ANALYSIS OF DEFERASIROX AND DEFERIPRON USE IN CHILDREN WITH PEDIATRIC β-THALASSEMA MAJOR

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ABSTRACT

β-Thalassemia major is a genetic disease and a decline in production due to imperfect of hemoglobin. Clinical manifestations are anemia, treated with regular blood transfusions. Blood transfusions lead to an increase in iron in the body that can lead to organ complications. Iron chelation drug delivery is expected to reduce complications due to an increase in the amount of iron in the body by measuring serum ferritin. The study aims to analyze the use of deferasirox and deferipron in patients with β-thalassemia major children at Dr. Kariadi Hospital of January 1, 2012 until December 31, 2013 as well as the need for blood transfusions. Patients who met the inclusion criteria, ie patients with β-thalassemia major children, retrospectively conducted observations of medical records include basic data and laboratory data. After descriptive analysis was performed to determine the use of two types of iron chelating drugs. In this study, 9 patients included in the inclusion criteria. A total of 5 people using deferasirox and 4 using deferipron at baseline. There are 3 people who turned deferipron be deferasirox. Serum ferritin values at study entry was > 1200 mcg/L, and at the end of the study serum ferritin is > 1200 mcg/L. The mean dose of deferasirox study was 19 ± 4.3 mg, and the dose deferipron mean was 80.8 ± 7.7 mg. Mean hemoglobin levels before transfusion was 6.60 ± 0.89 g/dL. The average number of blood transfusions given was 336.52 ± 73.85 ml. Type of blood transfusion is used Washed erythrocyte. Splenomegaly occurred in 2 patients. There is no change in renal function, and hepatic meaning. The final conclusion until the reduction target serum ferritin < 1000 mcg/L has not been reached. Deferasirox dose can be increased to achieve the expected serum ferritin. (FMI 2016;52:42-46)

Keywords: β-thalassemia mayor, children, deferasirox, deferipron

INTRODUCTION

In Indonesia the number of thalassemia patients by the year 2009 rose to 8.3% of 3,653 patients were registered in 2006 (Ruswandi 2009). β-thalassemia major is a genetic disease and a decline in production due to imperfect of hemoglobin, a molecule that is in the red blood cells that carries oxygen throughout the body. Patients with thalassemia may suffer from mild anemia
with or without effects, whereas other patients in need of serious therapy treatment. Routine blood cell transfusions eliminates the complications of anemia and cessation of erythropoiesis, and extend the holding time of thalassemia major patients (Olivieri & Weatherall 2006). Routine blood transfusions can cause a buildup of iron in the blood (Turgeon 2011). Excessive iron buildup can cause complications in other organs such as endocrine, liver, heart and death (Agarwal 2009).

Iron chelating drug used to bind the iron that is not bound to transferrin in the blood and eliminate through urine or feces. Deferoxamin given by parenteral administration, while deferipron and deferasirox administered orally (Olivier 1997). Combination use DFP for five days and continued DFO two days gave better results than the use DFP monotherapy for seven days in terms of the measurement of serum ferritin level, Liver Iron Concentration (LIC) (Aydinoğlu et al 2007). To deferasirox clinical trials in adult patients with a mean age range of 24.6 years showed a decrease in serum ferritin of 3175 μg/L to 2451 μg/L. Priyanti-ningsih’s research using deferasirox showed that for six months did not decrease significantly serum ferritin. The patient's baseline serum ferritin above 1000 mg/L, after six months the mean serum ferritin pediatric patients is 1182.3 μg/L (Priyatiningsih 2010). Currently, iron chelating drug studies in pediatric patients are still rare, especially in Indonesia. Based on this, this study aims to evaluate the effectiveness and safety of deferasirox in patients with β-thalassemia major children who received transfusions.

MATERIAL AND METHODS

The inclusion criteria of this study include pediatric patients hospitalized and outpatients with a diagnosis of β-thalassemia major for January 1, 2011 until July 31, 2014 patients received blood transfusions, patients have received the drug chelation of iron for two years. The presence of the examination of serum ferritin for administration iron chelating drug. Exclusion criteria such as patients who discontinue iron chelation therapy. Clinical data from these patients were obtained retrospectively by medical record review, and this study was approved by the Institutional Review Board of Medical school Diponegoro University.

Data collected for each patient consisted of the following: complete blood count (CBC); ferritin, serum creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels; concomitantly used drugs; and complications occurring between the start and end of deferasirox and deferiprone use. Continuous variables are summarized by descriptive statistics, including the mean and range. Categorical variables are presented as the number and percentage in each category.

RESULTS

Patient characteristics

Nine patients (4 boys and 5 girls; mean : 10 years) who were treated with deferasirox and deferiprone from January 1, 2012 to December 31, 2013 were enrolled in this study. The general clinical characteristics of these 9 patients are provided in Table 1.

Table 1. Demographic data for the 9 patients in the analysis of deferasirox and deferiprone use

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>0 – 5</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 5 – 11</td>
<td>5</td>
</tr>
<tr>
<td>&gt; 11 – 16</td>
<td>1</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Male</td>
<td>4</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
</tr>
<tr>
<td>Nutritional status</td>
<td></td>
</tr>
<tr>
<td>Good nutrition</td>
<td>8</td>
</tr>
<tr>
<td>Better nutrition</td>
<td>1</td>
</tr>
</tbody>
</table>

A total of 5 people using deferasirox and 4 using deferipron at baseline. There are 3 people who turned deferipron to deferasirox. The distribution of regimen change is shown in Fig. 1.

Change in serum ferritin

Among the 9 patients who met the requirements for the analysis, serum ferritin at baseline was > 1200 mcg/L, and after 24 months of chelator drug use, serum ferritin was still > 1200 mcg/L is shown in Fig. 2.

Deferasirox and deferiprone dose

The mean dose pediatric patients with β-thalassemia major in this study were (19.0 ± 4.3 mg) for deferasirox and (80.8 ± 7.7) mg for deferipron. In this study, there were 71% dosing and 29% dose below a dose of literature that is 20-30 mg/kg/day for deferasirox and 75-100 mg/kg/day for deferipron.
Fig. 1. Distribution of regimen change for 9 patients at baseline and after 24 months study

Fig. 2. Serum ferritin levels for the 9 patients included in the analysis of iron chelation drug

Fig. 3. Distribution of 9 patients for months undertdosage use
Giving blood transfusion in this study the most widely prescribed for once a month by 58%, giving two months as much as 23%, the provision for 3 months and less than once a month each as much as 6%, and 8% is given for the above three months. Given blood type is Washed Erythrocyte, namely red blood antibody that has been removed.

**DISCUSSION**

Thalassemia disease can be detected at an early age. This is caused by a disease thalassemia is a descendant of both parents. Generally, signs of the disease will appear at a younger age, usually after birth or a few months after birth (Ganie 2005). In the study in Korea, the number of samples is 17 patient study, derived from seven hospitals that receive iron chelation drug treatment for 3 years. The mean age of patients was 4 years old and the median age was 10.6 years. Administration of iron chelating drugs can be seen its effectiveness one through serum ferritin.

Target serum ferritin in patients with β-thalassemia major is <1000 ng/mL. In the survey results revealed that the serum ferritin is not appropriate treatment targets for two years administration of iron chelating drugs. This is indicated by serum ferritin values at study entry was >1200 ng/mL and at the end of the study >1200 ng/mL in 8 patients. There is one patient who had a serum values below 1000 ng/mL, which is the average of 801 ng/mL. Measurement of serum ferritin in this study has limited sensitivity of the tool. Checker tool can not detect the value of serum ferritin >1200 ng/mL. Another study by Won, there is a decrease in serum ferritin in pediatric patients who use deferipron for 3 years from the baseline 4677.8 ± 1130.9 ng/mL to 3363.9 ± 1149.7 ng/mL. Won the study showed a decline, but the decline is still not in accordance with the target serum ferritin (Won 2010).

Of the value of serum ferritin in patients receiving iron chelation drug known to change in serum ferritin values >1200 ng/mL. This shows the possibility of granting deferipron not show the expected results so that clinicians replace with deferasirox. Changes in iron chelation drug is still not showing the expected results. The mean serum ferritin patient is still > 1200 ng/mL with deferasirox administration at the end of the study. Deferipron doses given are in accordance with the normal dosage is 75-100 mg/kg/day. Deferasirox dose is 20-40 mg/kg/day. The mean dose pediatric patients with β-thalassemia major in this study were (19.0 ± 4.3 mg) for deferasirox and (80.8 ± 7.7) mg for deferipron.

Washed erythrocyte indicated in patients with allergies who need repeated transfusions, patients who have antibodies to plasma proteins, patients with nocturnal hemoglobinuria paroxysmal. The mean number of blood transfusions as much as 336.52 ± 73.85 ml. Giving such a blood transfusion Hb values adjusted to the patient before transfusion, the patient's weight, and the target Hb. Target Hb in patients with β-thalassemia major is 10 mg/dL. Number of transfusions is not given directly to the patient's children, but it is divided and given to the smaller volume first, followed with transfusion four hours later. It is intended that the heart load is not too large (Agarwal 2009). Results of previous studies stated thalassemia patients begin transfusion mean age of 3.78 years, and the frequency of transfusion mostly 1 month 1 time (87.5%). One of its management is to provide the required amount of blood by the blood provider for a blood transfusion in order that the needs of patients with
thalassemia can be fulfilled each time transfusing so that thalassemia patients can survive well.

After administration of deferasirox over three years in patients with β-thalassemia major children known to an increase in urea, increased creatinine, SGOT and SGPT not occur significantly. The normal value of urea is 15-39 mg/dL, creatinine normal value is 0.60 to 1.30 mg/dL, AST normal value is 15-37 U/L, ALT normal value is 30-65 U/L. There is one patient experienced an increase in AST and ALT more than 3 times. Deferasirox side effect is vomiting mild/moderate (8.3%), nausea (7.1%) and rash (7.5%) (Taher et al 2007). Complications of the disease β-thalassemia major, among others disturbance in endocrine, liver, and heart. A total of two patients had splenomegaly, or enlargement of the spleen. One of them has done splenectomy.

**CONCLUSION**

The reduction target serum ferritin <1000 mg/L has not been reached. Deferasirox dose can be increased to achieve the expected serum ferritin.

**REFERENCES**


