

THE SAFETY AND TOLERABILITY 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 tolerability 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 Ferriprox™ (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 ± SD serum ferritin at time of enrollment were 2521.9 ± 1458.9 µg/L (range: 1002-7480 µg/L). The oral solution was tolerated well by all but one child and there were no unexpected adverse reactions. The data currently available suggest that there was lower incidence of gastrointestinal adverse reactions (vomiting = 5% of patients; abdominal pain = 6% of patients and no reports of nausea) than what has been reported with the tablet formulation of deferiprone (nausea = 16% of patients; vomiting = 13%; abdominal pain = 14%). In summary, preliminary data suggest that treatment with the oral solution of Ferriprox™ was well tolerated by children, the frequency of adverse reactions was lower than what has been observed with the tablet formulation of deferiprone, and its use was not associated with new safety concerns.

Objective

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

The long term objective of this study is to assess the safety and tolerability of Ferriprox oral solution for the treatment of iron overload in pediatric patients with transfusion-dependent anemia and to assess the efficacy of Ferriprox oral solution in reducing iron overload in children.

Materials & Methods

A 24 week, multi-centre, open label, single treatment study was conducted in 3 countries having 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 concentration > 1000 µg/L.

A palatable liquid formulation of Ferriprox was created. Therapy was initiated at 50 mg/kg/day divided in 3 doses, for the first 2 weeks, then increased to 75 mg/kg/d. The dose could be further increased to 100 mg/kg/day for patients with ferritin > 2500 µg/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 and ECG.

Serum ferritin concentration was measured at baseline and every 4 weeks. The efficacy endpoint was the change in serum ferritin (SF) concentration from baseline.

Deferiprone was to be discontinued upon onset of moderate (0.5 x 10⁹/L = Absolute Neutrophil Count (ANC) < 1.0 x 10⁹/L, or severe neutropenia/agranulocytosis (ANC < 0.5 x 10⁹/L). Deferiprone was not discontinued at episodes of minor neutropenias (1.5 x 10⁹/L = ANC < 1.0 x 10⁹/L) and the neutrophil count was monitored daily until resolution of the event or progression to moderate neutropenia/agranulocytosis.

Results: Safety

- Of 100 patients enrolled, 80 completed the study and 16 are ongoing (2 withdrawn due to AE; 1 lost to follow-up; 1 voluntarily withdrawn)
- All 16 ongoing patients have completed at least 16 weeks of treatment.
- 2 patients experienced agranulocytosis. One had experienced 2 previous episodes of mild neutropenia, which had resolved without discontinuation of deferiprone. At onset of ANC < 1.0 x 10⁹/L, both patients discontinued deferiprone and were treated with GCSF. Resolution, defined as ANC counts > 1.5 x 10⁹/L for 2 consecutive days, occurred within 7 days and 10 days for these patients.
- 4 patients experienced episodes of mild neutropenia and had their ANC monitored daily. All those episodes resolved within 3-11 days, despite continued therapy with deferiprone.
- Gastrointestinal adverse reactions included reports of vomiting in 5% of patients and abdominal pain in 6% of patients. There were no reports of nausea.
- Other ADRs included: Neutrophil count decreased (11%); Increased liver enzymes (5%); Increased appetite (5%); Arthralgia (3%); Pharyngitis (1%).

Demographic and Baseline Data

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

- The primary diagnoses were thalassemia major (91%), E/Beta Thalassemia (8%) and Sickle Cell Disease (1%).

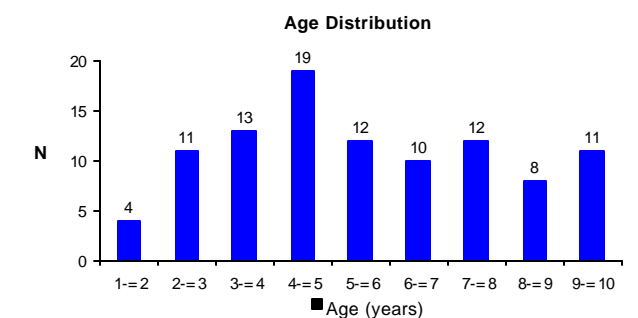
- Chelation therapy prior to study enrollment was deferasirox (8%), deferiprone (20%), and deferoxamine (52%). The remaining children (20%) were naïve to chelation therapy

Serum Ferritin and Blood Biochemistry at Baseline

Serum Ferritin Levels	Mean	SD	Range
= 2500 µg/L (N=60 patients)	1574.52	395.17	1002-2435
> 2500 µg/L (N=40 patients)	3942.95	1309.47	2590-7480

Baseline Blood Chemistry	Mean	SD	Range	Reference range
Alanine transaminase (IU/L)	45.2	29.9	6.0 - 159	5.0 - 65
Creatinine (µmol/L)	28.6	11.9	8.4 - 70.7	27 - 62
Zinc (µmol/L)	10.5	3.2	5.0 - 17.0	8.0 - 20

- The mean age of diagnosis was 1.3 ± 1.1 years (median: 1.0 years; range: 0.2-4.7 years)
- The mean age of subjects in the present study was 5.6 ± 2.4 years (median: 5.1 years; range: 1.5-10 years (Figure))



Discussion

The rationale for this study was to investigate the acceptability of a novel liquid formulation of Ferriprox™ for those patients who have difficulty taking tablets (e.g., pediatric patients)

- Two tolerability issues with tablets are GI upset and difficulty in swallowing the pills.
 - The new liquid formulation had a lower incidence of gastrointestinal adverse reactions than previously reported with the tablet formulation [vomiting 13% of patients; abdominal pain 14% of patients; nausea 16% of patients].
 - No issue with swallowing the liquid formulation.
- The use of the liquid formulation was not associated with any new adverse events or adverse reactions.

The liquid formulation of Ferriprox™ appears to be a viable alternative for patients who are unable to tolerate or comply with the use of tablets.