


A prospective randomized controlled trial on the safety and efficacy of alternating deferoxamine and deferiprone in the treatment of iron overload in patients with thalassemia

We compared the safety and efficacy of alternating deferoxamine and deferiprone with that of deferoxamine monotherapy. Sixty transfusion-dependent thalassemia patients regularly treated with deferoxamine were randomized to continue deferoxamine alone or to receive an alternating therapy for one year. Both arms resulted in equivalent decreases of serum ferritin and liver iron concentration. There was no significant difference in the proportion of patients with adverse events in the two therapy groups although the nature of the adverse events differed according to the chelation regimen.

Key words: thalassemia, deferoxamine, desferrioxamine, deferiprone, iron, chelation.

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The availability of deferiprone has enabled clinicians to tailor chelation therapy to the needs of the patient: possible regimens are monotherapy with either deferiprone or deferoxamine (DFO) or dual chelator therapy, whereby both drugs can be given on the same days (combination regimen) or on different days (alternating regimen). The benefits of combined therapy as an intensified regimen of chelation have been well-reported. Alternating therapy is currently very common in clinical practice, probably because, by reducing the weekly number of infusions, it may be a practical approach for patients poorly compliant to therapy with DFO alone. However, the safety and efficacy of this strategy has not yet been supported by evidence. The current study was designed to evaluate whether the use of a alternating chelation regimen, which would allow patients to reduce the nightly injections and in their place have some days of oral chelation with deferiprone, is safe and effective.

Design and Methods

Sixty patients with thalassemia major from three centers (Athens, Cagliari and Turin) were enrolled. The major inclusion criteria were: (i) 10 years of age or older, (ii) most serum ferritin values between 1000 µg/L and 4000 µg/L over the previous year, (iii) undergoing chelation with subcutaneous deferoxamine. Patients were randomized either to continue DFO (Novartis Pharma AG, Switzerland) at the same dose for 5 to 7 days per week for 12 months or to receive an alternating regimen of deferiprone (Apotex Inc, Canada), 25 mg/kg body weight, three times per day, orally 5 days a week and DFO the other 2 days of the week. During the study period no change was allowed in the dose of deferiprone, while the DFO dose could be adjusted on the basis of the ferritin levels. Compliance with deferiprone was assessed by pill counts, diary cards and an electronic cap (MEMS®, Aardex Ltd, Switzerland) that recorded the time and date of each opening of the tablet container.

Compliance with DFO was assessed by diary cards, weekly physical examination of infusion sites, and by the Crono™ infusion pump that recorded the number of completed infusions. The efficacy of the chelating regimens was estimated by changes in serum ferritin and in liver iron concentration (LIC). LIC was assessed by a superconducting quantum-interference device (SQUID) susceptometer (Hamburg, Germany) in the pre-treatment phase and after 12 months. A complete blood cell count was performed every week. Alanine transferase (ALT) levels were measured every 4 weeks and zinc levels every 6 months. The study was approved by the local Institutional Review Board of each participating center.

A two-sample t-test was performed to compare parametric characteristics. Trend analysis of serum ferritin and ALT data was performed using the repeated measures ANOVA (analysis of variance) approach. The incidence of adverse events was compared between the two regimens using the χ² test. The difference in the combined incidence of agranulocytosis and milder degrees of neutropenia between the two regimens was assessed by Fisher's exact test. All statistical analyses were performed using the SAS System for PC, Release
8.2. A type I error ($\alpha$) of 0.05 was used to determine statistical significance.

**Results and Discussion**

Baseline characteristics were similar in the two groups (Table 1). Only one patient discontinued the study prior to its termination. A 15-year old male randomized to alternating therapy developed flu symptoms and mild neutropenia on the second day of the study, while treated only with DFO. The patient was withdrawn from the study without having taken any dose of deferiprone.

**Efficacy**

There was no significant difference in transfusional iron input, as determined by red cell consumption, and in overall compliance with therapy between the two arms. Both treatments gave a similar decrease in serum ferritin (-248±791 µg/L for the alternating therapy group vs -349±573 µg/L for the DFO only group; $p=0.5802$), and LIC ($-65±165$ vs $-239±747$ µg Fe/g liver, $p=0.2263$). The trend analysis demonstrated no significant effects of the two treatments on rate of decline and average serum ferritin (Figure 1). There was no statistically significant difference in the proportion of patients with a negative trend between the two therapy groups. The mean DFO doses for the two study arms were equivalent at baseline (34.8±8.9 mg/kg/day in the alternating therapy group; 36.0±5.8 mg/kg/day in the DFO group and 33.3±6.64 mg/kg/day in the alternating therapy group; $p=0.05$), due to changes in serum ferritin levels.

**Safety**

Seven patients (24%) treated with the alternating therapy, and two patients (7%) treated with DFO only, experienced at least one adverse drug reaction ($p=0.08$). Different adverse drug reactions were found between the two therapies. The alternating therapy was associated with episodes of vomiting in five patients (17%), abdominal pain in three patients (10%), and diarrhea in one patient (3%). These events occurred mainly in the first weeks of therapy and were mild/moderate in severity. Daily infusions of DFO were associated with abscess at the site of infusion in one patient (3%), and allergic reactions in another patient (3%). New episodes of neutropenia besides the one described above were observed in only one other patient, also treated with DFO alone. This 33-year old female patient experienced neutropenia (absolute neutrophil count=1.24×10^9/L) in the 10th week of study, which resolved spontaneously within 1 week without her discontinuing DFO. There were no episodes of agranulocytosis. There was no significant change in ALT from baseline to end of the study for either group (data not shown) and there was no significant difference in trend between the two therapy groups in monthly ALT values. A difference in the overall frequency of ALT values above three times of upper limit was observed between the DFO and the alternating treatment groups for HCV-positive patients; these high ALT levels were observed transiently in 1/14 and in 5/12 patients in the two treatment groups ($p=0.06$). No significant change was detected in zinc levels from baseline to the end of study between the two therapies. No cases of arthropathy were observed in either therapy arm. To date, this is the first prospective randomized controlled trial comparing the efficacy and safety of alternating deferiprone and deferoxamine to deferoxamine.

<table>
<thead>
<tr>
<th>Table 1. Main characteristics of the patients.</th>
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<tbody>
<tr>
<td>Diferiprone alternated with deferoxamine</td>
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<tr>
<td>(n=29)</td>
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<tr>
<td>Females</td>
</tr>
<tr>
<td>13 (45%)</td>
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<tr>
<td>Mean age±S.D. (years)</td>
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<tr>
<td>18.7±4.8</td>
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<td>Patients positive for HCV antibodies</td>
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<td>12 (41%)</td>
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<td>Mean serum ferritin µg/L±S.D.</td>
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<td>2048±685</td>
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<td>Patients with baseline serum ferritin &gt; 2,500 µg/L</td>
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<td>8 (28%)</td>
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<tr>
<td>Mean liver iron concentration (µg/g wet weight)</td>
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<td>1629±744</td>
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<td>Splenectomized patients</td>
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<td>5 (17%)</td>
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<td>Compliance with DFO during the study</td>
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<td>96.1±5.0%</td>
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<td>Baseline DFO dose (mg/kg/day)</td>
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<tr>
<td>36.0±5.8</td>
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<td>End-of-study DFO dose (mg/kg/day)</td>
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<td>33.3±6.64</td>
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<td>Transfusional iron input (µL/Kg/year)</td>
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<td>109±20</td>
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![Figure 1. Mean monthly serum ferritin concentrations in the groups receiving deferoxamine alone (solid squares) and deferiprone alternated with deferoxamine (open triangles). The squares and triangles represent the mean serum ferritin values for 30 patients treated with deferoxamine alone, or 29 patients treated with the alternating therapy, respectively. Trend analysis demonstrated a significant negative trend (p=0.0469) at an estimated rate of decline of -24.8 ± 12.4 µg/L/month (mean±se) with no significant effect of therapy on the trend.](image-url)
alone. The effectiveness of the alternating use of deferiprone and DFO was initially reported by Aydinok et al. in a small non-controlled clinical study. Our study demonstrated that both alternating deferiprone/DFO and DFO alone resulted in similar decreases in serum ferritin and LIC, despite the increase in DFO dose in the group of patients treated with DFO only and the decrease in DFO dose in the group treated with the alternating therapy due to changes in serum ferritin.

The alternating regimen has the theoretical advantages of targeting more iron pools and achieving a longer period of chelation coverage. Recent retrospective studies have reported that oral deferiprone has a greater ability to reduce iron loading in the heart and a greater cardioprotective effect than has subcutaneous DFO. However, since this study was designed prior to these publications, it did not evaluate the effect of either therapy in removing iron from other tissues such as the heart.

The current study showed that the alternating use of DFO and deferiprone is not associated with new safety concerns. All adverse reactions observed have been previously reported. DFO infusions were associated with local reactions, while the oral chelation therapy was associated with transient gastrointestinal symptoms. ALT changes were transient, more common in HCV-positive subjects, and not considered of clinical relevance. Similar results have been obtained in patients on monotherapy with deferiprone; the mechanism has not been clarified.

The most serious adverse effect of deferiprone is agranulocytosis which occurs in 0.5% of patients. No agranulocytosis was observed in this clinical study, which could be due to the relatively small number of patients studied for a rarely occurring complication. On the other hand, it is noteworthy that the two patients who experienced milder episodes of neutropenia were receiving treatment with DFO alone, supporting the observation that this event occurs in thalassemia patients independently of deferiprole use. There appeared to be a lower frequency of arthralgia during alternating therapy, compared to the frequencies found in previous studies on deferiprone monotherapy, although a direct comparison could not be made. Nevertheless, having a deferiprole-free period may be sufficient to prevent the occurrence of these adverse effects.

In summary, the results of this study demonstrate that the alternating use of oral deferiprole with subcutaneous infusions of DFO, in the manner used in this study, had comparable efficacy to daily infusions of DFO alone in controlling the body iron load in transfusion-dependent patients. The alternating use of both chelators is not associated with increased iron chelation toxicity. Most importantly, the data provide support to clinicians who need to give patients a period of time in which injected chelation can be interrupted and replaced with oral chelation.

**References**


