RESEARCH PAPER

Hepatic and Cardiac Iron-load in Children on Long-term Chelation with Deferiprone for Thalassemia Major

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Objective: To evaluate the efficacy of prolonged deferiprone monotherapy in patients with β-thalassemia major. **Methods**: This cross-sectional study included 40 patients (age range 9 to 38 years) with thalassemia major receiving deferiprone for ≥5 years. Serum ferritin, and myocardial iron concentration (MIC) and liver iron concentration (LIC) assessed by T2*MRI were recorded. **Results**: The patients were receiving deferiprone for a mean (SD) duration of 12.1 (4.7) years. The median (IQR) dose of deferiprone was 85 (74.3, 95) mg/kg/day. The MIC was normal or had a mild, moderate or severe elevation in 29 (72.5%), 3 (7.5%), 3 (7.5%), and 5 (12.5%) patients. The LIC was normal or had a mild, moderate or severe elevation in 2 (5%), 4 (10%), 11 (27.5%) and 23 (57.5%) patients. **Conclusions**: The majority of patients receiving deferiprone had a moderate/severe hepatic but normal cardiac iron load. Prolonged deferiprone monotherapy was suboptimal for hepatic iron load in the majority.

Keywords: *Cardiac failure, Hemosiderosis, Hepatic fibrosis, Oral iron chelators*.

In low- and middle-income countries (LMIC), deferiprone is a popular and cost-effective option for iron chelation in patients with β-thalassemia major [1]. Desferrioxamine is seldom preferred due to its arduous route of administration and cost [2]. Serum ferritin is commonly performed to ascertain the iron overload in thalassemic patients. However, it is an acute phase reactant, and a trend is more indicative than a single value [3,4]. T2* magnetic resonance imaging (T2*MRI) has emerged as a non-invasive tool, providing a more accurate estimate of cardiac and hepatic hemosiderosis. We report the status of iron overload in patients with thalassemia major who were receiving deferiprone monotherapy for a prolonged duration.

Methods

This cross-sectional study was conducted in the thalassemia day care center in Department of Pediatrics at PGIMER, Chandigarh, India. Inclusion criteria were: (*i*) A diagnosis of thalassemia major confirmed by hemoglobin electrophoresis or high-performance liquid chromatography, (*ii*) receiving deferiprone monotherapy for a duration of ≥5 years, and (*iii*) a T2*MRI performed in the previous 12 months. The exclusion criteria included: (*i*) exposure to either desferrioxamine or deferasirox, (*ii*) poor compliance (defined as >3 episodes of missing >25% of the recommended dose/month) or a daily deferiprone dose <65 mg/kg. The patients were enrolled between January 2017 and March 2017. The mean serum ferritin over the previous 12 months was calculated. Serological evidence for Human immunodeficiency virus (HIV), Hepatitis B (HBsAg) and Hepatitic C (Anti-HCV-IgG) obtained in the preceding 12 months was also recorded.

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T2*MRI utilized a body coil on a 1.5-T magnetic resonance scanner (MAGNETOM Aera, Siemens Healthcare). An elevation in liver iron concentration (LIC) was categorized as: normal (<2 mg/g), mild (2-7 mg/g), moderate (7-15 mg/g) or severe (>15 mg/g) [5]. An elevation in myocardial iron concentration (MIC) was categorized as: normal (<1.16 mg/g), mild (1.16-1.65 mg/g), moderate (1.65-2.71) or severe (>2.71 mg/g) [5].

The study was approved by our Institute's Ethics Committee. An informed written consent was obtained from patients and/or their caregivers.

Statistical analysis: The data was analyzed with SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA). Comparison of proportions was performed with either Chi-square or

Fisher's exact test. The Spearman's rank-order correlation coefficient was utilized for assessment of correlation between MIC, LIC and serum ferritin.

RESULTS

Forty patients were enrolled (***Fig*. 1**). The mean (SD) age was 23.4 (7.1) years (range 9-38 years). The mean (SD) duration of receiving chelation with deferiprone was 12.1 (4.7) years (range 5-22 years). Twenty-nine (72.5%) patients were receiving deferiprone for ≥10 years. The median (IQR) dose of deferiprone at enrolment was 85 (74.3, 95.0) mg/kg/day. The median (IQR) frequency of blood transfusions administered to the patients was at 3 (3, 3) weekly interval. Thirteen (32.5%) patients had undergone a splenectomy. Serology was reactive for HBSAg, anti-HCV-IgG and HIV in 2 (5.3%), 4 (10.5%) and none of the 38 patients, respectively (reports were unavailable in two patients).

The median (IQR) serum ferritin was 2271.5 (1369.0, 3089.3) ng/mL. The distribution of iron overload based on MIC and LIC is illustrated in ***Table* I**. Amongst 32 patients with a normal/mildly elevated MIC, 27 (84%) had a moderate/severe elevation in LIC.

The serum ferritin correlated with LIC (r=0.499, *P*=0.001), but not with MIC (r=0.280, *P*=0.080). Neither MIC nor LIC correlated with the duration of deferiprone therapy.

Splenectomy did not influence cardiac (*P*=0.52) or liver iron overload (*P*=0.29). Viral infections did not affect cardiac (*P*=0.34) or liver iron overload (*P*=0.65). Presence of moderate/severe cardiac or liver iron overload did not differ among patients receiving ≤90 or >90 mg/kg/day of deferiprone (*P*=0.06 and 0.14, respectively).

DISCUSSION

In this study, we report a group of patients receiving deferiprone monotherapy – the mean duration of therapy exceeding a decade. In our study, while serum ferritin demonstrated correlation with LIC, there was a lack of correlation with MIC. Three-fourths of the patients had a normal or a merely mildly increased MIC. A moderate or severe iron overload was observed in 85% of the patients.

TABLE I DISTRIBUTION OF CARDIAC AND LIVER IRON OVERLOAD IN PATEIENTS RECEIVING DEFERIPRONE >5 YEARS (*N*=40)

Iron overload	*Myocardial iron concentration (MIC)*	*Liver iron concentration(LIC)*
Normal	29 (72.5)	2 (5)
Mild	3 (7.5)	4 (10)
Moderate	3 (7.5)	11 (27.5)
Severe	5 (12.5)	23 (57.5)

Values in no(%).

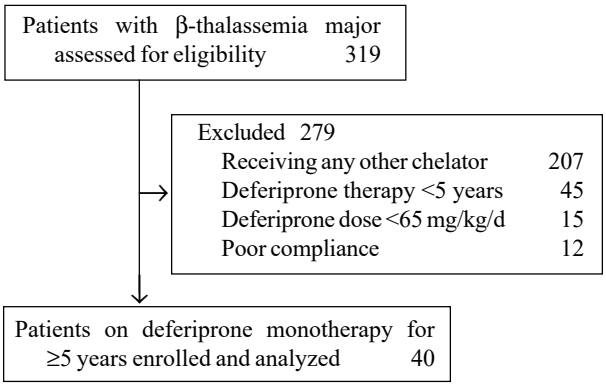

FIG. 1. *Flow of patients in the study.*

The limitations of this study include a cross-sectional design, and a lack of information on the dose of deferiprone administered in the preceding years. A proportion of patients were receiving deferiprone at a dose of 65-75 mg/kg/day. Historical assessment of compliance can also be unreliable. Adverse events of deferiprone were not described due to the cross-sectional design of the study. There was a lack of comparison with patients receiving desferrioxamine or deferasirox.

The cardiac chelating effect of deferiprone is reiterated by our study. Studies evaluating its efficacy have demonstrated improvement in myocardial hemosiderosis, comparable to or superior to desferrioxamine [6,7]. International guidelines concur on the importance of maintaining a low LIC in addition to MIC [3,8]. Several studies have demonstrated that deferiprone monotherapy lags behind desferrioxamine and deferasirox in reducing LIC [9-12]. A possible 'bottleneck effect', wherein, deferiprone is able to chelate merely the iron available in the chelatable pool is postulated [13]. An inferior iron chelation from the liver might in part be related to inadequate doses of deferiprone [14]. However, in our study, even patients receiving >90 mg/kg/day of deferiprone did not have a lower liver iron overload.

We conclude that patients of thalassemia major receiving long-term monotherapy with deferiprone have a high prevalence of moderate or severe hepatic iron overload and a relatively low prevalence of moderate or severe cardiac iron overload. Alternative chelation strategies may be considered in patients with a high LIC on monotherapy with deferiprone.

Contributors: ST: collected data, analyzed data and drafted the manuscript; DB: conceptualized and designed the study, collected data and edited the manuscript; AT, RJ: were pediatric

WHAT THIS STUDY ADDS?

- Long term chelation with deferiprone monotherapy in patients with β-thalassemia major was found to be suboptimal for liver iron overload in majority of the patients.

haematologists who contributed to clinical care and collection of clinical data, supervised and edited the manuscript; AK: was the adult haematologist who contributed to clinical care of older patients and collection of clinical data, supervised and edited the manuscript; AB, KSS: performed and reported T2*MRI scans, were responsible for methodology of T2*MRI, supervised and edited the manuscript; NK: standardized the software of the T2*MRI and reviewed all T2*MRI reports, supervised and edited the manuscript; PB, RD: reported serum ferritin, haemoglobin electrophoresis and high-performance liquid chromatography, supervised and edited the manuscript.

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