Deferasirox in Patients with Transfusion-dependent Thalassemia Low Transfusion Intensities

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BACKGROUND

Within the broadpectrum of thalassemia diseases severity, transfusion requirements vary substantially. Thus, for example, blood transfusion is higher in non-splenectomized than in splenectomized patients, and local clinical practice may also influence transfusion needs. As a result, blood intake can be very low in some patients with transfusion-dependent Thalassemia (TDT).

The threshold of <7 mL packed red blood cells (pRBCs)/kg/month (determined by assessor) has been used as criteria for defining transfusion in the last decade of our study period. Therefore, it is important that the safety and efficacy of iron chelation therapy with deferasirox is described in the patient group with low blood intake (<7 mL), as well as in the rest of the TDT population.

OBJECTIVE

To review the safety and efficacy of deferasirox in TDT patients with low-transfusion intensity in parallel with the rest of the study population, as assessed by monthly blood intake.

METHODS

Patient Data

- Patient data from six previously published studies of = 1-5 year duration in TDT patients treated with deferasirox were pooled.1-6
- Study inclusion criteria and dosing regimen varied across studies.

Analyses

- Blood intake was calculated and retrospectively categorized for each year at the threshold of 7 mL.
- Blood intake was reviewed for patients: those patients were subcategorized under the 7 mL group.
- Results were similar with or without these patients.
- Endpoints were adverse events (AEs) year of study and selected laboratory parameters (end of each year).
- Data were summarized by year and deferasirox dose categories for patients with low blood intake (<7 mL).
- In order to present the findings for the low blood intake group within the context of the more regularly transfused patients, subject the population receiving 27 mL pRBCs/kg/month (median value of 27 mL) as also presented in tables and figures.

RESULTS

Patient Characteristics

- Of the 262 patients with thalassemia included in the meta-analysis, 10-15% had low blood intake (<7 mL) in each year of the study period.
- Patient demographics and baseline characteristics are shown in Table 1. Patients in the 7 mL group had substantially lower transfusion median (range) in patients (27 mL pRBCs/kg/month), pRBCs/kg/month (median value of 27 mL) as also presented in tables and figures.

Table 1. Patient Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Blood intake &lt;7 mL pRBCs/kg/month</th>
<th>Blood intake ≥7 mL pRBCs/kg/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>22.3 (3.0-10.6)</td>
<td>16.8 (5.9)</td>
</tr>
<tr>
<td>Median</td>
<td>22.3 (23.7-7.2)</td>
<td>15.5 (23.6-7.2)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>170 (49.3)</td>
<td>827 (46.6)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>101 (30.2)</td>
<td>101 (30.2)</td>
</tr>
<tr>
<td>Median</td>
<td>3 (2.0)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>156 (46.2)</td>
<td>386 (42.0)</td>
</tr>
<tr>
<td>Median</td>
<td>12 (3.3)</td>
<td>14 (3.8)</td>
</tr>
<tr>
<td>Serum ferritin, ng/mL</td>
<td>306 (262-118.14)</td>
<td>2125 (232-260.26)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>74.4 ± 52.7</td>
<td>188.1 ± 51.4</td>
</tr>
<tr>
<td>Median</td>
<td>65.0 ± 52.7</td>
<td>154.1 ± 52.8</td>
</tr>
</tbody>
</table>
| AC, arthritis; SD, standard deviation

Exposure to Deferasirox

- The mean actual deferasirox doses received during Years 1 to 5 are shown in Figure 1. Although doses were similar, expectedly, after 1 year the average actual dose of deferasirox in the 7 to 27 mL group was greater than the 0 to 7 mL group.

Effect of Deferasirox on Serum Ferritin

- Serum ferritin decreased after 5 years of treatment to medians 1188 ng/mL (range 221-13,149 ng/mL) in the 0 to 7 mL group (7 mL group).

Figure 1. Serum Ferritin Levels and Actual Deferasirox Doses Among Transfusion-dependent Thalassemia Patients Receiving ≤7 or ≥7 mL pRBC/kg/month During 5 Years of Deferasirox Treatment

- Changes in serum ferritin with deferasirox dose were described. Figure 2: After 1 year, doses >10 mg/kg/day were insufficient to achieve decreases in serum ferritin and doses <4 mg/kg/day were the lowest reductions in serum ferritin. The dose-dependent trend continued up to 5 years of deferasirox treatment.

Figure 2. Dose-dependent Change in Serum Ferritin among Transfusion-dependent Thalassemia Patients Receiving <7 or ≥7 mL pRBC/kg/month During 1 year of Deferasirox Treatment

- Absolute CoE across dose categories after 1 year of treatment is shown in Table 3. After 5 years of deferasirox treatment, alanine aminotransferase (ALT) improved from 40 to 54 to 40 mL at baseline to 40 to 44 to 42 mL at 7 years, with a similar trend in AST patients (Figure 5).
- By dose categories, after 1 year of treatment, the greatest mean SD reduction in ALT for the ≤7 mL group was observed for patients receiving 11 to 15 mg/kg/day (CoE <7 mL), compared with an increase in patients receiving doses >10 mg/kg/day (71 ± 57 to 71 ± 46 U/L).
- For the 7 mL group, the ALT improvement was -71.0 ± 52.1 versus baseline 44.4 ± 45.5 at 7 years and >71 ± 46 U/L at 7 years.
- Patients with ALT ≥30 ~ uL upper limit of normal (ULN) were infrequent and frequency did not appear to increase over time (Figure 6).

Table 3. Cretinine Clearance by Dose Categories among Transfusion-dependent Thalassemia Patients Receiving <7 or ≥7 mL pRBC/kg/month after 1 year of Deferasirox Treatment

- The threshold of >30 ferritin was similar to the rest of the population assessed who were receiving 27 mL pRBC/kg/month.
- High iron burden in patients with low blood intake may be due to elderly age or suboptimal prior chelation.
- Deferasirox was effective for iron removal over the long term, with upwards dose adjustment over time. Water contamination was the most common cause of iron reduction across blood intake categories.
- Change in serum ferritin was dose dependent, with doses >20 mg/kg/day in the low blood intake group and 220 mg/kg/day in the 7 mL group leading to a marked reduction in serum ferritin.
- These data highlight the need for appropriate dose optimization, carefully considering a patient's blood intake, iron burden and safety parameters.
- Importantly, the safety profile of deferasirox in patients with low blood intake was consistent with the established safety profile, even at the highest dose category, 230 mg/kg/day.
- In the majority of AEs and SAEs were comparable between groups and incidence decreased over time.
- CoE decreased within the first year and then remained stable over subsequent years, consistent with prior observations that renal function does not worsen over time with deferasirox treatment,10 even in patients with low blood intake.
- This analysis is limited by heterogeneity of included studies and retrospective categorization of patients, and because only a small proportion of patients contributed to treatment.
- This study demonstrated that in this patient population with low transfusional intake yet substantial iron burden, beneficial effects of deferasirox treatment were observed over a 5-year period, with reduction in iron burden and an acceptable safety profile.

CONCLUSIONS

- Baseline iron burden in patients with low blood intake (<7 mL) was substantially higher than in the rest of the TDT population assessed, who were receiving 27 mL pRBC/kg/month.
- High iron burden in patients with low blood intake may be due to elderly age or suboptimal prior chelation.
- Deferasirox was effective for iron removal over the long term, with upwards dose adjustment over time. Water contamination was the most common cause of iron reduction across blood intake categories.
- Change in serum ferritin was dose dependent, with doses >20 mg/kg/day in the low blood intake group and 220 mg/kg/day in the 7 mL group leading to a marked reduction in serum ferritin.
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REFERENCES


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