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Original Article

Cost-effectiveness Analysis of Deferiprone and Deferasirox on Thalassemia Major Patients in Tangerang District Hospital, Indonesia

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ABSTRACT

Background: Blood transfusion are needed in improving the quality of life of thalassemia major patients. However since it can lead to excess iron, the iron chelation therapy is needed. Deferiprone and deferasirox are the most often used therapy in Indonesia. **Objective:** The aim of this study was to compare the cost-effectiveness of deferasirox with deferiprone with cost-effectiveness analysis (CEA). **Methods:** Data were taken retrospectively and sampling was done using total sampling based on medical records and hospital information system. Serum ferritin levels of patients consuming deferasirox (n=27) and deferiprone (n=33) were measured to observe the mean changes of serum ferritin levels as effectiveness' parameter. The cost was median of the total direct medical cost, summed from the cost of drugs, medical devices, hospitalization, administration, physician, laboratories and blood bags. **Results:** Based on the results of this study, the effectiveness of deferasirox (1164 ng/mL) was greater than deferiprone (692 ng/mL). Median total cost of deferasirox was more expensive (Rp 76,610,618.69) than deferiprone (Rp 51,869,965.64). Cost-effectiveness ratio of deferasirox (CER: Rp 65,816.68/effectiveness) was lower than deferiprone (CER: Rp 74,956.60/effectiveness). None of both medications was dominant and therefore we could not determine which medication was the most cost-effective therapy. Changing of medication from deferiprone to deferasirox requires an extra cost of Rp 52,416.64 per one incremental unit of effectivity. **Conclusion:** The policy maker in healthcare facility need to consider the budget and whether the incremental cost of deferasirox is proportional to its increased effectiveness.

Key words: Cost-effectiveness analysis, Deferiprone, Deferasirox, Iron chelation therapy, Thalassemia major.

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INTRODUCTION

Thalassemia is a blood disorder passed down through families characterised by decreased or absent the synthesis of normal globin chains.[1] This disease has several types and the most common type of thalassemia found is thalassemia beta major as much as 50%.[2] Thalassemia patients need a periodic blood transfusions during their lifetime to maintain normal hemoglobin levels. However, ironically the amount of iron deposited in the body due to transfusion can be the cause of death.[3] Therefore, an iron chelation therapy is required to prevent complications in other organs.[4]

Currently, in Indonesia, there are three kinds of iron chelation drugs available, which are deferoxamine (DFO) given subcutaneously, deferiprone (DFP) and defarasirox (DFX) given orally.[2] DFP and DFX are more often used in hospitals because there are less expensive and the level of compliance is higher than DFO.[5] In addition, DFP and DFX have some differences, both in terms of pharmacokinetics, side effects produced, eventhough both have good effectiveness in reducing the amount of iron, and also different prices as stated in the governmental e-catalog website that guides BPJS (Indonesian Social Health Insurance Provider) pricing. DFX has a slightly more expensive price than DFP.[6-7] Some studies suggest that once-daily DFX has a better effect than DFP used three times a day, for example studies conducted on pediatric patients in India showed that DFX decreased ferritin serum levels by 441.8 ng/mL, whereas DFP was only 230.5 ng/mL after 12 months of therapy.[8] On the other hand, studies in Italy showed that DFP was dominant, more cost-effective treatment than DFX and DFO for managing chronic iron overload in Thalasemmia Major patients and also beneficial in cost savings for Italian healthcare system.[9] The difference in effectiveness and cost between DFP and DFX, led to the need to know which iron chelation drug is more profitable for hospitals and government in Indonesia.

Both DFP and DFX are included in government-financed thalassemia packages with INA-CBG's (Indonesian Case Base Groups) payment patterns. The Tangerang District Hospital is one of the regional public hospitals that has thalassemia unit and receive BPJS patients. Up to now, 491 registered patients suffering from thalassemia major in Tangerang District Hospital and 373 patients are patients aged 5-18 years.[10]

There are several analytical methods to determine the most cost-effective drug.[11] Cost-effectiveness analysis is the most appropriate method in determining the most cost-effective therapy since the amount of effects and costs are different in some cases of thalassemia major patients. The results of this method are not measured in monetary units, but are described and measured in natural units, such as a change in serum ferritin levels.[12] Therefore we conducted analysis to compare the cost-effectiveness of deferasirox and deferiprone used in thalassemia major pediatric patients.

MATERIALS AND METHODS

Study design

This study was cross sectional and data were taken retrospectively. The processed data in this study were secondary data obtained from medical records and hospital information systems.

Table 1: Comparison of effectiveness and cost of treatment in thalassemia major patients using deferiprone and deferasirox

	Deferiprone (N=33)	Deferasirox (N=27)	p
Mean differences of serum ferritin level (6 months)	692±1088 (-1232-3877)	1164±1364 (-1452-3996)	0.333[b]
Median cost of iron chelator drugs (Rp)	34,650,000.00	59,324,989.50	0.000[a]
Median cost of administration (Rp)	800,000.00	800,000.00	0.897[b]
Median cost of hospitalization (Rp)	1,912,500.00	1,912,500.00	0.918[b]
Median cost of medical devices (Rp)	613,510.86	567,271.41	0.601[a]
Median cost of blood bags (Rp)	10,700,000.00	9,975,000.00	0.807[b]
Median cost of laboratory (Rp)	1,170,000.00	1,798,125.00	0.000[a]
Median of total cost (Rp)	51,869,965.64	76,610,618.69	0.000[a]

Data is expressed in mean +- SD or median; Description: p = Significance of different test; SD = Standard Deviation; a = Mann-whitney; b = Independent samples t test

Table 2: Cost-effectiveness ratio calculation (CER) in thalassemia major patients using deferiprone and deferasirox

Drugs	Effectiveness (ng/mL)	Median of total cost (Rp)	Cost-effectiveness Ratio (CER) (Rp)	Incremental Cost-effectiveness Ratio (ICER) (Rp)
Deferiprone (N=33)	692	51,869,965.64	74,956.60	52,416.64
Deferasirox (N=27)	1164	76,610,618.69	65,816.68	

Data is expressed in median; Description: p = Significance of different test; SD = Standard Deviation; a = Mann-whitney; b = Independent samples t test

Patients

This study was undertaken at the Tangerang District Hospital, Indonesia. Data collection was conducted between March to May 2017. During the period of study, there were 491 patients admitted at the department. Medical charts for admission of the period were reviewed for inclusion and exclusion criteria. Inclusion criteria included attending day care at BPJS Kesehatan class III; age 5-18 years; required monthly blood transfusion with three monthly serum ferritin determinations; serum ferritin ≥3500 ng/mL; and treated with film-coated deferiprone at doses of 75 to 99 mg/kg/day or dispersible tablets of deferasirox at doses of 20-30 mg/kg/day. Exclusion criteria included inflammatory or infectious diseases with leukocyte counts >10,600/µl; serum creatinine ≥1.3 mg/dL for men and ≥1.1 mg dL for women; blood ureum >50 mg/dL; ALT and AST>35 U/L for women and >50 U/L for men; and history of noncompliance. Exclusion criteria included patients who had incomplete, missing, or unreadable data.

Statistical analysis

Descriptive statistics were used to describe the data and appropriate parametric and nonparametric statistics will used to compare groups. A statistical significance was defined at $p<0.05$. Statistical analysis were performed with Microsoft Excel and IBM SPSS 20.0

Data sources: Effectiveness

Serum ferritin was determined every six months. The decrease of serum ferritin within six months interval was defined as effectiveness. Serum ferritin were done more frequently in patients with more severe disease who also received blood transfusion, if their hemoglobin level was <9 g/dL. However, only the difference in six monthly reading of serum ferritin was used to determine the effectiveness.

Data sources: Costs

The cost analyzed in this study was direct medical costs only due to time constraints in collecting other cost data which are were not available in the hospital information systems. Direct medical costs included cost of drugs, medical devices, hospitalization, administration, physician, laboratories and blood bags obtained from the Hospital Information System.

Data sources: Cost-Effectiveness ratio

Median cost was obtained from data of all patients and was divided by the average of effectiveness. The result was then defined as cost-effectiveness ratio (CER).

Sensitivity analysis

The sensitive analysis method used in this research was the method of one way sensitivity analysis. This method is a simulation of change in cost value with fixed value of effectiveness. Sensitivity analysis with cost changes illustrates the price uncertainty of the cost components involved. The analysis was done by simulating the median increase of total medical cost with percentage increase of 5%, 10%, 15%.

RESULTS

A total of 491 registered patients suffering from thalassemia major in Tangerang District Hospital and 373 patients are patients aged 5-18 years.[9] A number of 313 patients were excluded, with the final of eligible samples were 60 patients, consisted of 33 patients with deferiprone and 27 patients on deferasirox.

Effectiveness and costs

Effectiveness and costs were shown in Table 1.

Cost-Effectiveness Ratio (CER) and Incremental Cost-Effectiveness Ratio (ICER)

The results of CER calculation summarized in Table 2. Based on the calculation, the group of patients with deferiprone and deferasirox

Table 3: Sensitivity Analysis with simulation of increasing total cost of treatment.

Description	Deferiprone (N=33)	Deferasirox (N=27)
Median of total cost was increased:		
0% from total cost	Rp 51,869,965.64	Rp 76,610,618.69
5% from total cost	Rp 54,463,463.92	Rp 80,441,149.62
10% from total cost	Rp 57,056,962.20	Rp 84,271,680.56
15% from total cost	Rp 59,650,460.49	Rp 88,102,211.49
Effectiveness (ng/mL)		
Mean differences of serum ferritin level	692	1164
Increased CER		
0% increased	Rp 74,956.60	Rp 65,816.68
5% increased	Rp 78,704.43	Rp 69,107.52
10% increased	Rp 82,452.26	Rp 72,398.35
15% increased	Rp 86,200.09	Rp 75,689.19

CER indicates Cost-effectiveness ratio.

are in the non-dominant quadrant, so the decision-making in the cost-effectiveness analysis not only use the CER calculation. However, it is necessary to calculate the Incremental Cost to Effectiveness Ratio (ICER) to find out whether the additional benefits obtained are equal to its increased effectiveness

Sensitivity analysis

Sensitivity analysis revealed that cost-effectiveness of deferasirox was insensitive with the change of cost. This suggested that deferasirox was more cost-effective than deferiprone irrespective of cost variation (Table 3).

DISCUSSION

The effectiveness of both treatments was measured by the difference in serum ferritin changes after six months of study. Both treatments are effective in lowering serum ferritin levels if baseline of serum ferritin is >3500 µg/L. This condition had been proven in a study in Taiwan which showed that patients who consume DFX with baseline of serum ferritin 2500-5000 µg/L has a higher serum ferritin decline of 1717 µg/L, while for the patient group with serum ferritin level <2500 µg/L only decreased by 775 µg/L.[13] In addition, research in Thailand also stated that DFP has better effectiveness if baseline of serum ferritin is >3500 µg/L.[14] The results showed a significant decrease in serum ferritin levels during one year of treatment. Hence, in this study, subjects were selected also based on baseline serum ferritin levels which exceed 3500 µg/L. As seen in Table 1, it was found that the average of the decreased serum ferritin levels of patients with deferasirox is greater than patients with deferiprone (1164 ± 251.11 ng/mL vs 692 ± 189.43 ng/mL). Unpaired t-test result showed that there is no difference in effectiveness of decreased serum ferritin levels between DFP and DFX. This is in accordance with research conducted in India which stated that DFP and DFX have almost the same effectiveness, but its effectiveness is better when combined.[8]

The cost components that exist in each patient group are clarified, summed and taken the median value of the cost of each group described further on Table 2. The median value of iron chelator costs incurred in deferiprone group is Rp 34,800,360.00, while in deferasirox group is Rp 63,544,429.67. From these results, it can be seen that the price of deferasirox is much more expensive than the price of deferiprone. Thalassemia is one of disease that project biggest expenses due to the high cost of iron therapy and transfusion per month. Based on Mann-Whitney test, statistical significance obtained was 0.000. Therefore, it can be stated that there is a difference in drug costs iron chelation between deferiprone group and deferasirox group (p <0.05). This is results indicate that deferiprone price was much cheaper than deferasirox, thus making deferiprone more widely prescribed. Based on Indonesia's e-catalog website, one tablet of deferasirox 500 mg cost Rp 150,000.00 while one tablet of deferiprone 500 mg cost Rp 33.000,0.[7]

Another significant difference regarding the costs was the cost of laboratory tests. Before blood transfusion, the patient should performs a complete blood check to determine hemoglobin levels, monitor drug side effects and serum ferritin levels every three months to see the drug's effectiveness. Median fees incurred for laboratory checks were Rp 1,170,000.00 for deferiprone and Rp 1,798,125.00 for deferasirox. Those costs were then analyzed using Mann-Whitney test. The results showed that there are differences in laboratory costs between the two groups, significantly (p<0.05) with values significance of 0.000 (p<0.05). The existence of the cost difference is due to regular clinical tests of both groups including liver function test for deferiprone and renal function test for deferasirox. A clinical study had found that 7.5% of 642 patients deferiprone users have an increased ALT values. Four of them stop using deferiprone because of the increase of ALT and one person quitting due to an increase in ALT and AST.[15] Monitoring the liver and renal function for deferasirox patients is also necessary; because of one of the side effects that often occur due to deferasirox is a decrease of renal function characterized by increased creatinine levels.[16] Increased creatinine levels were reversible and have not been explained further. However, this may be due to the impact of decreased glomerular filtration rate which results from the pharmacological effects of deferasirox. Underlying mechanism increased creatinine may also be caused by excess drug in the body which is not equal to the amount of iron available. Hence, the possibility of deferasirox removes one of the iron enzymatic components which may be part of one or more controlling paths of glomerular filtration.[17]

The median total treatment cost is derived from the entire sum components of direct medical costs, including the cost of sailor drugs, medical devices, administration and services of doctors, laboratories, actions, and blood bags. The median total cost of deferasirox treatment was more expensive than deferiprone (Rp 76,610,618.69 vs Rp 51,869,965.64). Mann-Whitney test yield significance result (p<0.05). Therefore, it can be stated that there is a difference in total treatment costs between deferiprone and deferasirox group. Median total cost of each treatment will be used for further calculation in cost-effectiveness analysis, which includes cost to effectiveness ratio (CER), incremental cost to effectiveness ratio (ICER), and sensitivity analysis.

Cost Effectiveness Ratio (CER) and Incremental Cost Ratio (ICER)

The results of CER calculation summarized in Table 2. It can be assumed that deferasirox was more cost-effective than deferiprone. This result is contradictory with research conducted in Italy that showed DFP was dominant and more cost-effective than DFX in managing chronic iron overload in Thalassemia Major Patients. It can be due to the cost difference in Indonesia and in Italy.[9] Furthermore, patients' compliance that was not measured could also affect the different result. Based on the calculation, the group of patients with deferiprone and deferasirox are in the non-dominant quadrant. Hence, the decision-making in the cost-effectiveness analysis will not only use the CER calculation. However, it is necessary to calculate the Incremental Cost Effectiveness Ratio (ICER) to find out whether the additional benefits obtained are proportional to its increased effectiveness.

It showed that the total incremental cost is Rp 24,740,653,05, and within six months the incremental cost can improve the effectiveness of

deferiprone if compare with deferasirox. However, the treatment chosen depends on the restriction budget from decision makers and treatment characteristics.[18] Policies in healthcare facilities should consider whether the additional cost to be incurred is proportional to the increased effectiveness obtained.[12] Due to unknown budget/value limitation of decision makers, incremental cost gains of Rp 52,416.64 are assumed to be acceptable by decision maker. In addition, none of both medications was dominant and therefore we could not determine which medication was the most cost-effective.

CONCLUSION

The effectiveness of deferasirox is greater than deferiprone, but the cost is much higher. Change of medication from deferiprone to deferasirox requires an extra cost of Rp 52,416.64 per one incremental unit of effectivity. The policy maker in healthcare facility need to consider the budget and whether the incremental cost of deferasirox is proportional to its increased effectiveness.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ALT: Alanine aminotransferase; **AST:** Aspartate aminotransferase; **BPJS:** Badan Penyelenggara Jaminan Sosial (Indonesian Social Health Insurance Provider); **CEA:** Cost-effectiveness analysis; **CER:** Cost-effectiveness ratio; **DFO:** Deferoxamine; **DFP:** Deferiprone; **DFX:** Deferasirox; **ICER:** Incremental Cost-effectiveness Ratio; **INA-CBG's:** Indonesian Case Base Group

SUMMARY

Deferiprone and deferasirox are the most often used iron chelation for thalassemia major patients in Indonesia and both are included in government-financed thalassemia packages with INA-CBG's patterns. However existing studies showed differences in their effectiveness and cost, led to the need to know which one is better. This study showed that none of both medication was dominant. The policy maker need to consider whether the incremental cost of deferasirox is proportional to its increased effectiveness.

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