A holistic approach to iron chelation therapy in transfusion-dependent thalassemia patients with serum ferritin below 500 μg/L

To the Editor:

Transfusion-dependent thalassemia (TDT) patients require chronic iron chelation therapy (ICT)1 to balance the rate of accumulation due to blood transfusion and minimize the amount of non-transferrin bound iron (NTBI) which is toxic for lipids, proteins, and DNA through reactive oxygen species.2 ICT requires careful dose adjustments to avoid over-chelation.3 Currently, ICT is initiated after 10-20 units (about 100 mL/kg) of packed red blood cells, or when there is evidence of chronic iron overload or serum ferritin (SF) is >1000 μg/L.3 Few studies have evaluated the management of ICT in TDT in the presence of low SF levels. Deferasirox (DFX) is currently the first-line oral iron chelator worldwide, and its label suggests considering interruption when SF constantly falls below 500 μg/L while no specific indication is available for deferoxamine and deferiprone. However, this cut-off has been arbitrarily defined. Renal and hepatic adverse events (AEs) and increases in serum creatinine (SCr) and alanine aminotransferase (ALT) have been reported in patients with transfusion hemosiderosis treated with DFX,4,5 with most of the AEs occurring with high doses of the drug, independently of SF levels.6,7 In our center, we tailor ICT according to transfusion iron intake, SF, and T2* magnetic resonance imaging (MRI). Thus, the decision to interrupt ICT in TDT patients who are on a regular blood transfusion regimen is not based on SF only.

This study aims to determine the safety of iron chelation therapy in TDT patients with a mean value of SF <500 μg/L for a sustained period. We collected data from TDT patients with mean SF <500 μg/L for at least 24 months between January 2007 and December 2018. Linear (or quadratic when appropriate) regression models were fitted; standard errors (SE) were corrected by taking into account clustering of outcomes within subjects. Statistical analyses were performed with Stata 16 (StataCorp, 2019, College Station, Texas). The study was approved by the Ethics Committee of our institution.

Out of 198 TDT adults regularly treated in our center, 50 fulfilled the inclusion criteria (32 female, 18 male), with 5037 observations (range, 29-157 per patient) coincident with transfusion sessions between January 2007 and December 2018. Patients’ characteristics are presented in Figure 1A. Mean DFX dose was 15.51 mg/kg converted on tablet dosage. SF and myocardial iron concentration (MIC) were not associated (Figure 1B). Three patients had myocardial iron overload, despite SF values <500 μg/L; it took approximately 1 year of ICT for these patients to reach normal MIC values. A strong correlation between SF and liver iron concentration (LIC) (r = 0.46, P = .0001) was observed (Figure 1C), with seven patients with SF < 500 μg/L and a moderate liver iron load between 4 and 6 mg/g dw.

We evaluated DFX dose adjustments and safety. As ferritin decreased, DFX dose was adjusted, but not interrupted (Figure 1D). For patients with SF < 500 μg/L, DFX dose was maintained at an average of 14.5 mg/kg per day (tablet formulation), lower than in patients with SF > 500 μg/L (17.7 mg/kg) (P < .0001) (Figure 1E). With SF < 500 μg/L, glomerular filtration rate, estimated by EPI formula,8 remained within the normal range. There was no correlation between SF and SCr (P = .48). Moreover, all of our patients had a creatinine level below 2x the upper limit of normal (cut-off to define acute kidney injury in clinical trials).6 We did not observe any case of Fanconi syndrome related to DFX, which has been described in the literature, mainly in children.9

Liver function was unaffected: ALT values remained within the normal range, and no patient showed ALT values indicative of liver damage (ALT >10× upper limit of normal).

Our results show that the continuation of DFX treatment in the presence of SF values <500 μg/L is safe and not associated with an increased risk of renal and hepatic AEs. Previous studies showed that renal and liver AEs mainly appear for high doses of DFX, irrespective of ferritin levels, and are usually reversible after treatment interruption. To our best knowledge, no studies have evaluated the safety of DFX treatment or other chelators when ferritin is constantly <500 μg/L.

Consistent with previous results, our study confirms that SF strongly correlates with LIC.10 Of note, 5% of the patients with ferritin levels <500 μg/L still had some iron in the heart or the liver, confirming the need for ICT continuation. Thus, avoiding interruption and tailoring ICT to SF, iron intake, LIC, and MIC measured through T2* MRI seems advisable. If MRI is not available, it is mandatory to record iron intake in order to adjust the dose of DFX accordingly.11 Indeed, our data show that, as SF decreases, DFX dose should be adjusted, and for levels of SF <240 μg/L in a patient with a mean iron intake of 0.30 ± 0.07 mg Fe/kg per day, a mean dose of 14 mg/kg per day is suggested. Our results are consistent with those of Cohen et al.,11 which showed that the dose necessary to counterbalance a transfusion regimen with an iron intake of 0.3 mg Fe/kg per day is 20 mg/kg per day of the dispersible formulation equivalent to 14 mg/kg of the new formulation.
Some limitations of this study need to be acknowledged. First, being a retrospective study, we may have missed symptoms of over-chelation in the absence of biochemical abnormalities. Second, we did not assess 24-hour urine protein and creatinine for each event; however, we assessed these parameters once a year (unless clinically required, which was not the case for all our patients).

In conclusion, neither nephrotoxic nor hepatotoxic AEs have been observed with ICT when mean SF is <500 μg/L over 2 years. These findings support the notion that ICT can safely be tailored in TDT patients if accompanied by a rigorous follow-up and dose adjustment when necessary.

**FIGURE 1** A, Hematological and iron parameters of 50 transfusion-dependent thalassemia patients with ferritin <500 μg/L on iron chelation therapy. B, Correlation between serum ferritin and MIC. C, correlation between serum ferritin and LIC and D, deferasirox dose in patients with serum ferritin <500 and ≥500 μg/L. Hb: hemoglobin; MIC: myocardial iron concentration; LIC: liver iron concentration; eGFR: estimated glomerular filtration rate; ALT alanine aminotransferase; SD: standard deviation; DFX: deferasirox

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