EDITORIAL

Hepatic and Cardiac Iron Overload – Revising the Role of Deferiprone

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Thalassemia major (TM) is included in the transfusion-dependent thalassemias group and patients require regular blood transfusions at 3-4 weekly intervals [1]. In India, nearly 12,000 children with TM are born every year [2].

Blood transfusion therapy is the major cause of iron overload in TM. According to the recommended transfusion scheme for TM, about 100-200 ml of pure red blood cells per kg body weight per year are transfused. This amounts to 116-232 mg of iron/kg body weight / year, or 0.32-0.64 mg/kg/day. Normally, iron is bound to molecules such as transferrin, but in iron overload their capacity to bind iron is exceeded both within cells and in the plasma compartment (plasma non-transferrin bound iron – NTBI). The resulting 'free' iron causes cell death, increases risk of infections and organ toxicity. Organ damage in transfusional iron overload reflects the pattern of tissue iron uptake from NTBI. This iron is then stored as ferritin or hemosiderin which are detected by magnetic resonance imaging (MRI) technique. Iron accumulation is toxic and may cause heart failure, cirrhosis, growth retardation and multiple endocrine abnormalities [1]. In fact, cardiac failure and hepatic cirrhosis are the most common causes of mortality in these patients.

Monitoring of iron overload is essential in establishing effective iron chelation regimes. Iron load in the body can be detected by non-invasive tests and invasive tests like tissue biopsy. The former include - blood tests like serum ferritin, labile plasma iron, NTBI and imaging-based tests like MRI for detecting cardiac and hepatic iron load, Magnetic bio-susceptometry *i.e.* SQUID (superconducting quantum interference device). Serum ferritin is a simple, accessible and inexpensive test which correlates with iron stores and helps in identifying the trend. However, it is an indirect estimate of iron load, lacks organ specificity and can be falsely elevated in co-existing inflammation or hepatitis. [1] Studies have shown that it correlates with cardiac impairment and survival but has a poor correlation with hepatic iron. Serum ferritin maintained below 2,500 µg/L over a decade or more has been shown to lower the risk of cardiac disease and death in at least two-third cases [3]. LIC (Liver iron concentration) is the most reliable indicator of body iron load. Normal LIC values are up to 1.8 mg/g dry wt. Sustained high LIC (above 15-20 mg/g dry wt) have been linked to progression of liver fibrosis. Amongst the different MRI techniques, T2* technique (calibrated with biopsy) has been widely used. T2* values <20 ms correlate with a decreased left ventricular ejection fraction, and values <10ms are associated with a 160 fold increased risk for heart failure in the next 12 months. Iron tends to be accumulate initially in the liver and later in the heart but is also removed more rapidly from the liver than the heart by adequate chelation therapy. Thus, whilst high LIC increases the risk of cardiac iron overload, the measurement of LIC will not predict myocardial iron and hence cardiac risk reliably.

Chelation should be started after the first 10-20 transfusions, or when the ferritin level rises above 1,000 µg/L. Three iron chelators currently licensed for clinical use are Desferrioxamine (DFO), Deferiprone (DFP) and Deferasirox (DFX). DFO is a hexadentate parenteral iron chelator with very short half life, given intravenous/ subcutaneously as slow infusion over 8-12 hours at least 5 times a week. DFP is an oral bidentate iron given at 75-100mg/kg/day in three divided doses. DFX is a tridentate oral iron chelator given at 20-40 mg/kg/day [1]. DFP is more cardioprotective than DFO as it is smaller, more lipophilic and therefore, it could be more efficient in accessing intracellular iron. Conversely DFO is more effective in removing or preventing iron deposition in the liver [4]. The sequential combination of DFP and DFO has an additive, if not synergistic chelating effect [5]. Thalassemia International Federation (TIF) has provided guidelines on monitoring for all patients on transfusion and chelation therapy [1].

In this isssue Totadri, *et al*. [6] have presented their data on the efficacy of prolonged DFP monotherapy on cardiac and hepatic iron load in beta-thalassemia major patients. This cross-sectional study included 40 patients on DFP

therapy for ≥ 5 years. Iron load was estimated by serum ferritin and T2*MRI. It shows that DFP monotherapy was associated with moderate-severe hepatic iron overload in almost 85% patients compared to normal cardiac iron content in more than two-third patients. It also highlights the limited utility of serum ferritin correlation with cardiac iron overload, as most of the patients with raised ferritin had normal MIC by T2*MRI. Similarly, Pennell, *et al.* [7] showed that DFP monotherapy was significantly more effective than DFO over 1 year in improving asymptomatic myocardial siderosis in beta-thalassemia major. An Italian study [4] which compared all three iron chelators illustrated that both DFP and DFX were less effective than DFO for hepatic iron. The highlights of this study by Totadri, *et al*. [6] are mean duration of DFP monotherapy was 12 years and healthy median dose of DFP (85mg/kg/d). However, the current study has limitations in being retrospective and cross-sectional in nature, continuation of DFP alone despite hepatic iron overload, and suboptimal ferritin control (this is not standard of case anymore with availability of DFO and DFX). Also, clinical manifestations of hepatic/cardiac iron overload and adverse events to therapy have not been reported.

In conclusion, DFP is able to provide good chelation for cardiac iron overload, but it is highly inadequate for hepatic and thus overall iron overload. Alternative strategies for chelation should be considered in patients with persistent iron load in patients on monotherapy. Randomized controlled trials involving larger number of patients comparing the three iron chelators and various combinations of chelators is the need of the hour.

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