

THE SAFETY AND EFFICACY OF AN ORAL SOLUTION FORMULATION OF DEFERIPRONE IN CHILDREN WITH TRANSFUSIONAL IRON OVERLOAD

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Abstract

Limited data are available on the use of deferiprone (Ferriprox™) in young children. The current study evaluated the safety and efficacy of a new liquid formulation of Ferriprox in iron-overloaded pediatric patients with transfusion-dependent anemias. The study also evaluated the absolute neutrophil count (ANC) of children who were maintained on deferiprone therapy during episodes of mild neutropenia. One hundred children ranging from 1.5 to 10 years of age were enrolled. At enrollment, 52 children were being treated with deferoxamine (mean duration = 1.9 ± 2.1 years; range: 0.05-7.3 years), 20 with deferiprone (mean duration = 0.5 ± 0.6 years; range: 0.1-2 years), 8 patients with deferasirox (mean duration = 0.4 ± 0.5 years; range: 0.14-1.58 years) and 20 patients were naïve to chelation therapy. Mean \pm SD serum ferritin at time of enrollment was 2521.9 ± 1458.9 $\mu\text{g/L}$ (range: 1002-7480 $\mu\text{g/L}$). The oral solution was tolerated well by all but one child and there were no unexpected adverse reactions. The incidence of neutropenia and agranulocytosis were low. The data show that serum ferritin levels significantly decreased after 24 weeks of Ferriprox therapy, and that there was lower incidence of gastrointestinal adverse reactions (vomiting = 6% of patients; abdominal pain = 6% of patients and nausea = 1%) than what has been reported with the tablet formulation (nausea = 16% of patients; vomiting = 13%; abdominal pain = 14%). In summary, data suggest that treatment with the oral solution of Ferriprox was efficacious, well tolerated by children, the frequency of adverse reactions was lower than what has been observed with the tablet formulation, and its use was not associated with new safety concerns.

Objective

The objective of this study was to determine the safety and efficacy of Ferriprox Oral solution™ in pediatric patients.

Materials & Methods

A 24 week, multi-centre, open label, single treatment study to determine the safety and efficacy of an oral formulation of deferiprone (Ferriprox) was conducted in young children with iron overload requiring iron chelation. The protocol was approved by local IRBs. Inclusion criteria: (1) ≤ 10 years of age, (2) confirmed diagnosis of transfusion-dependent anemia other than Blackfan-Diamond anemia, (3) chronic iron overload requiring chelation therapy, (4) enrolment in a chronic transfusion program, having received at least 8 red blood cell transfusions/year for a minimum of 1 year, and (5) serum ferritin (SF) concentration > 1000 $\mu\text{g/L}$.

A palatable liquid formulation of deferiprone (Ferriprox) was initiated at 50 mg/kg/day divided in 3 doses, for the first 2 weeks, then increased to 75 mg/kg/day. The dose could be further increased to 100 mg/kg/day for patients with ferritin > 2500 $\mu\text{g/L}$ at baseline.

Assessment of: adverse events (AEs), concomitant medications, and CBC were performed weekly. Serum ALT, creatinine and zinc concentration were measured at baseline, week 12 and end of study. Serology for HCV and HBV were assessed at baseline and end of study. Serology for HIV was assessed at baseline only. Other safety assessments included medical history, physical examination including vital signs and ECG.

SF concentration was measured at baseline and every 4 weeks. The efficacy endpoint was the change in SF concentration from baseline.

Deferiprone was to be discontinued upon onset of moderate neutropenia ($0.5 \times 10^9/\text{L} \leq$ Absolute Neutrophil Count [ANC] $< 1.0 \times 10^9/\text{L}$), or severe neutropenia/agranulocytosis ($\text{ANC} < 0.5 \times 10^9/\text{L}$). Deferiprone was not discontinued at episodes of mild neutropenias ($1.0 \times 10^9/\text{L} \leq \text{ANC} < 1.5 \times 10^9/\text{L}$). In all cases neutrophil count was monitored daily until resolution of the event.

Results: Efficacy

• 100 patients enrolled; 54 Males, 46 Females (76 Caucasian (Egyptian), 24 Asian (9 Chinese, 13 Indonesian, 2 Malays))

• Chelation therapy prior to study enrollment was deferasirox (8%), deferiprone (20%), and deferoxamine (52%). The remaining children (20%) were naïve to chelation therapy. The mean \pm SD baseline SF for all patients was 2521.9 ± 1458.9 $\mu\text{g/L}$.

• After 24 weeks on deferiprone therapy, there was a significant reduction in SF values from baseline (table)

Change in Serum Ferritin from Baseline to Week 12, Week 24

SF change from baseline to:	n	Mean \pm SD	p-value
week 12	99	-247 \pm 1004	0.02
week 24	99	-356 \pm 978	0.0005

Results: Safety

- 95 patients completed the study; 2 patients were withdrawn due to AE; 1 lost to follow-up; 2 voluntarily withdrawn)
- 2 patients experienced agranulocytosis. One had experienced 2 previous episodes of mild neutropenia, which had resolved without discontinuation of deferiprone. At onset of $\text{ANC} < 1.0 \times 10^9/\text{L}$, both patients discontinued deferiprone and were treated with GCSF. Resolution, defined as ANC counts $> 1.5 \times 10^9/\text{L}$ for 2 consecutive days, occurred within 7 to 10 days for these patients.
- 6 patients experienced episodes of mild neutropenia and had their ANC monitored daily. All episodes resolved within 3-11 days, despite continued therapy with deferiprone. None progressed to agranulocytosis
- Gastrointestinal adverse reactions included reports of vomiting in 5% of patients, abdominal pain in 6% of patients and nausea in 1% of patients.
- Other ADRs included: Neutrophil count decreased** (16%); ALT increased (12%); Increased appetite (5%); Arthralgia (4%).

** Defined as $\text{ANC} < 1.5 \times 10^9/\text{L}$ which was $> 1.5 \times 10^9/\text{L}$ the next day.

Discussion

The rationale for this study was to investigate the acceptability, safety and efficacy of a novel liquid formulation of Ferriprox for young children requiring iron chelation therapy. Two tolerability issues with deferiprone tablets in some patients are GI upset and difficulty in swallowing the tablets

- The new liquid formulation had a lower incidence of gastrointestinal adverse reactions than previously reported with the tablet formulation as shown in the chart below

	Oral solution in children ≤ 10 yr old	Tablet formulation in children > 6 yr old and adults
Adverse Reaction (AR)	% Patients with AR	% Patients with AR
Nausea	1%	16%
Abdominal Pain	6%	14%
Vomiting	6%	12%
Arthralgia	4%	11%
Neutropenia ($0.5 \times 10^9/\text{L} \leq \text{ANC} < 1.5 \times 10^9/\text{L}$)	6%	6%
Agranulocytosis ($0.5 \times 10^9/\text{L} < \text{ANC}$)	2%	1%

- No issue with swallowing the liquid formulation.
- Importantly, the changes in SF from baseline to week 12 and week 24 were examined (two-sample t-test).
- The Mean \pm SD of the serum ferritin changes from baseline to week 12 was -247 ± 1004 ($p=0.02$) and from baseline to week 24 was -356 ± 978 ($p=0.0005$).
- The use of the liquid formulation was not associated with any new adverse reactions.

The liquid formulation of Ferriprox™ appears to be a viable alternative for young children requiring chelation therapy.