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Original Article

Long-Term Effectiveness, Safety, and Tolerability of Twice-Daily Dosing with Deferasirox in Children with Transfusion-Dependent Thalassemias Unresponsive to Standard Once-Daily Dosing

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Abstract. ***Background:*** **Patients with transfusion-dependent thalassemia *(*TDT*)* risk iron overload and require iron chelation therapy. Second-line therapy is warranted for patients demonstrating poor chelation responses.**
Patients and methods: **We retrospectively studied the serum-ferritin (SF), and liver-iron-concentration (LIC) outcomes of patients with TDT treated with twice-daily dosing of deferasirox (TDD-DFX) > 24 months, after failing to respond to once-daily deferasirox (OD-DFX).**
Results: **We enrolled 22 OD-DFX nonresponders (14 males and eight females; median age, 9.2 [3–15.5] years). The median blood transfusion was 216 (206–277) ml/kg/year. The median TDD-DFX treatment period was 30 (24–35) months. Before initiating TDD-DFX, the median SF level was 2,486 (1,562–8,183) ng/ml, while the median LIC was 6.6 (3.2–19) mg/g dry wt. There were 18 TDD-DFX responders (81.8%) and 4 TDD-DFX nonresponders. The median SF-level change was -724 (-4,916 to 1,490) ng/mL. The median LIC change was -2.14 (-13.7 to 6.8) mg/g dry wt. The 1-year and 2-year SF levels and LICs were statistically significant (SF, *P* = 0.006/0.005; and LIC, 0.006/0.005, respectively). There were no treatment interruptions secondary to adverse events. In the follow-up of the TDD-DFX responder group, 11 of the 18 had a reduced dose, whereas the remaining seven continued with the same dose.**
Conclusions: **TDD-DFX appears to be an alternative treatment approach for patients refractory to OD-DFX, with a favorable long-term safety profile. Further studies with larger groups and pharmacogenetic analyses of OD-DFX responders are warranted to determine the efficacy and safety profile of TDD-DFX.**

Keywords: Deferasirox; Iron chelation; Iron Overload; Thalassemia.

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Introduction. Thalassemia is one of the most common hereditary hemolytic anemias found in Southeast Asia, including in Thailand.[1] The severity ranges from asymptomatic to transfusion-dependent thalassemia (TDT). Patients with TDT requiring regular blood transfusion may succumb to iron overload. This

condition ultimately results in organ damage, especially cardiomyopathy and liver cirrhosis, secondary to cardiac and liver siderosis, respectively. Once-daily deferasirox (OD-DFX) dispersible tablets can be administered as an oral iron chelator to patients with transfusional iron overload, depending on factors such as the iron burden, rate of transfusion, and adequacy of the dosage.[2] Although the recommended dosage of OD-DFX is 30 mg/kg/day, about 30% of patients with TDT cannot maintain a negative iron balance with OD-DFX; they require a dosage greater than 30 mg/kg/day.[3] The dosage can be increased to 40 mg/kg/day while maintaining an acceptable safety profile.[4] Nevertheless, even when treated with a higher dosage, some patients still need other treatments to achieve adequate iron chelation. Our earlier research found that twice-daily dosing of DFX (TDD-DFX) showed improved clinical efficacy in patients with TDT who were OD-DFX nonresponders.[5] However, the long-term effectiveness, safety, and tolerability of TDD-DFX in children with TDT who were unresponsive to OD-DFX have not yet been studied. The primary objective of this study was to determine the clinical efficacy of TDD-DFX, and the secondary objective was to evaluate the safety and tolerability of TDD-DFX in patients with TDT who failed to respond OD-DFX during their long-term treatment.

Patients and Methods. Patients with TDT who were treated with OD-DFX at Siriraj Hospital, Mahidol University, Bangkok, Thailand, between January 2013 and December 2020 were retrospectively analyzed. The red blood cell (PRC) transfusion was given every 3–4 weeks at a dosage of 12–15 mL/kg, depending on the pretransfusion hemoglobin level, to maintain the pretransfusion hemoglobin level at greater than 9 g/dL. On two consecutive tests, iron chelation was initiated in patients with TDT if their serum ferritin (SF) level was greater than 1,000 ng/mL. Monitoring of the treatment regimen was based on the results of the patients' trimonthly SF level assessments. Cardiac T2* magnetic resonance imaging (MRI) and liver iron concentration (LIC) monitoring were performed every 6 to 12 months at our institute.[6] The dose of DFX was initiated at 15-20 mg/kg/day and adjusted according to their SF-level and MRI results. Patients unable to undergo an MRI study were monitored solely by SF concentration. Complete blood count, liver function test, renal function test, and urine analysis were monitored every 6 to 8 weeks, depending on the transfusion schedules. In addition, an ophthalmic examination and audiometry were performed annually during treatment with DFX. OD-DFX nonresponders were defined using modified criteria by Chirnomas et al. as follows: (1) their average DFX-OD dosage exceeded 35 mg/kg/day for six months and (2) their SF level tended to increase, and/or there was less than a 30% reduction in their SF level relative to baseline for three consecutive months with more than 2 SF measurements exceeding 1,500 ng/mL during the time that dosage exceeded 35 mg/kg/day.[7] The OD-DFX nonresponders were switched to TDD-DFX, using the same dose as the previous OD-DFX regimen. Treatment responses after TDD-DFX were reviewed one year after initiation of the chelators, with evaluations based on the patients' SF levels and MRI studies. TDD-DFX responders were defined based on our institutional criteria as follows: (1) their 1-year SF level declined by more than 15% of the baseline, or (2) their LIC decreased from the baseline value. Patients did not respond to TDD-DFX were classified as TDD-DFX nonresponder. Tolerability to DFX and treatment compliance were evaluated by history taking and reviewing the drug dosages prescribed during the study period. Patients with grade I proteinuria were advised to have adequate hydration without dose adjustment. Those who experienced > grade I proteinuria were tested for urine protein/creatinine ratio. If the ratio was greater than 0.5 for two consecutive times, the medication was temporarily omitted. The 50% reduction dose was restarted if the ratio was less than 0.5. Treatment toxicity was graded according to the US National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.03). Before the commencement of this research, its protocol was approved by the Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand *(*COA 175/2564, IRB4*).*

Statistical Analysis. Statistical analyses were performed using STATA IC (release 16; StataCorp LLC., College Station, TX, USA). Continuous variables were analyzed and reported using descriptive statistics (medians and ranges). In addition, a Wilcoxon matched-pairs signed-rank test compared SF levels, LICs, and other parameters at the baseline, 1-year, and 2-year time points. Statistically significant differences were defined as *P* values of < 0.05.

Results. Of the 22 OD-DFX nonresponders in this study, 21 had hemoglobin E/β thalassemia, while 1 had β thalassemia major. The baseline characteristics of the patients are summarized in **Table 1**. No patient had cardiac T2* MRI < 20 ms. The median TDD-DFX treatment time was 30 (24–35) months. The median dose of OD-DFX was 37.5 (35-40) mg/kg/day.

With 17 of the OD-DFX nonresponders, their responses were based on their SF-level and MRI results, whereas with the other 5 OD-DFX nonresponders, the responses were determined by SF level only. In all, there were 18 TDD-DFX responders (81.8%) and 4 TDD-DFX nonresponders. Fifteen of the 18 TDD-DFX responders had evidence of declined LICs, while the remaining 3 TDD-DFX responders only exhibited

Table 1. The baseline clinical characteristics of the enrolled OD-DFX nonresponders.

Parameters	Overall OD-DFX nonresponders (n = 22)	TDD-DFX responders (n = 18)	TDD-DFX nonresponders (n = 4)
Age (years)	9.2 (3–15.5)	10.4 (3–15.1)	10 (7.7–15.5)
Sex (male)	14	10	4
The median erythron transfusion (ml/year)	216 (206–277)	213 (206–277)	216 (210–270)
The median dose of OD-DFX (mg)	37.5 (35–40)	37.5 (35–40)	37.5 (35–40)
The median baseline of SF (ng/ml)	2,486 (1,562–8,183)	2,369.5 (1,562–8,183)	2,944 (1,610–3,883)
The median baseline of LIC	6.6 (3.2–19)	6.25 (3.2–19)	6.95 (6.7–7.2)

Abbreviations: LIC, liver iron concentration; OD-DFX, once-daily deferasirox; SF, serum ferritin; TDD-DFX, twice daily defrasirox.

Table 2. The clinical efficacies of the twice-daily dosing of deferasirox (TDD-DFX) regimen and other laboratory parameters of the OD-DFX nonresponder group.

Parameters	Baseline	12 months	24 months	*P* value
Number of patients evaluated	22	22	18	NA
Number of responses (%)	NA	18 (81.8%)	18 (100%)	NA
Median SF (range), ng/mL	2,486 (1,562–8,183)	1,456 (434–4,302)	881.5 (432–3,265)	NA
Median change in SF (range) (%)	NA	-724[a] (-4,916 to 1,490)[a] (-29.1%)[a]	-1,228[b] (-5,622 to -331)[b] (-45.3%)[b]	0.006[a] 0.005[b]
Median LIC (range), mg/g dry weight	6.6 (3.2–19)	3.5 (0.8–14)	2.7 (0.8–10)	NA
Median change in LIC (range) (%)	NA	-2.14[a] (-13.7 to 6.8)[a] (-31.9%)[a]	-3.5[b] (-13.9 to -0.6)[b] (-52.2%)[b]	0.006[a] 0.005[b]
BUN (mg/dL)	10.15 (6.7–14.5)	10.3 (7.8–15.1)	10.75 (6.7–15.4)	0.93[a] 0.01[b]
Creatinine (mg/dL)	0.56 (0.41–0.74)	0.64 (0.47–0.78)	0.65 (0.45–0.78)	0.005[a] 0.002[b]
Total bilirubin (mg/dL)	1.8 (1.4–3.5)	1.85 (1.4–3.6)	1.95 (1.2–3.4)	0.97[a] 0.58[b]
Direct bilirubin (mg/dL)	0.5 (0.4–0.7)	0.5 (0.4–0.8)	0.45 (0.4–0.7)	0.57[a] 0.14[b]
AST (IU/L)	32.5 (15–72)	38.5 (18–74)	37.5 (20–64)	0.47[a] 0.68[b]
ALT (IU/L)	25.5 (14–45)	30 (14–47)	33.5 (14–46)	0.12[a] 0.32[b]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; BUN, blood urea nitrogen; EOS, end of the study; LIC, liver iron concentration; NA, not applicable; OD-DFX once daily dose deferasirox. [a] BL vs 12 months and [b] BL vs 24 months.

decreased SF levels. The four patients, classified as TDD-DFX nonresponders one year after commencement of the TDD-DFX regimen, were switched to a combination of DFX and deferoxamine. The median changes in the SF levels and LICs at the 1-year-post-treatment and 2-year-post-treatment time points for the TDD-DFX therapy are detailed in **Table 2**. Of 3 TDD-DFX responders who only exhibited decreased SF levels, the median reduction of SF at a 1-year time point was 31% (range 23-62%). **Figure 1** illustrates the changes in the SF levels and LICs of the TDD-DFX responders. As to the TDD-DFX nonresponder group, 2 of the four patients experienced increased SF levels and LICs, while the other two only saw a rise in their SF levels. A disparity between the SF level and the LIC was observed in 2 patients: both were TDD-DFX responders with a decline in the LIC but an elevation in the level of SF. In the follow-up study of the 18 TDD-DFX responders, 11 could be treated with a reduced TDD-DFX dose (median, 17.04 mg/kg/day), but the other seven patients continued with the same TDD-DFX dose (median, 37.4 mg/kg/day). There were no reported incidents of gastrointestinal intolerance or skin reaction. However, three patients developed grade I proteinuria, which was resolved without interruption or reducing the TDD-DFX therapy. Neither severe transaminitis (alanine aminotransferase > 3 times of the upper limit of normal) nor abnormal renal function test results were reported for all 18 patients (**Table 2**). Although the blood-urea-nitrogen and creatinine levels were significantly increased at the 1-year-post-treatment and 2-year-post-treatment timepoints relative to baseline, they were still within the

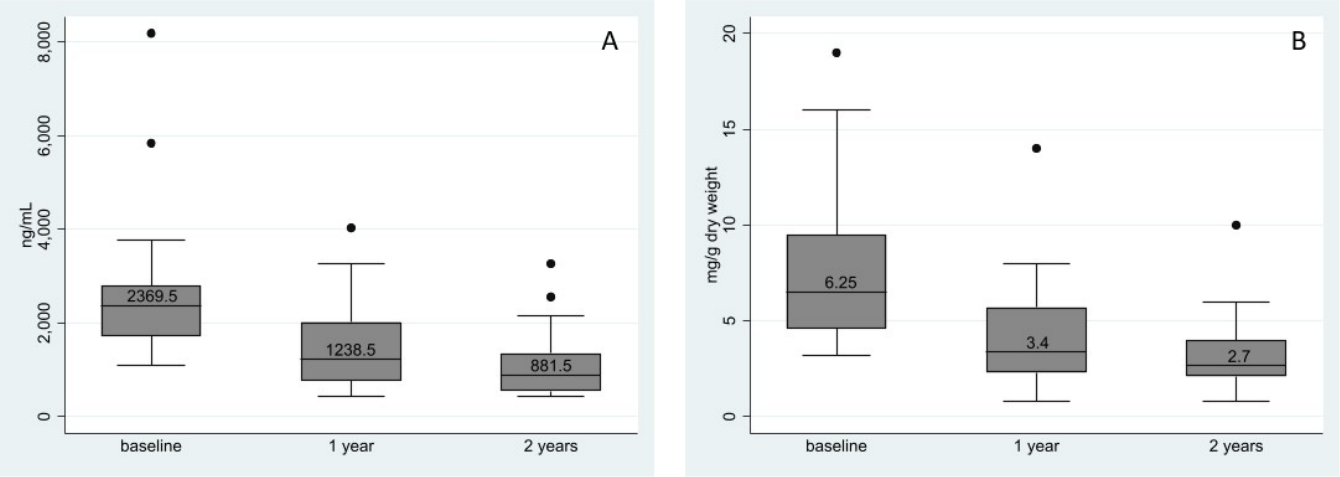

Figure 1. Changes in the serum ferritin (SF) levels (**A**) and liver iron concentrations (LICs) (**B**) of the TDD-DFX responder group.

normal ranges for age. The ophthalmic examinations and audiometry results were normal throughout the treatment with TDD-DFX.

Discussion. Although the survival of patients with TDT has improved dramatically with the use of effective iron chelators, research showed that 40% of patients had poor responses to standard monotherapy.[7,8] For example, in our previous study, 44% of patients with TDT were OD-DFX nonresponder.[5] Fortunately, the alternative approach of using TDD-DFX can modify the response in the majority of such recalcitrant cases (81.8%). In the current investigation, 18% (4 of 22) of the TDD-DFX nonresponders required other chelations (**Figure 2**). As we previously reported, the combination of DFX and another chelator should be considered for such patients.[9] Hepatic siderosis was common in our study. All those with analyzable LICs experienced liver siderosis, and 40% of such patients were classified as having moderate to severe disease.

Nevertheless, those with moderate to severe hepatic siderosis still responded to the TDD-DFX regimen. Likewise, other clinical factors of the TDD-DFX responder and TDD-DFX nonresponder groups were comparable, for example, SF level, age, and sex. Thus, this response may highlight the value of TDD-DFX therapy even for patients with a high iron accumulation.

A study of TDD-DFX in an animal model revealed that it might yield a broader suppression of non-transferrin-bound iron and a lower peak concentration than OD-DFX, resulting in improved efficacy and decreased toxicity, respectively.[10] Similarly, a pharmacokinetic study in humans demonstrated that TDD-DFX tended to produce higher Cmax and Ctrough values than OD-DFX, especially at a dosage exceeding 30 mg/kg/day. Moreover, the difference between the Cmax and Ctrough values for TDD-DFX was less than that for OD-DFX. Hence, a more sustainable drug level with TDD-DFX may account for the improved chelation results in patients who failed to respond to OD-DFX. A clinical study conducted by Chang and associates demonstrated that the efficacy of TDD-DFX was equivalent to that of OD-DFX during a 6-month treatment period, with a favorable tolerability for patients experiencing gastrointestinal intolerance from OD-DFX.[3] In a longer study of 1 year, Pongtanakul and coauthors reported the clinical efficacy of TDD-DFX for children with TDT who had responded poorly to the standard OD-DFX therapy. They found that TDD-DFX improved the children's chelation response and had a favorable safety profile.[5] Other studies also demonstrated the feasibility of TDD-DFX in terms of reduced iron deposition and improved tolerability. However, the evaluations of most of those investigations were based solely on the SF levels at the 6-month treatment timepoint.[11,12] An exception was the work of Karimi and colleagues, which used a combination of the SF level and LIC as well as a 1-year follow-up.[13] In the present study, the response to TDD-DFX was sustained for more than one year when evaluated with SF and LIC. In terms of tolerability, our study revealed a statistically significant increase in the serum creatinine level from the baseline value to the 1-year follow-up. Nevertheless, the rise seemed to be mild and nonprogressive since the median serum creatinine level at the 2-year time point was static and within the normal range for age. Furthermore, all patients could continue the TDD-DFX therapy without any treatment interruption caused by gastrointestinal disturbance or other adverse events. As the TDD-DFX appears to have favorable safety profiles, it should be considered for those experiencing side effects of OD-DFX before deciding to change to other chelations.

This study has some limitations. Firstly, consistent with the nature of retrospective studies, some data were missing. More specifically, the LICs could not be evaluated for some patients because of the generally limited ability of young children to cooperate; the evaluation in some patients was solely based on SF. Hence, the LICs that were obtained may not truly reflect

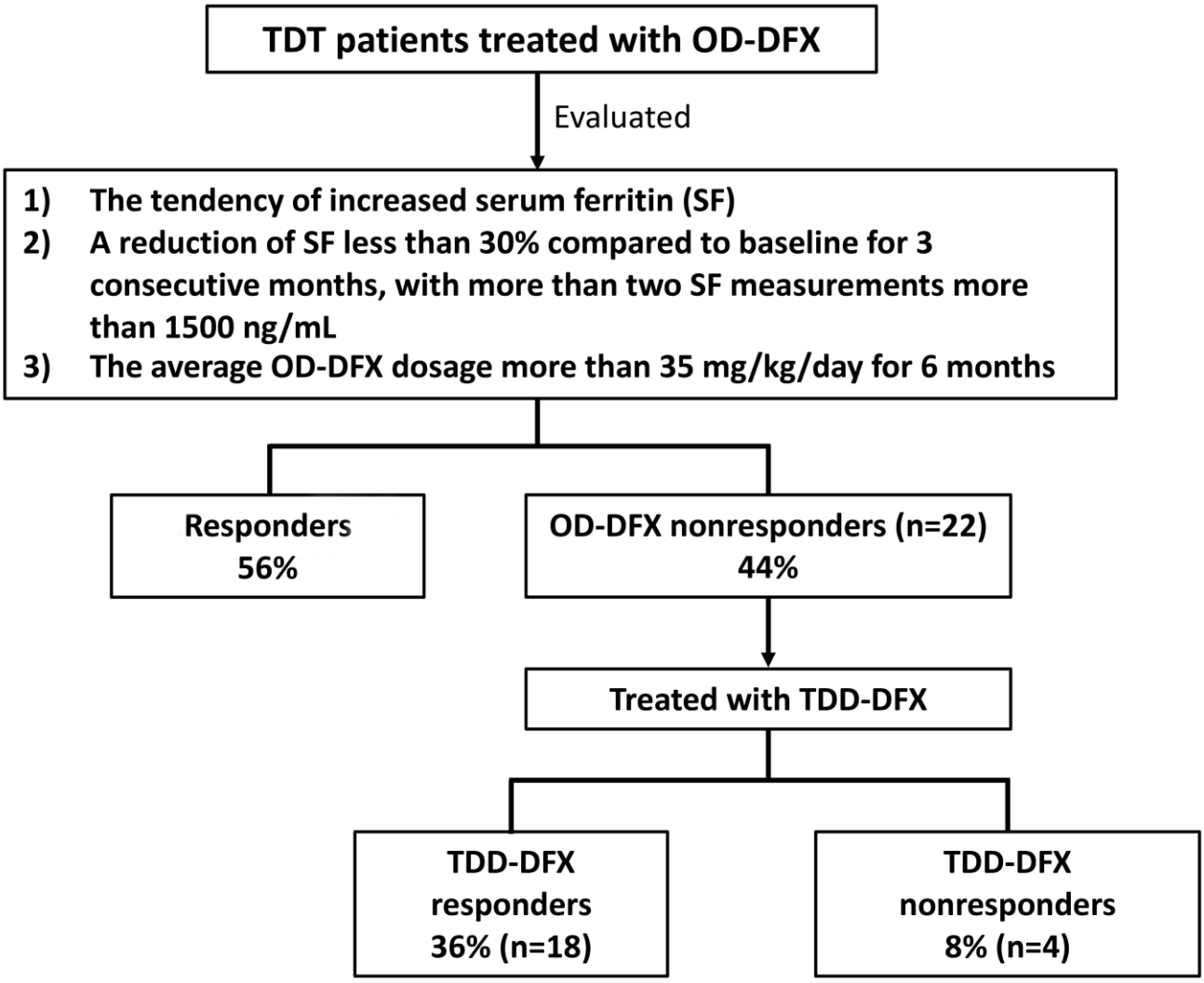

Figure 2. Responses of the patients with transfusion-dependent thalassemia (TDT) to the once-daily deferasirox (OD-DFX) and twice-daily dosing of deferasirox (TDD-DFX) regimens.

the overall outcomes of the study cohort. Moreover, due to the small number of patients, the efficacy and toxicity of the study may not be salient. Furthermore, factors that could be used to predict the response to OD-DFX therapy could not be determined by this study. Lastly, the study could not evaluate the effect of TDD-DFX on cardiac siderosis since all 22 patients had normal MRI T2* values.

Conclusions. To summarize, TDD-DFX may be regarded as a second-line therapy for those unresponsive to OD-DFX. Further studies with a larger cohort, a longer follow-up, and pharmacogenetic analyses of inadequate-response patients are warranted to elucidate the efficacy and safety profile of TDD-DFX.

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