Twice daily dosing of deferasirox significantly improves clinical efficacy in transfusion dependent thalassemias who were inadequate responders (IR) to standard once daily dose

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Introduction

• Clinical efficacy of deferasirox (DFX), a once daily oral iron chelator in patients with transfusional iron overload depends on factors such as iron burden, rate of transfusion and appropriate dose. At present, the recommended dose approved as a label indication is 30 mg/kg/day, though doses up to 40 were studied in patients with cardiac siderosis with acceptable safety profiles.

• Recent several studies have shown in a non-clinical trial setting that a proportion of patients could not achieve satisfactory iron balance at 30 mg/kg/day or even at higher dose. These patients were labeled as inadequate responder (IR).

• In our center, surprisingly 44.2% of transfusion dependent thalassemia patients were classified as IR to DFX since the drug was registered in 2007.

• Difference in bioavailability with a lower area under the curve (AUC) of each IR individual was the only main mechanism identified earlier (Neufeld E, et al. Blood 2009).

Objective

• We hypothesize that adjusting DFX dose from once daily into two dividing dose per day might improve drug exposure and chelating efficacy in such patients.

Methods

• A retrospective cohort of clinical response to deferasirox in Thai thalassemia patients was performed after an informed consent. This study was approved by a local ethical committee at Siriraj Hospital, Bangkok, Thailand.

• A standard guideline for the use of deferasirox at our hospital including SF and MRI monitoring, adverse events (AEs) evaluation and standard laboratory evaluation was set by both authors and this was applied to all patients participated into this study.

• Patients with IR was primarily defined as (1) having a rising serum ferritin (SF) trend or (2) having a reduction of SF less than 30% of baseline levels (BL), at least 3 consecutive months, with more than two SF measurements higher than 1500 ng/mL; and (3) receiving once daily DFX at an average dosage > 35 mg/kg/day for at least 6 months.

• DFX administration schedule was switched to twice daily with the same total dose per day.

• CBC, renal function, urine analysis were performed every 3 weeks to monitor possible adverse effects. SF and liver function test were checked every six weeks.

• Tolerability and compliance to DFX were evaluated by direct history taking and drug account prescribed during study period.

• Clinical diagnosis
  - Hb E / thal.
  - β thal major
  - Hb Bart hydrops

• Average SF (ng/mL)
- at baseline
- before switching
- median % change (range)
  3,632 ± 2,031.02
  3,044 ± 1,444.3
  -15.6% (-29.8 to +104%)

• Median follow up time (months)
- before switching
  15.3 ± 6.3
- after switching
  20.8 ± 10.3

• SF: serum ferritin, NA = not applicable

Results

Nineteen patients were met inclusion criteria; 2 patients were excluded from further study due to poor compliance and a short follow up period (less than 6 mths). Total 17 patients (7 male, 41%) were eligible with a mean (± SD) age of 10.22 ± 4.1 yrs (range; 2.1-18 yrs).

• Clinical efficacy of deferasirox (DFX); a once daily oral iron chelator in patients with transfusional iron overload depends on factors such as iron burden, rate of transfusion and appropriate dose. At present, the recommended dose approved as a label indication is 30 mg/kg/day, though doses up to 40 were studied in patients with cardiac siderosis with acceptable safety profiles.

• Recent several studies have shown in a non-clinical trial setting that a proportion of patients could not achieve satisfactory iron balance at 30 mg/kg/day or even at higher dose. These patients were labeled as inadequate responder (IR).

• Although 3 patients had a SF reduction < 30%, all showed a reducing trend; −11.5%, −25.7% and −38.08 % after an informed consent. This study was approved by a local ethical committee at Siriraj Hospital, Bangkok, Thailand.

• Five from 17 patients were evaluated for liver iron concentration (LIC); average LIC at BL and at the end of study (EOS) were significantly reduced from 11.2 to 5.85 mg/g dry wt. None had cardiac T2* < 20 msc.

• All patients except two tolerated well with DFX at before and after switching (up to 12 months) with minor adverse events (AEs). One patient had significant proteinuria after 6 months and one with severe transaminitis (ALT > 3 x UNL). They were temporarily discontinued with DFX and both AEs were completely resolved and did not recur when they were resumed on the twice daily regimen.

• Twice daily DFX was shown to be effective in patients with DFX intolerance. We show herein that patients with IR might also be beneficial from a twice daily dosing with clinically well-tolerance and acceptable compliance.

• Dividing DFX into twice daily dose might provide a better bioavailability in selected patients with sustainable therapeutic levels of DFX throughout 24 hr-exposure resulting in a better clinical efficacy.

• Further pharmacokinetic and pharmacogenetic study in IR patients is warranted and this can provide additional insights on the next level of tailoring iron chelation therapy in patients with transfusional iron overload.

Conclusions

• There are no relevant conflicts of interest to disclose.

Table 1: Patient characteristic and Clinical efficacy of deferasirox twice daily dose at 6 and 12 mths

<table>
<thead>
<tr>
<th>Response to switch dose2</th>
<th>At 6 months, cases</th>
<th>Mean SF</th>
<th>Median % change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No response to switch dose</td>
<td>14 (82.4%)</td>
<td>3,844 ± 1,444.3</td>
<td>-15.6% (-29.8 to +104%)</td>
<td>p&lt; 0.05</td>
</tr>
<tr>
<td>Decrease of SF &gt; 30% of the baseline levels</td>
<td>3 (17.6%)</td>
<td>3,632 ± 2,031.02</td>
<td>-38.08 %</td>
<td>p&lt; 0.05</td>
</tr>
</tbody>
</table>

*Median dose of DFX 37.22 ± 2.3 mg/kg/day, #Decrease of SF > 30% of the baseline levels

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