Original article

Safety and efficacy of a liquid formulation of deferiprone (GPO-L-ONE®) monotherapy among iron-overloaded young children with transfusion-dependent thalassemia

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Abstract:

Background: *Iron chelation for children aged 2-6 years is limited.* ***Aim:*** *Safety and efficacy of a liquid formulation of deferiprone (GPO-L-ONE®) monotherapy among young children was reported.* ***Subjects and Methods:*** *Deferiprone in a daily dose of 50-100 mg/kg divided in 3 doses was given to thalassemia children aged 2-12 years with transfusion-induced iron overload. Efficacy was defined as responder and nonresponder by the ≥ 15 or < 15% reduced serum ferritin compared with the initial ferritin level.* ***Results:*** *Nineteen patients (7 males and 12 females) with thalassemia at the median age of 4.1 years were enrolled. The median daily iron load from regular transfusion was 0.41 mg/kg. Eighteen and 8 of 19 patients completed the first and second year study, respectively. The maximum daily dose of deferiprone was 100 mg/kg. The median baseline ferritin 1,470 ng/mL changed in +633 and +64.5 ng/mL at the end of the first and second years, respectively. However, only 4 of 19 patients (21%) were defined as responders with significantly reduced serum ferritin starting from the 6th month of treatment. Ten adverse events of transminitis (n = 3), severe neutropenia (n = 1), neutropenia (n = 2) and thrombocytopenia (n = 4) were found among 5 patients who spontaneously recovered without medical intervention.* ***Conclusion:*** *A liquid formulation of deferiprone (GPO-L-ONE®) at a daily dose of 100 mg/kg was tolerable among young children. However, efficacy was limited by responsiveness to negative iron balance in 4 of 19 patients (21%).*

Keywords : ● *Liquid formulation* ● *Deferiprone* ● *Iron overload* ● *Thalassemia*

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นิพนธ์ต้นฉบับ

ความปลอดภัยและประสิทธิภาพของการใช้ยาดีเฟอริโพรน (GPO-L-ONE®) ชนิดน้ำชนิดเดียวในผู้ป่วยเด็กโรคธาลัสซีเมียชนิดพึ่งพาเลือดที่มีภาวะธาตุเหล็กเกิน

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บทคัดย่อ

ความเป็นมา *ยาขับเหล็กสำหรับผู้ป่วยอายุ 2-6 ปีมีจำกัด* ***วัตถุประสงค์*** *รายงานความปลอดภัยและประสิทธิภาพของการใช้ยาดีเฟอริโพรน (GPO-L-ONE®) ชนิดน้ำชนิดเดียวในผู้ป่วยเด็กโรคธาลัสซีเมียชนิดพึ่งพาเลือดที่มีภาวะธาตุเหล็กเกิน* ***ผู้ป่วยและวิธีการ*** *ผู้ป่วยเด็กโรคธาลัสซีเมียชนิดพึ่งพาเลือดที่มีภาวะธาตุเหล็กเกินอายุ 2-12 ปีได้รับยาดีเฟอริโพรนขนาด 50-100 มก./กก./วัน แบ่งให้วันละ 3 ครั้ง ประสิทธิภาพของการขับธาตุเหล็ก กำหนดเป็นตอบสนองหรือไม่ตอบสนองขึ้นกับการลดลงของระดับเฟอร์ริติน มากกว่าหรือเท่ากับร้อยละ15 หรือน้อยกว่าร้อยละ 15 เมื่อเปรียบเทียบกับระดับเฟอร์ริตินก่อนได้รับยา* ***ผลการศึกษา*** *ผู้ป่วยโรคธาลัสซีเมีย 19 ราย (ชาย 7 และหญิง 12) ที่มีอายุเฉลี่ยเท่ากับ 4.1 ปีเข้าร่วมในการวิจัย ค่าเฉลี่ยปริมาณธาตุเหล็กที่ได้รับจากการรับเลือดสม่ำเสมอเท่ากับ 0.41 มก./กก./วัน ผู้ป่วย 18 และ 8 จากจำนวนทั้งหมด 19 รายได้รับยาเฟอริโพรนนาน 1 และ 2 ปีตามลำดับ ปริมาณยาเฟอริโพรนสูงสุดที่ได้รับเท่ากับวันละ 100 มก./กก. ค่าเฉลี่ยของระดับเฟอร์ริตินก่อนได้รับยาดีเฟอริโพรนเท่ากับ 1,470 นาโนกรัม/มล. และค่าเฉลี่ยของระดับเฟอร์ริตินที่เปลี่ยนแปลงเท่ากับ +633 และ +64.5 นาโนกรัม/มล. เมื่อสิ้นสุดการรักษาปีที่ 1 และ 2 ตามลำดับ อย่างไรก็ตาม มีเพียงผู้ป่วย 4 รายจากจำนวนทั้งหมด 19 ราย คิดเป็นร้อยละ 21 ที่ได้รับการวินิจฉัยเป็นผู้ป่วยที่ตอบสนองต่อยาดีเฟอริโพรนโดยเริ่มมีระดับเฟอร์ริตินลดลงอย่างมีนัยสำคัญทางสถิติตั้งแต่เดือนที่ 6 ของการรักษา และพบภาวะแทรกซ้อนจากการใช้ยาดีเฟอริโพรน 10 ครั้งในผู้ป่วย 5 ราย ได้แก่ระดับเอ็นไซม์ของตับเพิ่มขึ้น (transminitis) 3 ครั้ง จำนวนเม็ดเลือดขาวต่ำกว่า 500 เซลล์/ไมโครลิตร 1 ครั้ง จำนวนเม็ดเลือดขาวต่ำกว่า 1,500 เซลล์/ไมโครลิตร 2 ครั้งและภาวะเกล็ดเลือดต่ำ 4 ครั้ง ซึ่งหายเป็นปกติโดยไม่ต้องรับยารักษา* ***สรุป*** *ยาดีเฟอริโพรนชนิดน้ำ (GPO-L-ONE®) ในขนาดวันละ 100 มก./กก. มีความปลอดภัยในผู้ป่วยเด็ก แต่ประสิทธิภาพในการลดภาวะธาตุเหล็กเกิน พบว่ามีการตอบสนองในผู้ป่วยเพียง 4 รายจากจำนวนทั้งหมด 19 รายคิดเป็นร้อยละ 21*

คำสำคัญ : ● *Liquid formulation* ● *Deferiprone* ● *Iron overload* ● *Thalassemia*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2564;31:47-56.

Introduction

Children with thalassemia having severe anemia and hepatosplenomegaly usually receive medical attention before 2 years of age. They require regular transfusion and effective iron chelation aimed at reducing iron overload. Iron excess will affect all tissues in the body, primarily the liver, heart and endocrine glands[1-3]. Without appropriate treatment, these affected children will experience severe failure to thrive and shortened life expectancy[4,5]. They are in need of effective and affordable iron chelation to counteract transfusion-induced iron overload. Currently, the goal of iron chelation has shifted from treating iron overload to preventing iron accumulation and iron-induced various organ complications to achieve complication-free survival with a better quality of life[6,7]. Although both deferoxamine and deferasirox are recommended for children aged 2 to 6 years[8], patients and parents face various constraints. The subcutaneous infusion of deferoxamine for 8 to 12 hours of 5 days weekly among young children resulted in poor compliance with ineffective chelation[9] while the cost of deferasirox is too high for most parents and caregivers to afford. The tablet form of deferiprone has been another oral iron chelation alternative available for the past 30 years[10-12]. The price of deferiprone is less expensive than deferasirox. Importantly, a liquid formulation of deferiprone (Ferriprox®) was introduced among young children in 2010[13] and a safety profile among nine Thai young children was also reported in 2016[14]. The Thai Government Pharmaceutical Organization (GPO) has produced a liquid formulation of deferiprone (GPO-L-ONE®) locally since 2016.

This study reports the safety and efficacy of a liquid formulation of deferiprone (GPO-L-ONE®) monotherapy among young thalassemia children with transfusion-induced iron overload.

Subjects and Methods

A liquid formulation of deferiprone (GPO-L-ONE®) in a daily dose of 50 to 100 mg/kg divided in 3 doses, was given to transfusion-dependent thalassemia children aged 2 to 12 years with iron overload at the Division of Hematology-Oncology, Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University from January 2017 to December 2019. This study employed a single-arm prospective design with the primary objective of safety and the secondary objective of efficacy of the locally-produced liquid formulation of deferiprone. Approximately 20 patients were recruited in the current study to obtain some insight of the safety and efficacy of locally-produced deferiprone. The study was conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki and was approved by the Faculty Ethics Committee (ID 10-58-14) and Thai Clinical Trial Registry (TCTR 20170907001). Written informed consent was obtained from parents.

The diagnosis of thalassemia was confirmed by hemoglobin typing and DNA analysis. Clinical manifestations and hematologic and molecular genetic findings were collected from medical and electronic records. Patients with transfusion-dependent thalassemia (> 10 transfusions within 1 year) when their serum ferritin was ≥ 1,000 ng/mL, based on 2 consecutive values ≥ 4 weeks apart, were enrolled in the study. Complete patient history was taken and physical examination was conducted at each regular visit at 1- to 3-month intervals. Leucocyte-depleted packed red cell transfusions were regularly given at a dose of 10 to 15 mL/kg every 3 to 4 weeks to maintain the pretransfusion hemoglobin level at > 9.0 g/dL. The severity of disease was classified using the reported scoring system of HbE/β-thal[15] based on 6 independent parameters of hemoglobin at a steady state, age at receiving first transfusion, requirement for transfusion, size of spleen or splenectomy, age at thalassemia presentation and growth. The total scores, ranging from 0 to 3.5, 4 to 7 and 7.5 to 10 were defined as mild, moderate and severe manifestations, respectively. The mean (SD) severity scores of the studied patients was 6.2 (1.1) representing a moderate degree. All studied patients had hepatitis A and B vaccinations. Screening

for hepatitis B, C and human immunodeficiency virus (HIV) was performed on an annual basis. Importantly, all patients and parents were periodically reminded to maintain a healthy diet of rice, meat, milk, lipids, vegetables and adequate water intake. Food with high iron content such as liver was avoided.

Patients naïve to iron chelation received an initial dose of deferiprone of 50 mg/kg while those with a history of other oral liquid forms of deferiprone had a wash-out period of 2 weeks and received a similar dose as their previous prescription. Then the dose of deferiprone was gradually increased to achieve the maximum daily dose of 100 mg/kg when the serum ferritin reduced < 15% of the initial value. Serum ferritin was the single parameter used to assess the efficacy of iron chelation determined by the Vitros Ferritin Assay (Ortho Clinical Diagnostics, Johnson & Johnson, Pencoed, Bridgend, UK) before the study and thereafter on a 3-month basis. Compliance in taking deferiprone was checked during every visit concerning the ingested dose and number of consumed bottles of medication.

Complete blood count (CBC), serum blood urea nitrogen (BUN), creatinine (Cr), alanine aminotransferase (ALT) and urinalysis to monitor adverse events using standard methods were determined before the study and thereafter every 1 to 3 months. Deferiprone administration was terminated when the absolute neutrophil counts (ANC) fell below $0.5x10^9$/L, and serum Cr was above the upper limit of normal for age or significant proteinuria (urine protein/urine Cr > 0.5 mg/mg). When ANC fell below $1.5x10^9$/L, deferiprone was temporarily interrupted and a CBC was repeated within 24 hours. When neutropenia was confirmed, deferiprone was discontinued for 4 weeks. Following this period, provided that ANC recovered to > $2.0x10^9$/L, deferiprone was resumed at one half the previous dose and ANC levels were monitored weekly. When a patient displayed satisfactory ANC levels after 4 weeks of monitoring, the titration was increased aiming at returning to the dose administered before neutropenia had occurred. When the level of ALT reach > 250 units/L, deferiprone was discontinued for 4 weeks and re-challenged at one half of the previous dose when the ALT fell below 100 units/L and gradually titrated to the dose before discontinuing, similar to neutropenia.

The efficacy of deferiprone was defined as responder and nonresponder. Nonresponder was defined as patients failing to achieve ≥ 15% reduced serum ferritin on the last visit compared with the initial ferritin level despite increasing the daily deferiprone dose to the maximum of 100 mg/kg or the maximum tolerated dose among patients who dropped out due to adverse events. The remaining patients were defined as responder.

In addition, DNA was extracted from the studied patients' venous blood using a salting-out method. The UDP glucuronosyltransferase 1 (UGT 1) family polypeptide A6 (UGT1A6) of wild-type allele of *1 and mutant alleles of *2,*3 and *4 were determined among the studied patients and 44 additional patients with thalassemia as control using polymerase chain reaction-restriction fragment length polymorphism analysis[16].

Statistical analysis

Demographic data and clinical characteristics of the studied patients were summarized in term of mean (standard deviation, SD), median (interquartile range, IQR), range of minimum to maximum and frequency (percent). The nonparametric analysis of Mann-Whitney U or Wilcoxon signed rank test was used for continuous data. The level of significance was set at $p \leq 0.05$.

Results

Nineteen patients (7 males and 12 females) with thalassemia including HbE/β-thal (n = 15), one each of β-thal major, δβ-thal/β-thal, Hb E/δβ-thal and hemoglobin H with Constant Spring, were enrolled at the median age of 4.1 years (range 2.1 to 11.0). The genotype of the β^0-globin gene included codon 41/42 (-TTCT) (n = 10), codon 17 (A>T) (n = 7) and codon 7172 (+A) (n = 1) while the $\delta\beta^0$-globin gene included 12 kb deletion. Only one patient with HbE/β-thal possessed an additional

$$\frac{\text{Total volume of packed red cell transfusion in 1 year (mL) x 1.08 mg of elemental iron}}{\text{Average BW in 1 year x 365 days}}$$

α-globin gene of $-\alpha^{3.7}$ (rightward). The median age of first transfusion was 1.4 years (range 0.7 to 9.2) and the median duration of transfusion before deferiprone administration was 1.9 years (range 0.7 to 9.5). The mean (SD) pretransfusion Hb was maintained at 9.8 (1.2) g/dL. The median volume of transfused packed red cells in 1 year before the study entry was 2,500 mL (range 1,080 to 4,400) and equal to 139.3 mL/kg (range 112.5 to 216.6). This contained a median daily iron load of 0.41 mg/kg (range 0.33 to 0.64) calculated using the formula shown above[17].

Thirteen patients naïve to iron chelation initially received the daily dose of deferiprone of 50 mg/kg while six patients with a history of oral chelation of deferiprone (Ferriprox®) at the median age of 2.4 years (range 1.9 to 4.9) received a daily dose of deferiprone at 75 mg/kg. Eighteen of 19 patients achieved 1 year follow-up except 1 patient who withdrew from the study due to adverse reactions of transminitis and neutropenia at the ninth month of treatment. The remaining studied patients gradually switched to deferasirox due to adverse reactions and unresponsiveness to deferiprone and the number of patients continuing the study reached 15 months (n = 17), 18 months (n = 14), 21 months (n = 9) and 24 months (n = 8). The median duration to achieve the maximum dose of deferiprone was 9 months (range 3 to 24 months). The median maximum daily dose of deferiprone at the end of the first and second years was similar at 98 mg/kg (range 66 to 100). The median pretreatment ferritin was 1,470 ng/mL (range 857 to 3,229) with the median change from baseline of +633 ng/mL (range -1,283 to +2,915) and +64.5 ng/mL (range -1,156 to +2,352) at the end of the first and second years, respectively, as shown in Figures 1 and 2. The median percentage change from baseline in serum ferritin was +30.8% (range -51.6 to +202) and +4% (range -60 to +213) at the end of the first and second years, respectively as shown in Figure 3.

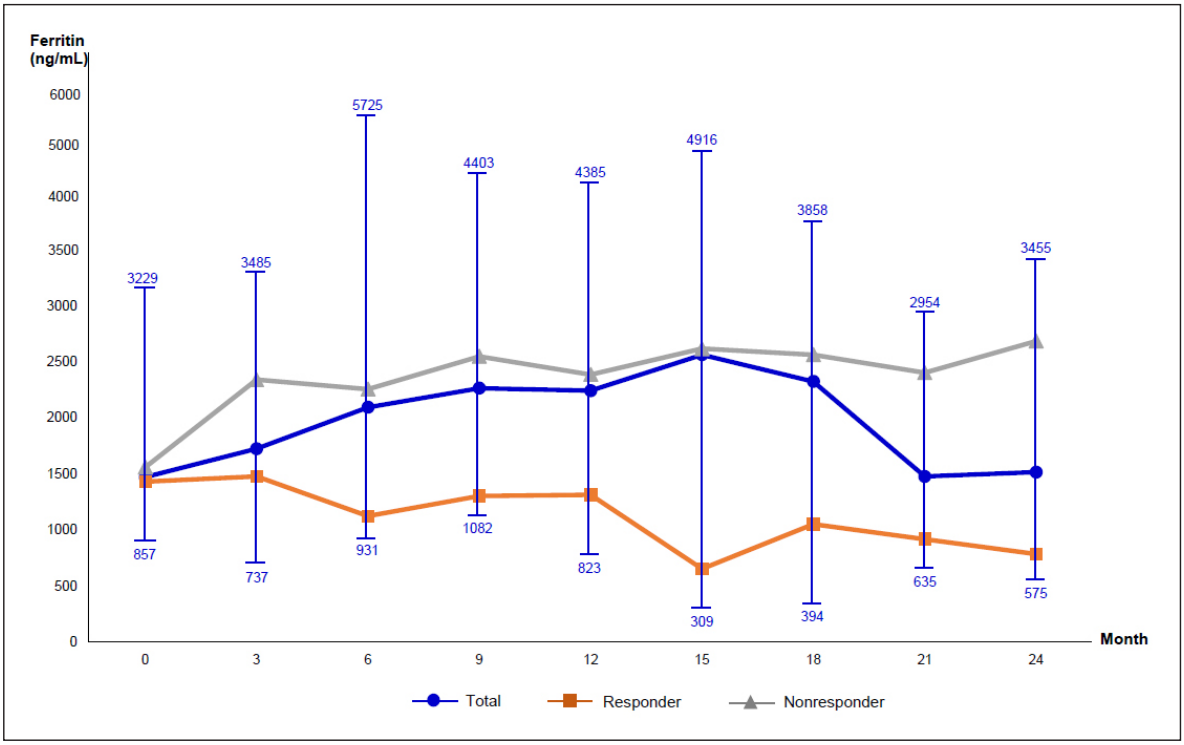

Figure 1 Median level of serum ferritin with range among total patients; responders included patients with reduced serum ferritin ≥ 15% from baseline value.

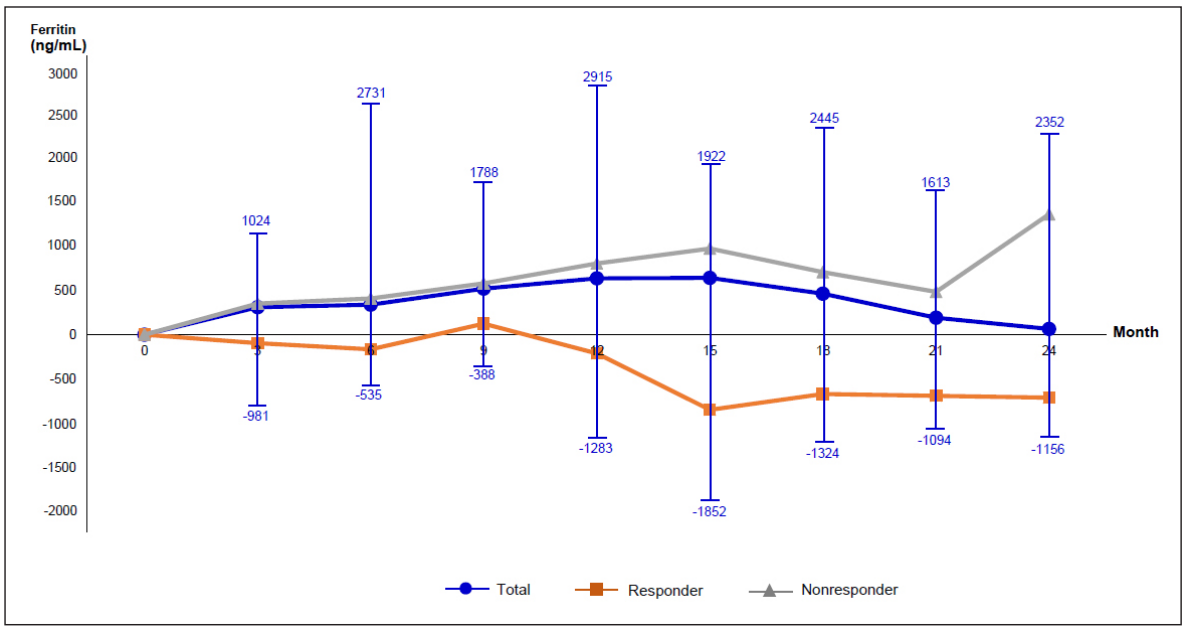

Figure 2 Median change from baseline in serum ferritin with range among total patients; responders included patients with reduced serum ferritin ≥ 15% from baseline value.

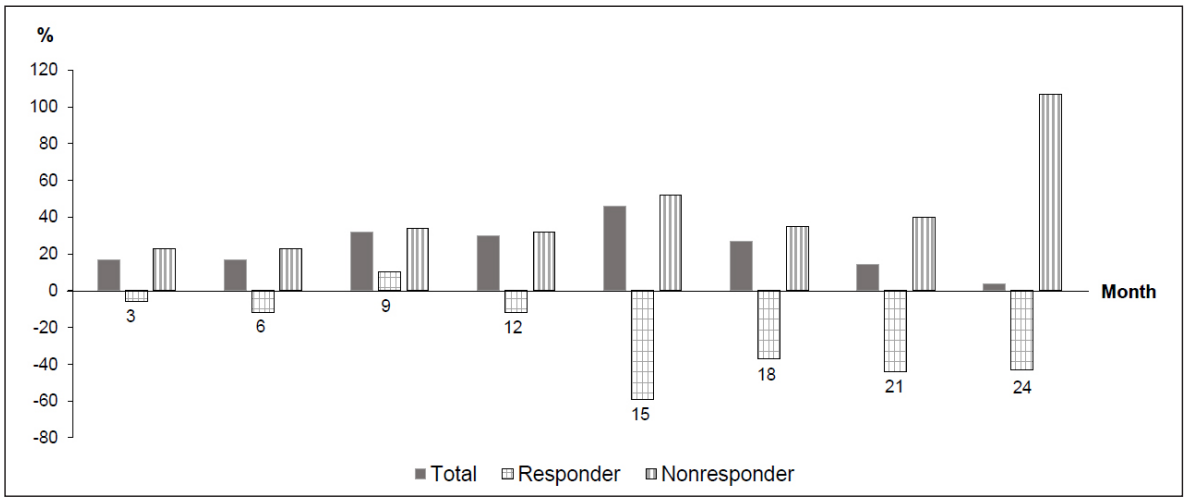

Figure 3 Median percentage change from baseline in serum ferritin; responders included patients with reduced serum ferritin ≥ 15% from baseline value.

However, 4 of 19 patients (21%) were defined as responders while the remaining 15 patients were defined as nonresponders. The median level of serum ferritin among responders at the end of the first and second years was significantly lower than those of nonresponders (1,314 *vs.* 2,385 ng/mL, p = 0.012; 785 *vs.* 2,683 ng/mL, p = 0.029). The median change from baseline in serum ferritin among responders at the end of the first and second years was also significantly more reduced than those of nonresponders (-209 *vs.* +800 ng/mL, p = 0.056; -705 *vs.* +1,351 ng/mL, p = 0.029). Moreover, the percentage change from baseline in serum ferritin among responders at the end of the first and second years was more reduced than those of nonresponders (-12% *vs.* +32%, p = 0.127; -42% *vs.* +107%, p = 0.029) as shown in Figures 1 to 3. The significantly reduced serum ferritin levels in responders started from the sixth month of treatment. Interestingly, the severity scores of thalassemia, amount of transfused packed red cells, duration to achieve the maximum dose and maximum dose of deferiprone among responders and nonresponders did not significantly differ.

All patients could tolerate oral deferiprone without gastro-intestinal disturbance. Neither adverse reac-

tions of arthralgia, arthritis or rash were found. Ten adverse events were found among 5 patients. Transminitis was found among 3 patients with ALT of 413, 279 and 249 units/L at the 9th, 18th and 18th month of treatment while receiving a daily dose of deferiprone at 84, 79 and 100 mg/kg, respectively. The first patient was switched to deferasirox as the second line iron chelation when ALT decreased to 72 units/L after discontinuing deferiprone for 4 weeks. The second and third patients also discontinued deferiprone for 4 weeks with the recovery of ALT at 53 and 24 units/L. They could gradually tolerate the challenging deferiprone to reach the dose before discontinuing deferiprone. Severe neutropenia of ANC $0.32x10^9$/L was found in 1 patient at the 27th month of treatment while receiving a daily dose of deferiprone at 98 mg/kg. Although the ANC spontaneously recovered within 1 week and reached the normal range in 4 weeks without any rescue treatment, she was switched to deferasirox as the second line iron chelation. Neutropenia of absolute neutrophil of $1.15x10^9$/L and $1.03x10^9$/L were found in 2 patients at the 9th and 12th month of treatment while receiving the daily doses of deferiprone at 84 and 96 mg/kg, respectively. The first patient was the same patient with transminitis at the 9th month of treatment who switched to deferasirox although the ANC normalized after discontinuing deferiprone for 1 week. The second patient continued deferiprone and ANC spontaneously recovered to $3.06x10^9$/L within 1 week. This patient also exhibited mild thrombocytopenia of platelet counts at $114x10^9$, $115x10^9$, $141x10^9$ and $125x10^9$/L at the 6th, 9th, 12th and 15th month of treatment when the daily doses of deferiprone were at 88, 88, 89 and 96 mg/kg, respectively compared with her baseline platelet count of $164x10^9$/L. Ultimately, deferiprone was terminated in only 2 patients with severe neutropenia ($0.32x10^9$/L) and elevated ALT (413 units/L) and discontinued for 4 weeks in the other 2 patients with elevated ALT at 279 and 249 units/L. The other adverse events were considered so mild that deferiprone was uninterrupted. All 10 events spontaneously recovered without either patient requiring medical intervention.

The allele frequencies of UGT1A 6 of wild type *1 and mutant alleles of *2 and *4 were found at 0.82, 0.16 and 0.02, respectively among 44 patients with thalassemia as controls. For the studied patients, only 1 responder patient possessed the homozygous mutant allele of UGT1A6 of *2/*2. The remaining responder patients had homozygous wild type of UGT1A6 of *1/*1. On the contrary, 2 nonresponder patients were heterozygous UGT1A6 of *1/*3 and *2/*4, respectively.

No significant increase in body weight or appetite was reported upon increasing deferiprone dose. All patients had normal liver and renal profiles and were negative for hepatitis B, C virus and HIV status.

Discussion

This study employed a single-arm prospective design. The sample size was based on the feasibility and clinical considerations rather than statistical considerations. We understood that the protocol should include more patients to illustrate robust effectiveness. To our knowledge, this constitutes the first study of the liquid formulation of deferiprone among young Thai children with thalassemia.

The Thai health care system provides national coverage free of charge for all Thai citizens. Patients with thalassemia receive leucocyte-depleted packed red cells, folic acid, multivitamin, vitamin E and iron chelation of subcutaneous deferoxamine and oral deferiprone. Deferasirox was indicated as the second line therapy for Thai patients aged more than 6 years unresponsive to deferiprone or exhibiting adverse events to deferiprone. Unresponsiveness was defined by a level of serum ferritin > 2,500 ng/mL while receiving the maximum daily dose of 100 mg/kg with either no change or increase in the level of serum ferritin after receiving deferiprone for 1 year or reduced serum ferritin < 15% after receiving deferiprone for 2 years. Adverse events include systemic allergic reaction, ALT > 250 units/L, severe neutropenia

of ANC < $0.5x10^9$/L, recurrence of neutropenia (ANC < $1.0x10^9$/L), severe arthropathy and gastro-intestinal disturbance after rechallenging.

When this study was initiated in January 2017, iron chelation was limited for Thai children aged 2 to 6 years. Deferasirox (Exjade®) has not been recommended as the first line therapy in the national coverage for thalassemia children aged 2 to 6 years with transfusion-induced iron overload until April 2018[18]. These young patients were essentially in need of oral chelation. However, the cost of deferasirox was too high for the patients' parents to afford. They inevitably received the commercial liquid formulation of deferiprone (Ferriprox®) for which their parents were able to pay the cost by themselves. When the Thai GPO successfully produced a liquid formulation of deferiprone in addition to the tablet form, these parents were willing to enroll their children in the study although clinical data were limited. It remains unknown whether the liquid formulation of deferiprone monotherapy will reach the efficacy of 45.2% as previously reported in the tablet form[19].

The liquid formulation of deferiprone was tolerable among young children with thalassemia in the current study. No arthralgia and arthritis were found as previously reported in the tablet form[19,20]. The current study showed the safety of the liquid formulation of deferiprone with few adverse events including severe neutropenia (n = 1) and transminitis (n = 3). Patients spontaneously recovered by discontinuing deferiprone for 4 weeks without rescue therapy was needed. In addition, neutropenia (n = 2) and mild thrombocytopenia (n = 4) were so mild that deferiprone remained uninterrupted. However, the efficacy was unsatisfactory. Upon the end of the first year, the median percentage change from baseline in serum ferritin among 18 of 19 studied patients was 30% increment while the daily iron load was rather high at 0.41 mg/kg to maintain the median pretransfusion hemoglobin at 9.8 g/dL. Although the median percentage change from baseline in serum ferritin at the end of the second year was markedly improved and reached only 4% increment, the number of enrolled patients was just 8 cases and the nonresponders were switched to the second line therapy of deferasirox, free of charge supplied by the government starting in April 2018. Deferiprone is more effective among those with higher iron burden > 3,500 ng/mL[19] but not with values below 2,500 ng/mL[21-23]. An increasing daily dose of deferiprone from 75 mg/kg to 100 mg/kg has been suggested[24, 25]. The baseline serum ferritin in the current study was 1,470 ng/mL and was provided to the less responsive group. but the daily dose had already increased to 100 mg/kg. In other words, deferiprone administration among children with transfusion-dependent thalassemia in the current study was just the maximum needed to maintain iron homeostasis, but was unable to achieve the negative iron balance. On the contrary, only 4 of 19 patients (21%) showed responsiveness with negative iron balance starting from the 6th month of deferiprone administration. The maximum dose of deferiprone of 100 mg/kg would be gradually decreased when the levels of ferritin declined to < 500 ng/mL.

The preparation of deferiprone in the liquid formulation is not similar to the tablet formulation. The key property of an orally active iron chelator is its ability to be efficiently absorbed from the gastro-intestinal tract and to cross biological membranes; thereby, gaining access to the desired target sites such as the liver. The limitation of the current study was the lack of a pharmacokinetic study of deferiprone in plasma and urine among individual studied patient. The crucial 3-hydroxyl functionality of the deferiprone for scavenging iron is also the prime target for glucuronidation to be the nonchelating 3-O-glucuronide conjugate[26]. Moreover, the variation of batch to batch preparation depends upon the quality assurance of the production process. Therefore, a further comprehensive study is warranted.

The UGT1 family is involved in the hepatic glucuronidation of bilirubin and numerous drugs including deferiprone. The allele frequency of UGT1A6*2 among Thai thalassemia controls (0.16) was slightly lower than

that of the healthy Thai volunteers (0.19)[27] and those of Japanese, white and African-American populations (0.213, 0.274, 0.243) respectively[16,28]. In the current study, only 1 responder patient was homozygous *2/*2 of UGT1A6; he could have had a higher maximum serum deferiprone concentration and area under the serum deferiprone concentration-time curve from time zero to infinity than those of the homozygous wild type (*1/*1) or heterozygous alleles (1*/*3, 2*/4*). However, the number of the studied patients was rather small, so further study among a higher number of patients is warranted.

Starting in April 2018, the Thai government has provided deferasirox (Exjade®) as the first line iron chelation for children aged 2 to 6 years with transfusion-induced iron overload. Therefore, deferasirox should be the first line iron chelation for children aged 2 to 6 years except some young children who could not drink 200 mL of the dissolved deferasirox completely early morning before breakfast. Then the liquid formulation of deferiprone would be the second choice for them, and the effectiveness should be closely monitored. Cases of unresponsiveness after 6 to 12 months of administration should be switched to deferasirox.

Apart from the budget to purchase the commercial medicine[29], the GPO has the urgent task to produce deferasirox locally at a cheaper price. Moreover, a liquid formulation of deferasirox is essentially required.

In conclusion, the liquid formulation of deferiprone (GPO-L-ONE®) at the maximum daily dose of 100 mg/kg was tolerable among young children with transfusion-dependent thalassemia and iron overload. The most serious adverse event of severe neutropenia was found in 1 of the 19 studied patients while other adverse events were mild. However, efficacy was limited with responsiveness to negative iron balance in 4 of 19 patients (21%).

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Disclosure Statement

The authors state that they have no interests which might be perceived as posing a conflict or bias.

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