CC	0.8521
	CC—Death	0.1478
Jadenu	WCC—WCC	0.9870
	WCC—CC	0.0051
	WCC—Death	0.0078
	CC—CC	0.8521
	CC—Death	0.1478

CC = cardiovascular complications, WCC = without cardiovascular complications.

2.4. Costs

Direct medical costs are captured, and direct non-medical costs, like transportations and accommodations were not included (assuming the similarity of in the 2 arms). No statistically significant difference was found between deferasirox and deferoxamine with regard to the number of participants experiencing “any adverse events”.^[9] That is why the side effects did not included in model. Direct medical cost included the cost of medicine and laboratory tests were calculated in both arms. The cost of medical equipment for every infusion session and also an infusion pump per year were added to deferoxamine arm. As these 2 medications dosage are weight dependent, the patients were categorized to age groups and mean weight was estimated for each category. The minimum weight was considered 8 kg for the category of 2-year-old patients and gradually increased to 45 kg for 18-year-old category and older and the cost of medicine consumption was calculated. The mean daily dosage was considered 40 mg /kg for Desferal and 21 mg /kg for Jadenu.^[11]

The annual cost of cardiac complication management was derived from a previous study that has been conducted in Iran^[15] and the final price was estimated considering the inflation rate of the health sector.

Also, indirect costs such as transfusion time cost were considered only in sensitivity analysis according to the study's perspective. The cost of productivity loss was also calculated for Desferal. BTM patients consume Desferal 6 days a week on average. The patient and his companion spend 3 hours for each infusion, which will be 120 hours per month, and according to the standard, the number of hours worked per week is 198 hours. The minimum monthly salary is 262 US\$. Thus, the cost of productivity loss was estimated at 159.5 US\$ per month and 1914.3 US\$ per year. This measure was entered in the sensitivity analysis section and the calculations were carried out in the model regardless of it.

In calculating costs, total health care services split as 90% public sector tariff and 10% private sector tariff. According to Iran's central bank statistics, dollar currency rate was considered 42,000 Iranian Rial (IRR)/1 US\$ (December 6, 2019).

2.5. Budget impact analysis

Two scenarios were adopted to perform the budget impact analysis. In the first scenario, Jadenu will only takes 33% share of the Desferal market (determined by pharmaceutical policy), thalassemia market is covered and managed by government, at

the study time about 33% of the market need covered by Desferal and they want to evaluate replacement of Jadenu with Desferal. Just for robustness and finding out the threshold of replacement of Jadenu with generic form of deferoxamine (which is not proposed by government) we assumed another scenario in which Jadenu takes 10% share of the generic form of deferoxamine. According to the healthcare reports, there were almost 15,000 patients receiving deferoxamine in Iran, out of which about 2500 patients needs covered by the brand form. The cost of using generic deferoxamine and Desferal compared to Jadenu and the budget impact of this replacement were calculated and reported in results section.

2.6. Ethical review

The ethical approval was not necessary, because the study did not include patient information.

3. Results

3.1. Systematic review

A total of 381 records were retrieved from the electronic database search. Two studies were included according to the inclusion criteria (Fig. 1).

One of these studies is a clinical trial comparing the Jadenu with Exjade^[15] and another study is a systematic review that compares deferasirox with Desferal.^[9] In fact, there have not been any studies comparing the efficacy of Jadenu with Desferal. For this reason, due to the similar efficacy of Exjade and Jadenu, we used the systematic review comparing the overall efficacy of Desferal with deferasirox. It should be noted, however, the clinical trial study^[15] was used in the modeling section so as to factor in the indicator of medication compliance.

The results of a systematic review show that deferasirox is recommended as an essential therapeutic option for BTM patients. Based on available data, deferasirox has superiority to deferoxamine. Although it seems that both medications can result in the same efficacy depending on the dose administered. The data available in clinical trials on long-term safety and toxicity of these medicines are still limited. However, after discussing the potential risks and benefits, deferasirox can be suggested as a first-line treatment option for people who tend to or who have low compliance to deferoxamine.^[9]

Additionally, Effectiveness of these 2 medication based on their utility were obtained from Keshtkaran et al.^[14] Results of this study are presented in the Table 2.

3.2. Cost results

The direct costs of BTM patients include the cost of medication and monitoring is shown in Tables 3–5. The cost of treatment for later years will be 89.13 US\$ due to less request for lab tests. An additional 190.47 US\$ per year was considered for patients using deferoxamine due to the need to use an injection pump for. The cost of medical equipment for every infusion session (7.732 US\$) was also add to deferoxamine arm. The annual cost of cardiac complication management in Iran was estimated 371.75 US\$ considering the inflation rate of the health sector.

3.3. Cost effectiveness analysis

Jadenu was associated with an Incremental Cost Effectiveness Ratio (ICER) of 1470.6 and 2544.7 US\$ vs Desferal in 2

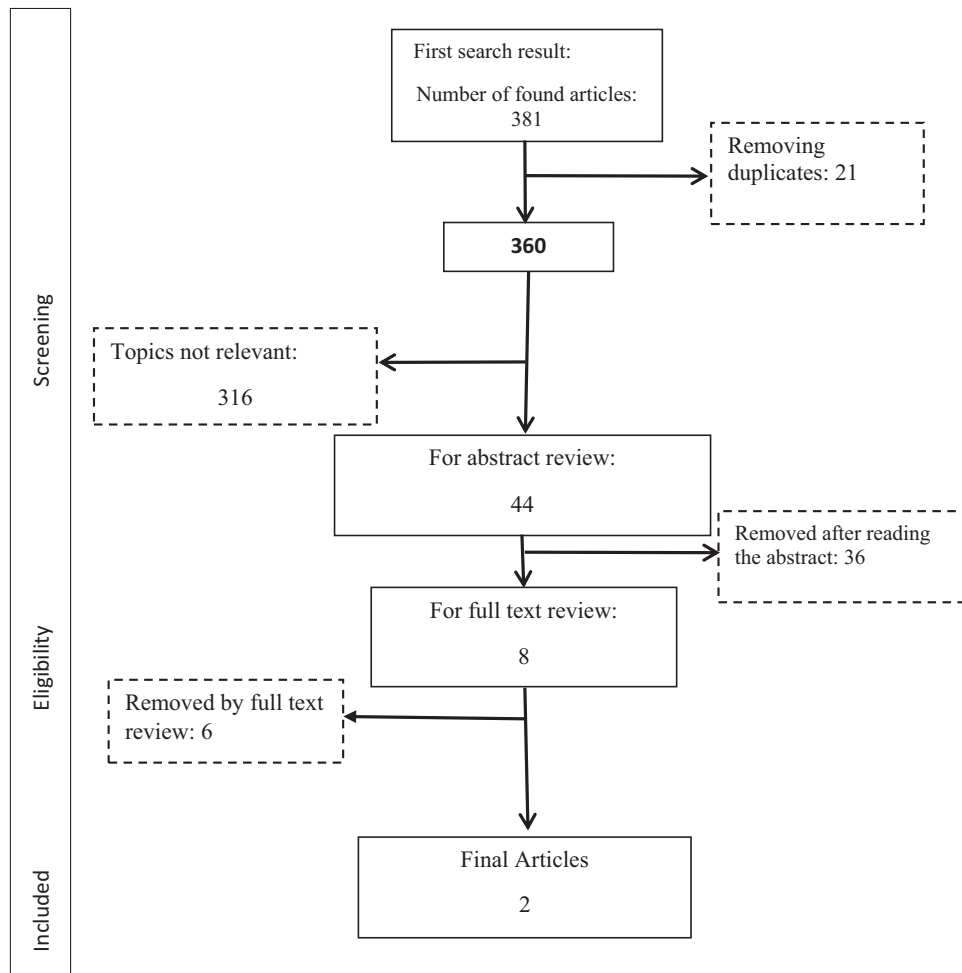


Figure 1. The PRISMA diagram for included studies.

scenarios (start age at 2 and 18 years old) respectively. The estimated ICER for Jadenu compared to generic forms of deferoxamine in Iran pharmaceutical market was 2837.0 US\$ for first scenario (start age at 2 years old) and 6924.1 US\$ for adult patients (>18 years old). According to the World Health Organization guideline, ICER less than 3 times gross domestic product per capita (GDP/capita) considered to be cost-effective.^[10] For all scenarios Jadenu is presumed as cost-effective option based on calculated ICER (Table 6) which was lower than 1 GDP/capita in the Iran healthcare system. The ICER for the comparison between Jadenu and deferoxamine generic form in adults (over 18 years old) was 6924 US\$, which is negotiable due to its proximity to 1 GDP/capita.

3.4. Sensitivity analysis

In this study, one-way sensitivity analysis was conducted on the price of Jadenu and Desferal, utility, and cost discount, the average dose of Jadenu, and the cost of productivity loss. The results are being presented in format of tornado diagram in Figure 2.

Sensitivity analysis results indicate the consistency of the results in most cases and the results will only exceed the threshold by reducing the discount rate to 0% or increasing it to 6%. These results indicate the relative low sensitivity of the model to price changes and other variables.

It is worth mentioning that in case of considering indirect costs; there will be a sharp drop in ICER, which reduces this ratio by 86%. This decrease reflects the great value of the Jadenu option compared to Desferal.

3.5. Budget impact analysis

The estimated cost of chelating therapy for patients using Desferal (based on the market share of this brand of medicine) was 44,021,478 US\$ in 3 years vs 42,452,606 US\$ in replacing one third of brand market share with Jadenu. This replacement corresponded to the cost saving of almost 1,568,872 US\$ for the payers in 3 years. The calculated cost of using generic

Table 2

Utility for 2 medication.

Medicine name	State	Utility score
Desferal	WCC	0.56
	CC	0.42
Jadune	WCC	0.82
	CC	0.70

CC = cardiovascular complications, WCC = without cardiovascular complications.

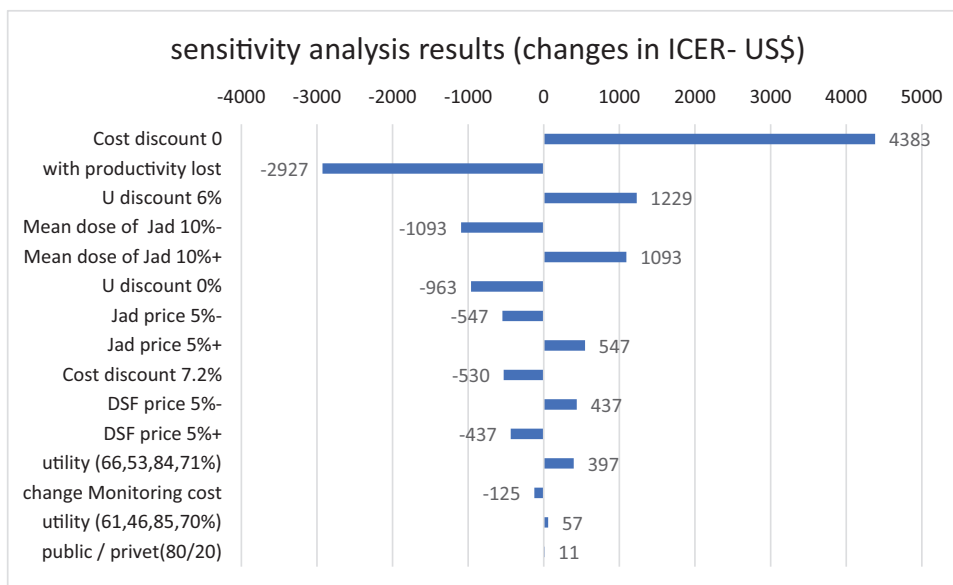


Figure 2. The Tornado Diagram.

deferoxamine in all patients was 68,948,392 US\$ per year. As this scenario just assumed for robustness and finding out the threshold of replacement of Jadenu with generic form of deferoxamine (which is not proposed by government) the number of patients calculate for first year and for second and third year the number decreased due to death of patients. The increase in the cost of using Jadenu for 10% of all patients for first year, in this scenario would be 934,427 US\$ (1.36%) US\$ at the first year and this increment, would be decreased in 2 consecutive years with a gentle slope (1.32%–1.31%). The results of budget impact analysis were reported in Table 7.

4. Discussion

Patients with BTM face with many problems, such as medical expenses and psychological problems due to lifelong blood

transfusions and medicine-therapy. In this study we assess deferasirox (Jadenu, Novartis) cost-effectiveness in comparison with deferoxamine (Desferal, Novartis) in patients with BTM in Islamic Republic of Iran health care system.

This economic evaluation in the payer perspective claims that Jadenu is cost-effective alternative according to ICER, in comparison with Desferal in patients with BTM. Comparing Jadenu and generic deferoxamine, Jadenu is presumed as cost-effective option in case the model starts at age 2. Likewise Jadenu is introduced as a cost-effective strategy in a study done by Karnonand colleagues from the UK National Health Services perspective.^[16] In a model-based study that was done by Delea and colleague from the US Health Care System, Jadenu was reported as a cost-effective alternative and the ICER was \$US28,255 from health care perspective.^[12] In a similar study was done by keshtkaran and colleague in Iran healthcare system, oral Deferasirox was reported as cost-effective alternative in

Table 3
Daily dosage and cost of pharmacotherapy for comparative arms.

Medicine	Daily dose (mg/kg)	mg/day		Cost/day (US\$)		Cost/year (US\$)	
		Start age=2	Start age=18	Start age=2	Start age=18	Start age=2	Start age=18
Desferal	40.0	320.0	1800.0	2.7	15.4	856.1	4815.7
Jadenu	21.0	168.0	945.0	2.8	15.8	876.4	4929.8
DFO (generic)	40.0	320.0	1800.0	2.1	12.0	667.7	3756.0

DFO = deferoxamine.

Table 4
Cost of monitoring for Desferal (US\$).

Tests	Frequency/year	Governmental tariff	private tariff	Cost/test MAX	Cost/test MIN	Average cost
Audiometry	4	2.27	9.81	12.08	8.46	26.08
Ophthalmology	4	3.31	8.62	15.36	–	
Ferritin	4	0.45	0.93	0.40	–	
Admission	4	0.16	0.33	0.05	–	
Total monitoring cost/year				27.90	24.27	

Table 5
Cost of monitoring for Jadenu (US\$).

Jadenu	Frequency/year	governmental tariff	private tariff	Cost/test MAX	Cost/test MIN	Total cost (mean)
Audiometry	1	2.27	9.81	3.02	2.11	109.51
Ophthalmology	1	3.31	8.62	3.84	–	
Ferritin	12	0.45	0.93	1.20	–	
Admission	15	0.16	0.33	0.18	–	
Serum creatinine	15	0.45	0.93	1.50	–	
ALT	15	0.57	1.17	2.35	–	
AST	15	0.57	1.17	2.35	–	
ALP	15	0.57	1.17	2.35	–	
Albumin	15	0.48	0.98	1.66	–	
Protein	15	0.48	0.98	1.66	–	
Bilirubin	15	0.88	1.82	5.72	–	
GGT	15	2.47	5.09	44.67	–	
LD	15	2.13	4.39	33.22	–	
PT	15	0.82	1.68	4.87	–	
Urinalysis	15	0.43	0.89	1.36	–	
Total monitoring cost/year				109.96	109.06	

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate transaminase, GGT = gamma-glutamyl transferase, LD = lactate dehydrogenase, Max = maximum, Min = minimum, PT = prothrombin time.

comparison with infusional deferoxamine in transfusion-dependent β -thalassemia patients.^[14]

Results showed Jadenu was cost-effective option considering the ICER, which is below commonly accepted thresholds for cost-effectiveness for Iranian healthcare system, but it is not the only reason. Jadenu improves the adherence and provides a greater quality of life for patients due to convenience use^[13,15,17,18] compared with parenteral deferoxamine, and it is the most important issue for success of treatment in patient with lifelong condition.

According to the cost calculation in this study, replacing 33% of brand market share with Jadenu was corresponded to the cost saving of almost 1,568,872US\$ for the payers in 3 years. Also increase in the cost of replacing Jadenu for 10% of β -thalassemia patients who are consuming deferoxamine is 1.31% in 3 years. This is a very important point that health policymakers should

pay attention to, in order to properly understand the budgetary impact of using this new intervention.

5. Conclusions

The results of the cost–utility analysis of Jadenu vs Desferal showed that Jadenu is a cost-effective option for patients with BTM from payer perspective. ICER were estimated below 1 GDP/capita in Iran healthcare system. Also based on the budget impact analysis the replacement of Jadenu with Desferal for one third of patients corresponded to the cost saving of almost 1,568,872 US\$ for the payers.

Due to the fact that in Iran and many developing countries, the government is responsible for covering the medical expenses of BTM patients, the results of this study can be considered as a suggestion to replace the Jadenu instead of Desferal. This

Table 6
Cost – effectiveness of 2 medications (life-time Markov model).

	Cost DFO	Cost JAD	Utility DFO	Utility JAD	ICER
Start age = 2*	5.39E+07	6.58E+07	9546.29	17593.7	1470.67
Start age = 18*	7.32E+07	8.29E+07	5103.16	8918.28	2544.71
Generic DFO [†]	4.30E+07	6.58E+07	9546.29	17593.7	2837.09
Generic DFO [‡]	5.65E+07	8.29E+07	5103.16	8918.28	6924.13

DFO = deferoxamine, JAD = Jadenu.

* Cost and utility calculated with Desferal.

[†] Calculated for start age at 2 years old.

[‡] Calculated for start age at 18 years old.

Table 7
Budget impact analysis.

DFO generic	First year	2nd year	3rd year	Just replace with Desferal	First year	2nd year	3rd year
Cost with 10% Jadenu share	6.99E+07	6.56E+07	6.14E+07	Cost with 33% Jadenu share	1.41E+07	1.41E+07	1.42E+07
Cost with deferoxamine alone	6.89E+07	6.47E+07	6.06E+07	Cost with Desferal alone*	1.46E+07	1.47E+07	1.47E+07
Budget impact	9.34E+05	8.54E+05	7.95E+05	budget impact	–5.13E+05	–5.24E+05	–5.33E+05
% change	1.36%	1.32%	1.31%	% change	–3.50%	–3.57%	–3.62%

* Based on market share for brand form in Iran's pharmaceutical market (3,000,000 vial per year).

DFO = deferoxamine

replacement of the therapeutic strategies would be increased the quality of life of patients as well as cost saving.

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Author contributions

All authors contributed in the design and preparation of the manuscript. PS reviewed the analyzed data and drafted the paper and finalized the manuscript. EK implemented the project and data analysis. HPh drafted the paper. MGh implemented systematic review. MS designed the method, data analysis and supervised the project. All authors read and approved the final manuscript.

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