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

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Short Running Title: Iron chelation therapy in transfusion dependent thalassemia patient with serum ferritin < 500 µg/l

Compliance with Ethical Standards

Funding The preparation of this correspondence was not supported by any external funding.

Conflict of interest:

NS, DC, CA, AM, EC, GG have nothing to disclose. IM reports receiving honoraria from Sanofi-Genzyme. MDC is member of Vifor, Sanofi-Genzyme, Celgene, Novartis and Bluebird advisory board.

Family Names highlighted in yellow

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ajh.25860

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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[1]. 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.

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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 for TDT patients with mean SF <500 µg/L for at least 24 months between January 2007 and December 2018. Linear (or quadratic when adequate) 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). 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 F, 18 M), 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 MIC were not associated (Figure 1B). Three patients had myocardial iron overload, despite SF values <500 µg/L: it took approximately one year of ICT for these patients to reach normal MIC values. A strong correlation between SF and LIC (r=0.46, p=0.0001) was observed (Figure 1C), with 7 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<0.0001) (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=0.48). Moreover, all of our patients had a creatinine level below two times 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> 10X 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[6] 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.

Consistently 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, according 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 die, 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 die 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-hours urine protein and creatinine for each patient; 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.

References

1. In: rd, Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V, eds. *Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT).* Nicosia (CY)2014.
2. Cadenas E. Biochemistry of oxygen toxicity. *Annu Rev Biochem.* 1989;58:79-110.
3. Piga A, Fracchia S, Lai ME, et al. Deferasirox effect on renal haemodynamic parameters in patients with transfusion-dependent beta thalassaemia. *Br J Haematol.* 2015;168(6):882-890.
4. Cappellini MD, Bejaoui M, Agaoglu L, et al. Iron chelation with deferasirox in adult and pediatric patients with thalassemia major: efficacy and safety during 5 years' follow-up. *Blood.* 2011;118(4):884-893.
5. Origa R, Piga A, Tartaglione I, et al. Renal safety under long-course deferasirox therapy in iron overloaded transfusion-dependent beta-thalassemia and other anemias. *Am J Hematol.* 2018;93(7):E172-E175.
6. Cappellini MD, Cohen A, Piga A, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. *Blood.* 2006;107(9):3455-3462.
7. Bird ST, Swain RS, Tian F, et al. Effects of deferasirox dose and decreasing serum ferritin concentrations on kidney function in paediatric patients: an analysis of clinical laboratory data from pooled clinical studies. *Lancet Child Adolesc Health.* 2019;3(1):15-22.
8. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-612.
9. Dee CM, Cheuk DK, Ha SY, Chiang AK, Chan GC. Incidence of deferasirox-associated renal tubular dysfunction in children and young adults with beta-thalassaemia. *Br J Haematol.* 2014;167(3):434-436.
10. Porter JB, Elalfy M, Taher A, et al. Limitations of serum ferritin to predict liver iron concentration responses to deferasirox therapy in patients with transfusion-dependent thalassaemia. *Eur J Haematol.* 2017;98(3):280-288.
11. Cohen AR, Glimm E, Porter JB. Effect of transfusional iron intake on response to chelation therapy in beta-thalassemia major. *Blood.* 2008;111(2):583-587.

	Hb g/dL	Ferritin µg/L	iron intake mg/kg	LIC mg/g dw	MIC mg/g dw	creatinine mg/dL	eGFR ml/min/1.73 m^2	ALT U/L
	(n = 5019)	(n = 5020)	(n = 148)	(n = 311)	(n = 311)	(n = 5005)	(n = 5037)	(n = 4914)
Mean ± SD	9.5 ± 0.9	470 ± 317	0.30 ± 0.06	2.38 ± 1.46	0.59 ± 0.25	0.84 ± 0.20	93.9 ± 16.0	20.6 ± 17.4
Median, 25-75%	9.5, 9-10.1	391, 284-536	0.30, 0.26-0.35	1.89, 1.42-2.17	0.55, 0.48-1.52	0.82, 0.34-0.96	96.1, 0.34-0.96	16.0, 12-22

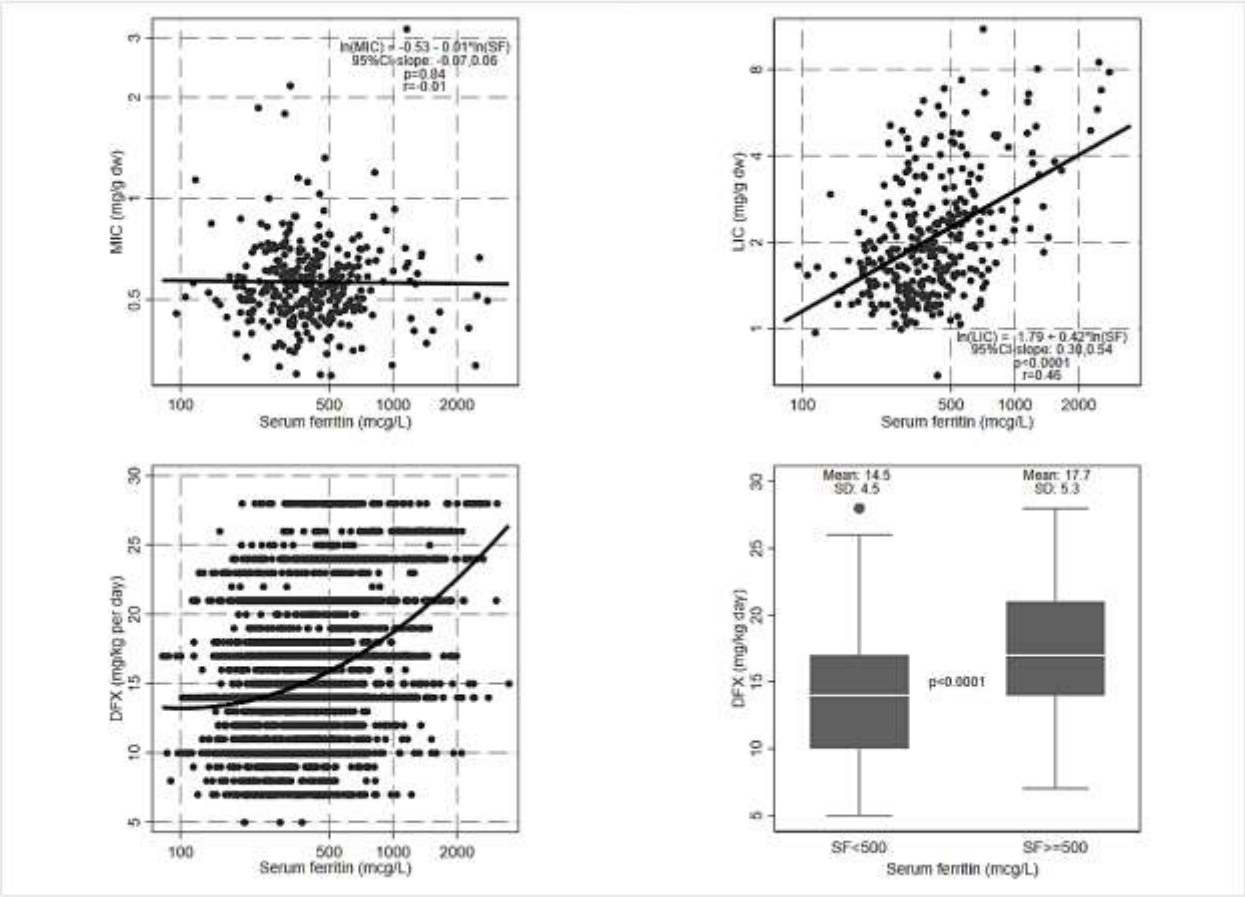

Figure 1. (A) Hematological and iron parameters of 50 transfusion-dependent thalassemia patients with ferritin <500ug/L on iron chelation therapy. (B) Correlation between serum ferritin and MIC, (C) correlation between serum ferritin and LIC and (D) deferasirox dose in patients with serum ferritin <500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