

Original Article

Effectiveness of Deferiprone (GPO-L-ONE®) Chelation Therapy in Adult Thalassemia Patients with Iron Overload

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Abstract: Iron overload is one of the major causes of morbidity in patients with thalassemia (Thal). **Objective:** To assess outcomes after deferiprone (GPO-L-ONE®) treatment of iron overload in thalassemia patients. **Materials and Methods:** A prospective study was conducted in thalassemia patients at Chiang Rai Hospital, Chiang Rai, Thailand. The patients with serum ferritin level above 1,000 µg/L were treated with 50–75 mg/kg/day of deferiprone (GPO-L-ONE®) chelation. Serum ferritin levels were measured every three months for one year. Laboratories and clinical safety monitoring were performed. Serum ferritin reduction was analyzed with repeated measurement ANOVA. **Results:** Eighty seven patients were enrolled: 24 homozygous β-thalassemia, 52 β-thalassemia/Hb E and 11 Hb H disease. The serum ferritin decreased in all 87 patients, from $3,357 \pm 2,586$ to $1,551 \pm 1,179$ µg/L ($p < 0.001$). The most common side effect was gastrointestinal discomfort. **Conclusion:** Deferiprone (GPO-L-ONE®) is an effective oral iron-chelating agent for treatment of iron overload in thalassemia. Close safety monitoring is required.

Key Words : ● Thalassemia ● Iron overload ● Chelation therapy

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Introduction

Iron overload is one of the major causes of morbidity in patients with thalassemia major. The deferiprone, an orally active iron chelator, emerged from an extensive search for new drugs to treat iron overload.¹ The drug also was shown to be effective in lowering body iron stores in patient with thalassemia intermedia.² The deferiprone appeared to be as effective as desferrioxamine (DFX) given subcutaneously on five or more days per week at the dose of 40 mg/kg.³ Two recent studies suggested that deferiprone at a daily dose of 75 mg/kg/day was more effective than DFX in decreasing myocardial iron deposition.^{4,5} The multicenter study

confirmed that cardiomyopathy, poor compliance with chelation therapy and high ferritin levels contributed to the risk of death in patients with thalassemia major. It also suggested that including the oral chelator deferiprone in the therapeutic plan might protect against mortality.⁶

The oral chelator deferiprone (GPO-L-ONE®) was approved by the Thai Food and Drug Administration (FDA) in 2008 and began being administered at the provincial hospital in 2009.⁷ Deferiprone has a well-known long-term safety profile. Agranulocytosis is the most serious side effect occurring in about 1% of the patients. More common but less serious side effects are gastrointestinal symptoms, arthralgia, zinc deficiency, and fluctuating transaminase levels.¹

The aim of the study was to report outcomes (serum ferritin reduction and adverse effects) after deferiprone (GPO-L-ONE®) use for the treatment of chronic iron

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overload in adult thalassemia patients.

Materials and Methods

The total of 87 adult (≥ 15 years) thalassemia patients with iron overload who were treated at the hematology outpatient clinic, Chiang Rai Hospital, Chiang Rai, Thailand were prospectively evaluated from November 2009 to November 2010. All patients had the diagnosis of homozygous β -thal, β -thal/Hb E and Hb H disease established by Hemoglobin (Hb) analysis utilizing high performance liquid chromatography (HPLC) and their serum ferritin levels were above 1,000 $\mu\text{g/L}$. At baseline screening neither patient was pregnant nor had elevated aspartate transaminase (AST) and/or alanine transaminase (ALT) exceeding 250 IU/L or absolute neutrophil counts (ANC) less than 1,500 cells/ mm^3 . Bone marrow diseases including malignancy, aplastic anemia and myelodysplastic syndrome were also excluded. No patients used other iron chelating agents. All patients had normal ophthalmic examinations and audiometry tests.

The physician follows the clinical practice guidelines for deferiprone treatment in patients with iron overload⁷, evaluated drug compliance and early side effects during an initial two to four weeks run-in period. The patients received 30 mg/kg/daily of deferiprone (GPO-L-ONE[®]) divided three doses each day after meals. Patients without any serious adverse effects with good compliance continued with the therapy. Compliance was defined as taking more than 90% of the assigned doses evaluated by verifying the packs of tablets and pill counts. Then the dosage was raised from 30 to 50 mg/kg/day for patients not requiring regular transfusions and 75 mg/kg/day for patients receiving regular transfusions (number of red cell transfusion ≥ 10 units/year). All were screened for hepatitis and HIV. Complete blood counts and liver function tests were evaluated every two weeks for the first month then every month. Renal functions were evaluated initially and every three months as well as serum ferritin levels were measured every three months for one year of treatment. Cessation of treatment was

indicated as the following criteria: serum ferritin levels below 500 mg/L, elevated transaminase levels more than three times of upper limit of normal value or exceeding 250 IU/L, ANC less than 1,500 cells/ mm^3 , severe infection, drug allergy approved by pharmacist, pregnancy, visual disturbance, hearing loss and the patients preference. The participants were given drug information from their physicians including dosing, contraindications, precautions and side effects. Clinical and laboratory profiles were used to monitor safety and compliance.

The study protocol was approved by the institutional research ethics committee and was carried out in accordance with the Declaration of Helsinki. All patients signed the consent forms.

Statistical analysis

Descriptive statistics were used. These data were presented by frequency, percentage, mean, median, standard deviation (SD), inter-quartile range (IQR), and p-value. Repeated measurement analysis was used to assess changes over time in the laboratory finding and serum ferritin level serially. A p-value of less than 0.05 was considered as statistically significant.

Results

Eighty seven patients (24 homozygous β -thal, 52 β -thal/Hb E and 11 Hb H disease) received the deferiprone (GPO-L-ONE[®]) therapy (Table 1). The mean age was 30.95 ± 17.07 years. The serum ferritin decreased in all 87 patients, from $3,357 \pm 2,586$ to $1,551 \pm 1,179$ $\mu\text{g/L}$ ($p < 0.001$), with values of less than 1,000 $\mu\text{g/L}$ in 34 patients (39.08%) and less than 500 $\mu\text{g/L}$ in 6 patients (6.9%). There were no significant overall changes in hemoglobin, absolute neutrophil count, platelets and serum creatinin levels, while AST and ALT levels fell significantly at 12 months (Table 2). The serum ferritin fell progressively during the first three months after starting deferiprone therapy (Figure 1). Twelve patients who received regular transfusions and had high serum ferritin levels tolerated a 75 mg/kg/day dose of this

Table 1. Clinical and laboratory data of the eighty seven patients studied.

Characteristics	n = 87	%
Gender		
Male	39	44.83
Female	48	55.17
Age (years)	30.95 ± 17.07	
Weight (kg)	41.34 ± 7.52	
Height (cm)	151.14 ± 10.66	
Type of thalassemia		
Homozygous β-thal disease	24	27.59
Number of red cell transfusion (units/year)	10.67 ± 5.37	
β-thal/Hb E disease	52	59.77
Number of red cell transfusion (units/year)	5.56 ± 4.52	
Hb H disease	11	12.64
Number of red cell transfusion (units/year) median (IQR)	0 (4)	
Splenectomy	55	63.22
Hemoglobin (g/dL)	6.42 ± 1.18	
Corrected white blood cells x10 ³ /mL	11.95 ± 6.07	
Platelets x10 ³ /mL	487.43 ± 349.21	
Nucleated RBC/100 WBC (n) median (IQR)	76 (215)	
Aspartate transaminase (IU/L)	60.43 ± 33.25	
Alanine transaminase (IU/L)	46.93 ± 28.81	
Total bilirubin (mg/dL)	2.65 ± 1.33	
HBsAg positive	2	2.30
Anti-HCV positive	6	6.90
Serum creatinine (mg/dL)	0.73 ± 0.33	
Serum ferritin (μg/L)	3,357 ± 2,586	

Table 2. Initial, period treatment and final laboratory findings in 87 patients treated with deferiprone (GPO-L-ONE[®]).

Laboratories*	Initial	3 months	6 months	12 months	p-value
Hemoglobin (g/dL)	6.42 ± 1.18	6.43 ± 1.23	6.5 ± 1.15	6.47 ± 1.23	0.613
ANC x10 ³ /mL	5.09 ± 2.63	4.49 ± 2.27	5.31 ± 3.01	5.30 ± 6.13	0.345
Platelets x10 ³ /μL	487.42 ± 349.21	515.23 ± 333.18	504.92 ± 330.48	482.46 ± 310.91	0.494
AST (IU/L)	60.43 ± 33.25	55.15 ± 33.09	51.89 ± 31.79	46.26 ± 25.84	< 0.001
ALT (IU/L)	46.93 ± 28.81	42.48 ± 31.92	37.08 ± 24.81	30.16 ± 23.17	< 0.001
Serum creatinine (mg/dL)	0.73 ± 0.33	0.71 ± 0.34	0.73 ± 0.37	0.73 ± 0.38	0.750
Total Serum ferritin (μg/L)	3,357 ± 2,586	2,193 ± 1,504	1,822 ± 1,353	1,551 ± 1,179	< 0.001
Homozygous β-thal	4,499 ± 3,128	2,582 ± 1,575	2,054 ± 1,489	1,734 ± 1,314	< 0.001
β-thal/Hb E	2,960 ± 2,235	2,010 ± 1,355	1,718 ± 1,201	1,486 ± 1,115	< 0.001
Hb H disease	2,742 ± 2,279	2,214 ± 1,965	1,810 ± 1,761	1,454 ± 1,236	< 0.001

* repeated measurement ANOVA

ANC = absolute neutrophil count; AST = aspartate transaminase; ALT = alanine transaminase

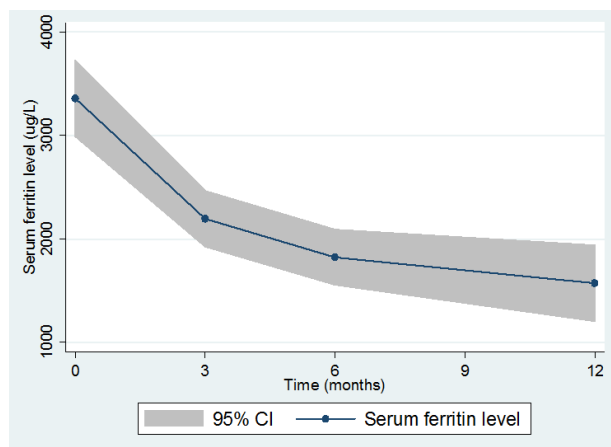


Figure 1. Changes in the mean value of serum ferritin levels of 87 patients during treatment with deferiprone (GPO-L-ONE®).

Table 3. Adverse effects of deferiprone (GPO-L-ONE®).

Adverse effects*	n = 87	%
Nausea	12	13.79
Anorexia	9	10.34
Transaminitis	8	9.2
Arthralgia	7	8.05
Dizziness	6	6.9
Sleepy	2	2.3
Abdominal pain	1	1.15
Increase appetite	1	1.15
Fatigue	1	1.15
Insomnia	1	1.15
Neutropenia	1	1.15
Renal insufficiency	1	1.15
Increase stool frequency	0	0
Hematuria	0	0
Thrombocytopenia	0	0

*In the table, some patients had more than one side effect.

drug. Four patients with Hb H disease required dosage reduction from 50 mg/kg to 30-40 mg/kg because of gastrointestinal side effects.

Table 3 summarized the adverse effects of the 87 patients. Twenty two patients complained of gastrointestinal symptoms (nausea, abdominal pain, and anorexia) within the first few weeks of treatment. Seven patients had arthralgia, commonly affecting the knee joints without signs of arthritis. The liver enzymes were temporarily elevated less than three times in eight patients. One patient had a slight increase of their serum creatinine

levels from 2.0 mg/dL to 2.5 mg/dL. Ophthalmic and auditory studies showed no changes. None of the patients dropped out from the study.

Discussion

These results were consistent with previous studies that deferiprone was effective in reducing iron overload in patients with β -Thal major receiving 75 mg/kg daily for one year^{8,9} and in patients with β -thal intermedia who did not require regular transfusions receiving 25-50 mg/kg daily.¹⁰ The Government Pharmaceutical Organization (GPO) of Thailand recommended dose of deferiprone (GPO-L-ONE®) for patients with thalassemia major requiring regular blood transfusions at 75 mg/kg/day and for thalassemia intermedia patients with less transfusion requirements at 40-50 mg/kg/day. The physicians were slow to step up treatment for patients with high serum ferritin levels because of side effect concerns.

In this study, most patients tolerated this drug with no serious side effects. However, some of them had slightly elevated liver transaminase activities that subsequently improved after dose reduction. NSAIDs were effective in controlling joints pain; therefore, treatment discontinuation was not required. One patient developed mild neutropenia (ANC 1,483 cells/mm³) at 12 months. Although the zinc levels were not measured, signs of zinc deficiency were not found after chelation therapy.

In the study from Siriraj Hospital, adverse effects of deferiprone were reported in 60 Thai that developed 31.6% gastrointestinal symptoms, 13.3% transaminitis, 8.3% arthralgia and 8.3% neutropenia. Other side effects included dizziness, increased appetite, diarrhea, fatigue, thrombocytopenia, hematuria and zinc deficiency.⁷ However, the prognostic significance of adverse drug effects remains unclear. Although oral chelation is more convenient for patients than subcutaneous desferoxamine, combined therapy with deferiprone (GPO-L-ONE®) and desferoxamine may be needed to treat patients who cannot tolerate high dose deferiprone (GPO-L-ONE®) alone.

The drug was generally well tolerated and overall compliance was greater than 90%. The author did not find the evidences of visual or hearing abnormalities due to the drugs in one year follow up.

Conclusion

Deferiprone (GPO-L-ONE®) is an orally effective iron-chelating agent in the treatment of iron overload in thalassemia. Close safety monitoring is required in a patient receiving this drug in specialty care. The author declares no conflict of interest.

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ผลการรักษาด้วยยา Deferiprone (GPO-L-ONE®)

ในโรคธาลัสซีเมียผู้ใหญ่ที่มีภาวะธาตุเหล็กเกิน

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บทคัดย่อ ภาวะธาตุเหล็กเกินเป็นสาเหตุสำคัญที่ก่อให้เกิดความเจ็บป่วยในผู้ป่วยธาลัสซีเมีย **วัตถุประสงค์** เพื่อประเมินผลการรักษาด้วยยา Deferiprone (GPO-L-ONE®) ในโรคธาลัสซีเมียผู้ใหญ่ที่มีภาวะธาตุเหล็กเกิน **วัสดุและวิธีการ** ศึกษาที่โรงพยาบาลเชียงรายประชานุเคราะห์ โดยติดตามผู้ป่วยธาลัสซีเมียที่มีระดับ ferritin ในซีรัมเกิน 1,000 ไมโครกรัม/ลิตร และได้รับการรักษาด้วยยาขับเหล็ก Deferiprone (GPO-L-ONE®) ขนาด 50-75 มก./กก./วัน เป็นเวลา 1 ปี วัดระดับ ferritin ในซีรัมทุก 3 เดือน วิเคราะห์โดย repeated measurement ANOVA และเฝ้าติดตามความปลอดภัยระหว่างใช้ยา **ผลการศึกษา** ผู้ป่วย 87 รายเข้าร่วมการศึกษา โดยเป็น homozygous β -thal 24 ราย β -thal/Hb E 52 ราย และ Hb H disease 11 ราย ระดับ ferritin ในซีรัมลดลงจาก $3,357 \pm 2,586$ เหลือ $1,551 \pm 1,179$ ไมโครกรัม/ลิตร แตกต่างกันอย่างมีนัยสำคัญทางสถิติ ($p < 0.001$) ผลข้างเคียงที่พบบ่อยคือ อาการของระบบทางเดินอาหาร **สรุป** ยา Deferiprone (GPO-L-ONE®) มีประสิทธิภาพในการรักษา ภาวะธาตุเหล็กเกินในผู้ป่วยธาลัสซีเมีย จำเป็นต้องเฝ้าติดตามผลข้างเคียง และความปลอดภัยในการใช้ยาอย่างใกล้ชิด

Key Words : ● Thalassemia ● Iron overload ● Chelation therapy

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