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COST-EFFECTIVENESS OF ORAL IRON CHELATION IN PATIENTS WITH THALASSEMIA MAJOR: A SYSTEMATIC REVIEW

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ABSTRACT
Thalassemia major, as a red blood cell disorder that is passed from both parents to their children, requires high costs and the use of iron chelation drugs throughout the patient's life. Pharmacoeconomics studies in patients with thalassemia major needs to be conducted to determine the efficiency and effectiveness of selecting oral iron chelation drugs. This study aims to analyze the cost and cost-effectiveness of using oral iron chelation drugs such as deferasirox and deferiprone. This systematic review was conducted from Pubmed and Scopus, to identify the cost-effectiveness of deferasirox and deferiprone. Eight studies met the inclusion criteria for the review. farthermor selected the papers, extracted the data, and assessed the methodological quality of the included documents. In brief, deferasirox is cost-effective than deferiprone. Moreover, the cost-effectiveness is not an absolute issue when in different countries (regions) the results are opposite for other countries (regions). As a result, the local/national context had a substantial influence on the results of the pharmacoeconomic evaluation. From the average cost-effectiveness ratio, it can be concluded that deferasirox is more cost-effective than deferiprone.
Keywords: cost-effectiveness analysis*, Thalassemia, Oral iron Chelation, deferasirox, deferiprone*

INTRODUCTION

Thalassemia major, as a group of thalassemia disease, is a blood cell disorder that is inherited from both parents. Patients with thalassemia major require routine blood transfusions and optimal administration of iron chelation drugs to maintain their quality of life. Lifelong blood transfusions are required by the patient to treat anemia and maintain hemoglobin levels of 9-10 g/dl. However, this repeated transfusion also has an unfavorable impact on the patient, namely excessive accumulation of iron in various organs of the body which causes cell damage and death (Rund & Rachmilewitz, 2005).

Iron chelating agents/chelating agents are substances used to prevent or reverse the toxic effects of a heavy metal on enzymes or other cellular targets, or to

accelerate the elimination of metals from the body (Katzung et al., 2016). In Indonesia, there are two oral iron chelation drugs, namely deferasirox and deferiprone. Both of these drugs require large financing with a fairly high cost difference. The needs for one child with thalassemia major weighing 20 kg for blood transfusions and iron chelation drugs reaches 300 million per year (Kemenkes, 2018).

In line with the existence of health technology in the form of drugs, medical devices, diagnostic methods, or treatment that continues to develop, another problem arises and must be faced by users of these health/drug technologies. The problem is the relatively high prices of existing drugs. This is logically acceptable considering that the drugs used are able to provide additional value and solutions towards existing health problems. The problem regarding to the high price causes the costs needed to be able to use the new drug to be even more expensive (Didik et al., 2017).

To compare two or more health interventions that provide different levels of effectiveness, a cost-effectiveness analysis (CEA) can be used. In CEA, treatment outcomes are not measured in monetary units, but they are defined and measured in natural units. The results of CEA are described as the cost-effectiveness ratio (C/E ratio), the numerator of the ratio represents the total cost, and the denominator of the ratio describes the effectiveness/effectiveness variable outputs. So, it is presented in terms of cost to effect.

Moreover, the study aims to analyze the cost and cost-effectiveness of using oral iron chelation drugs such as deferasirox and deferiprone.

RESEARCH METHODS

Systematic search strategy

For this systematic review, a comprehensive electronic search to identify eligible studies was conducted in relevant databases until 2020. The search terminologies used included “cost-effectiveness analysis”, “Oral Iron Chelation”, “deferasirox” and “deferiprone”. References from identified articles were also reviewed to determine relevant publications. The search was limited to the English language. The search terms in the databases are detailed in Supplementary Material 1. Furthermore, The Preferred Reporting Items for Systematic Review and Meta Analyses (PRISMA) 32 checklist was used for this systematic review.

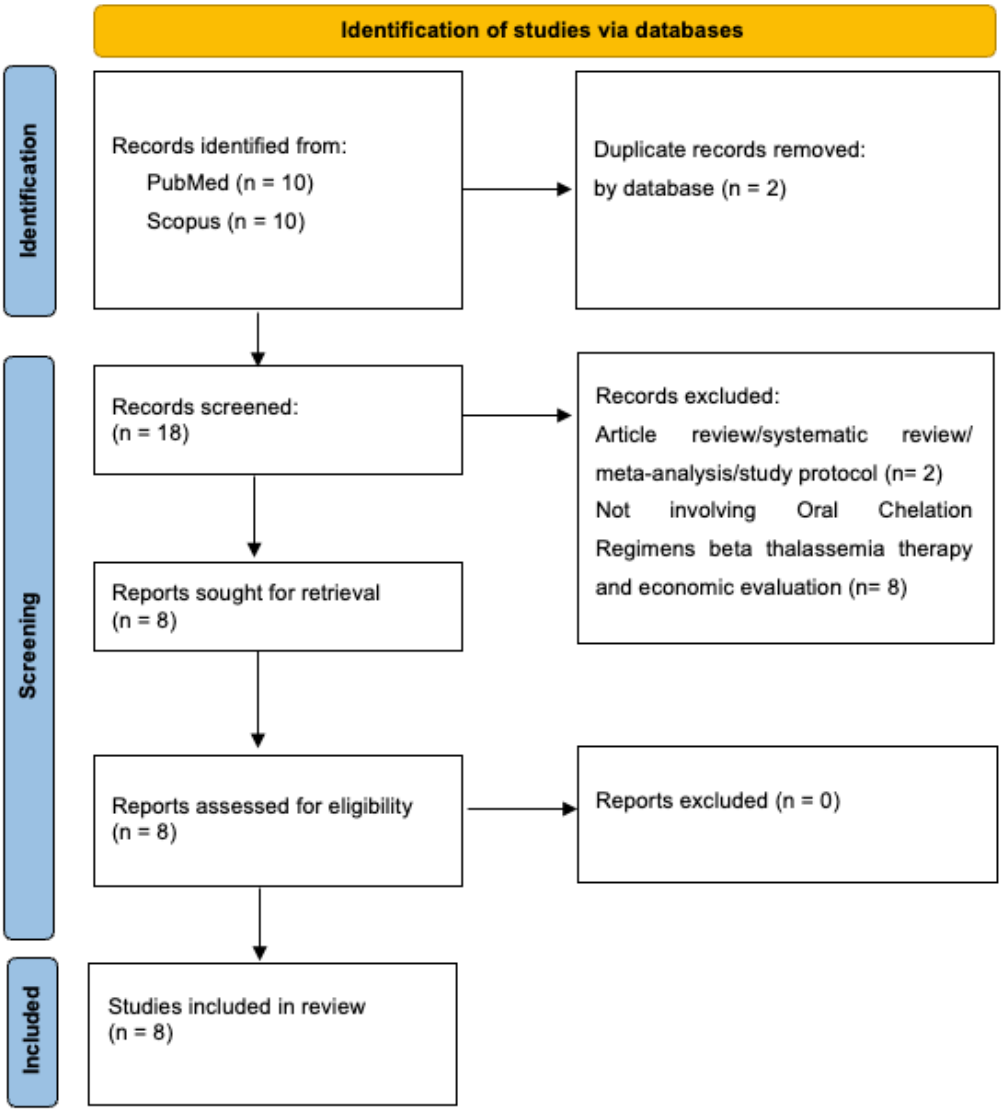

Figure 1. Prisma 2020 flow diagram for systematic reviews

Eligibility and study selection

The eligibility criteria comprised published economic evaluation studies on postpartum depression screening. Exclusion criteria included intervention-only studies, studies without screening for postpartum depression, studies with participants outside the postpartum period, and studies without economic evaluation outcomes related to screening accuracy and effectiveness. Literature reviews, systematic reviews, research protocols, case reports, case series, and conference abstracts were also excluded.

In order to maintain the precision of the selection process, two reviewers conducted independent screenings of the articles, both during the initial title-and-abstract screening and the full-text screening. Any duplicate or irrelevant articles were excluded from consideration. The eligibility of the remaining studies was

evaluated independently by the two reviewers, and any disagreements were resolved through consensus. For all the included studies, a comprehensive data extraction and quality assessment were conducted. The full-text articles were carefully examined, and pertinent information regarding the characteristics of the studies and safety outcomes was extracted. The study selection process is visually represented in Figure 1 of the manuscript, which displays the PRISMA flow diagram.

Data collection and quality check

Data extraction was conducted independently by two reviewers using a pre-designed data extraction form. The extracted data included information about study design and methodology, participant demographics and baseline characteristics, screening tool used, intervention or comparison, outcomes measured, and cost-effectiveness data. If data were missing, the corresponding author of the study was contacted to obtain the necessary information.

The data collection process involved using Zotero as reference manager to store and organize the records retrieved from the search. Two independent reviewers screened each record and report retrieved to determine if they met the inclusion criteria for the review.

To determine eligibility, the reviewers screened the titles and abstracts of all identified articles. Full-text articles were obtained for studies that met the inclusion criteria or where eligibility was unclear. The full-text articles were then independently screened for eligibility by the reviewers, and disagreements were resolved through discussion and consensus. If disagreements could not be resolved, a third reviewer was consulted.

The data synthesis was reported with economic evaluation outcome measures of screening for postpartum depression that were cost-effective or not cost-effective.

RESULTS AND DISCUSSION

Table 1. Research Results

No	Name and Year of Researcher	Research Results
1	Esmaeilzadeh F, Azarkeivan A, Emamgholipour S, Akbari Sari A, Yaseri M, Ahmadi B, Ghaffari M. (2016).	The high costs of treatment of patients with thalassemia major, it seems necessary to adopt new policies in short term including full insurance coverage and giving subsidies to the patients to reduce the costs that the patients have to pay. In addition, due to the low costs of thalassemia screening 24, and high costs of treatments, new decisions must be made in relation to doing thalassemia screening even with higher costs than the usual ones. Active screening as well as making it free in areas with a high prevalence of minor thalassemia where the residents have low income seems to be effective.
2	Li J, Lin Y, Li X, Zhang J. (2019).	Nine studies of DFX versus DFO had contradictory results. Out of the nineteen studies, three studies of DFX versus DFP established that using DFP was cost-effective. Three studies of DFP versus DFO proved that using DFP was cost-effective. One survey of DFO+DFP versus DFO found that using DFO was cost-effective. One study of DFO+DFP versus

No	Name and Year of Researcher	Research Results
		DFP found that using DFP was cost-effective. Moreover, there were two studies of DFO+DFP versus DFX, but we cannot be sure which one of two chelation regimens was cost-effective.
3	Ghafoor M, Sabar MF, Sabir F. (2021).	At present only one government funded project "Punjab Thalassemia Prevention Program" existed in Punjab province, and providing free of cost services for beta thalassemia screening and prenatal diagnosis. Complete blood count and haemoglobin electrophoresis remains the preliminary test for screening, while chorionic villi sampling and amplification refractory mutation system method have been most widely used for molecular diagnosis of beta thalassemia. Modern molecular techniques, non-invasive prenatal diagnosis, and pre-implantation diagnosis are in trial phases.
4	Esmaeilzadeh F, Ahmadi B, Vahedi S, Barzegari S, Rajabi A. (2022).	In this study, it was found that thalassemia screening is much more effective than treating thalassemia patients and generates net income. Therefore, the net income of each preventive thalassemia major case (estimated in this study) can be used to promote thalassemia screening to reduce the incidence of the disease. In addition, according to the results of the sensitivity analysis, in areas with a higher prevalence of thalassemia minor, the net income from screening has increased significantly compared with treatment. Thus, given the high probability of the incidence of thalassemia major in such areas, more money should be spent on screening for thalassemia than in other areas.
5	Phengsavanh A, Sengchanh S, Souksakhone C, Souvanlasy B, Sychareun V. (2022).	The prevalence of α-thal in Lao PDR is 26.8%. There was high prevalence of homozygous (12.8%) and heterozygous (39.7%) Hb E among migrant workers from Lao PDR who crossed the border to work in Thailand. Iron chelation, blood transfusion, prenatal screening and diagnosis, comprehensive treatment are still the major problems. Splenectomy is still performed. A national registry has still not been established. This is a national economic burden for the country. Thalassemia prevention and control strategy should be established and advocated by the government in order to reduce morbidity and premature mortality.
6	Li J, Wang P, Li X, Wang Q, Zhang J, Lin Y. (2020).	DFP was the most cost-effective chelation regimen for β-TM patients, followed by DFO, DFX, and DFO+DFP. Using DFP as the primary treatment regimen may potentially result in cost-savings and QALY gains for the Chinese healthcare system. To increase these benefits, the Chinese government should take measures to lower DFX and DFO drug costs, and Chinese clinicians should choose the cheaper DFX and DFO, increase the utility of DFO+DFP and reduce mortality and morbidity of DFP. Changes in influential parameters easily affect the results of DFX versus DFO+DFP and of DFP versus DFO; clinicians should focus on such parameters and adjust the regimens accordingly.
7	Thuret I, Ruggeri A, Angelucci E, Chabannon C."	Despite remarkable clinical efficacy, 2 major hurdles to gene therapy access for TDT patients materialized in 2021: (1) a risk of secondary

No	Name and Year of Researcher	Research Results
	(Thuret et al., 2022).	hematological malignancies that is complex and multifactorial in origin and not limited to the risk of insertional mutagenesis, (2) the cost—even in high-income countries—is leading to the arrest of commercialization in Europe of the first gene therapy medicinal product indicated for TDT despite conditional approval by the European Medicines Agency.
8	Moirangthem A, Phadke SR. (2018).	The data of 261 patients with a median age of 127 mo was collected. The median age at diagnosis was 9.8 mo. The total treatment expenses of a patient per year ranged from US$ 629 (INR 41,514) to US$ 2300 (INR 151,800), in the different age groups, at an average of US$ 1135 (INR 74,948). More than half (53%) of this was spent on medications. On an average, 38.8% of the family income was spent on the treatment of a thalassemia patient annually. Only 19 of 262 cases had an average pre-BT Hb ≥ 9 g/dl and serum ferritin ≤1500 ng/dl.

Systematic search

Data found in the Pubmed and Scopus databases were 20 research results, then the data were excluded due to duplication of data so that 18 research results were obtained. Data were filtered and then obtained 8 research results. Then the data were identified for eligibility so that 8 were obtained, then the journals were selected according to the research objectives as many as 8, then the journals were excluded and 8 journals were obtained which were used as material in this study. Data analysis in systematic literature review involves the process of assessing the quality of the studies reviewed, extracting data from studies and synthesizing findings from various studies.

Main characteristics of included studies

The main characteristics included in this study were studies involving beta thalassemia therapy with Oral Chelation Regimen and economic evaluation.

Study design

The study design in this research is Systematic Literature Review (SLR). Systematic Literature Review (SLR) is a research method used to collect, evaluate, and summarize all relevant and current research related to a particular topic. The SLR process is carried out with structured and systematic steps, starting from the identification of relevant sources of information to the synthesis of findings to provide a comprehensive overview of the research topic. This systematic review was conducted from Pubmed and Scopus, to identify the cost-effectiveness of deferasirox and deferiprone.

Main findings

Thalassemia prevention and control strategy should be established and advocated by the government in order to reduce morbidity and premature mortality (Phengsavanh et al., 2022). But, the high cost of government treatment has led the Thalassemia Prevention Program in Punjab province to provide free services for beta thalassemia screening and prenatal

diagnosis. Whole blood examination and hemoglobin electrophoresis remain the initial tests for screening, while chorionic villus sampling and amplification refractory mutation system methods have been widely used for molecular diagnosis of thalassemia beta. Modern molecular techniques, non-invasive prenatal diagnosis and pre-implantation diagnosis are in the trial stage (Ghafoor et al., 2021).

Due to the low costs of thalassemia screening 24, and high costs of treatments, new decisions must be made in relation to doing thalassemia screening even with higher costs than the usual ones (Esmaeilzadeh et al., 2016).

Thalassemia screening is much more effective than treating thalassemia patients and generates net income. Thus in areas with a higher prevalence of thalassemia minor, the net income from screening is significantly increased compared to treatment (Esmaeilzadeh et al., 2022). The survey found that thalassemia treatment with DFO and DFP is cost-effective (Li et al., 2019). DFP was the most cost-effective chelation regimen for β-TM patients, followed by DFO, DFX, and DFO+DFP. Using DFP as the primary treatment regimen may potentially result in cost-savings and QALY gains for the Chinese healthcare system (Li et al., 2020).

Despite remarkable clinical efficacy, 2 major hurdles to gene therapy access for TDT patients materialized in 2021: (1) a risk of secondary hematological malignancies that is complex and multifactorial in origin and not limited to the risk of insertional mutagenesis, (2) the cost—even in high-income countries—is leading to the arrest of commercialization in Europe of the first gene therapy medicinal product indicated for TDT despite conditional approval by the European Medicines Agency (Thuret et al., 2022). The data of 261 patients with a median age of 127 mo was collected. The median age at diagnosis was 9.8 mo. The total treatment expenses of a patient per year ranged from US$ 629 (INR 41,514) to US$ 2300 (INR 151,800), in the different age groups, at an average of US$ 1135 (INR 74,948). More than half (53%) of this was spent on medications. On an average, 38.8% of the family income was spent on the treatment of a thalassemia patient annually. Only 19 of 262 cases had an average pre-BT Hb ≥ 9 g/dl and serum ferritin ≤1500 ng/dl (Thuret et al., 2022).

Discussion

Thalassemia (thal) is an autosomal recessive, hereditary, chronic hemolytic anemia due to a partial or complete deficiency in the synthesis of α-globin chains (α-thal) or β-globin chains (β-thal) that compose the major adult hemoglobin (α 2β 2). It is caused by one or more mutations in the corresponding genes (Fibach & Rachmilewitz, 2017). The clinical severity of β-thalassemia syndromes is also influenced by genetic factors unlinked to globin genes as well as environmental conditions and management. Transfusions and oral iron chelation therapy have dramatically improved the quality of life for patients with thalassemia major. Previously a rapidly fatal disease in early childhood, β-thalassemia is now a chronic disease with a greater life expectancy (Origa, 2017). An increased understanding of the molecular and pathogenic factors that govern the disease process have suggested routes for the development of new therapeutic approaches that address the underlying chain imbalance, ineffective erythropoiesis, and iron dysregulation, with several agents being evaluated in preclinical models and clinical trials (Taher et al., 2018).

The diagnosis of thalassemia is based on clinical criteria, hematological criteria, and DNA criteria. Thalassemia management is currently focused on supportive therapy, namely blood transfusion. In addition, thalassemia management can be considered with splenectomy, Hematopoietic Stem Cell Transplantation (HSCT), or induction of fetal hemoglobin (HbF) production (Haq et al., 2023). Beta-thalassemia is divided into three types that also distinguish the various symptoms it may cause. The three types are major, intermedia, and minor. The major type presents itself in the first 2 years of life with symptoms of severe anemia, poor growth, and bone abnormalities, and requires regular blood transfusions for life. The intermedia type requires only periodic blood transfusions and symptoms are less frequent, while the minor type requires no specific treatment and is usually asymptomatic (Suryoadji & Alfian, 2021).

The cost of providing therapy for thalassemia patients is quite expensive. Estimating the cost of thalassemia care is important for the optimization of care planning, resource allocation and the empowerment of patient advocacy. However, available evidence is heterogeneous, reflecting diverse healthcare systems and cost estimation methods (Eleftheriou et al., 2022).

Three types of iron cehlators are available. The three drugs are

1) Desferrioxamine (DFO), which is administered subcutaneously.
2) Deferriprone (DFP),
3) Deferasirox (DFX) which can be given orally.

Deferiprone is an orally active iron chelator which has emerged from an extensive search for new treatment of iron overload. Comparative studies have shown that at comparable doses deferiprone may be as effective as deferoxamine in removing body iron. Retrospective and prospective studies have shown that deferiprone monotherapy is significantly more effective than deferoxamine in improving myocardial siderosis in thalassemia major. Agranulocytosis is the most serious side effect associated with the use of deferiprone, occurring in about 1% of the patients (Galanello, 2007). DFX is the most widely used drug. The dose of iron chelation DFX ranges from 500-1500mg/day. While DFP had a range of 1500-4500mg/day (Newsunair, 2021).

The use of oral iron chelation in patients with thalassemia major has been shown to provide significant cost-effectiveness. Clinically, oral iron chelation can reduce the accumulation of iron in the patient's body, which in turn can reduce the risk of serious complications such as liver disease, cardiac disorders and endocrine problems. Although the initial cost of oral iron chelation treatment may seem high, this investment can be considered a preventive measure that can result in substantial savings in the long run.

In terms of reduced cost of care, the use of oral iron chelation can spare patients from the additional costs that may arise from treating excessive iron complications. Patients receiving oral iron chelation tend to require fewer additional treatments, such as intravenous iron chelation therapy or other medical measures that can be financially burdensome. Overall, although the initial cost of oral iron chelation may seem high, the cost-effectiveness from a long-term perspective may be reflected in reduced treatment costs, improved quality of life, and avoidance of serious complications that can arise from iron

overload in patients with thalassemia major.

CONCLUSION

In this study, it was found that deferasirox showed a tendency to be more cost-effective compared to deferiprone. However, it is important to note that cost-effectiveness is not consistent across countries or regions. Differences in results emerged between different countries or regions, indicating that the local or national context has a significant impact on pharmacoeconomic evaluation. Through analysis of the average cost-effectiveness ratio, the conclusion can be drawn that in general deferasirox shows more superiority in terms of cost-effectiveness when compared to deferiprone.

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