β-thalassemia trait and iron overload: is it time to consider oral iron chelators? Comment on: "A case series of patients with β-thalassemia trait and iron overload: from multifactorial hepcidin suppression to treatment with mini-phlebotomies"

In a recent issue of *Haematologica*, Busti *et al.*[1] described 30 individuals with β-thalassemia trait (βTT) and liver iron overload assessed by magnetic resonance imaging or liver biopsy. They found variable serum ferritin levels (from 441 to 3,650 mg/L), transferrin saturation (from 28 to 100%), and extent of iron overload (from mild to severe). It is known that βTT is characterized by mild ineffective erythropoiesis, erythroid hyperplasia, and hepcidin suppression, possibly leading to increased iron absorption.[2] Although hyperferritinemia is relatively common in individuals with βTT, this is the first report to show that some have elevated liver iron concentrations (LIC) that may warrant iron removal. Busti *et al.*[1] showed that in addition to ineffective erythropoiesis, most patients had a history of heavy alcohol consumption, metabolic alterations and fatty liver, homozygous HFE variants (p.C282Y and p.H63D), and a history of previous intravenous iron treatments and multiple transfusions in various combinations, which likely contributed to iron overload and hyperferritinemia.

A major issue faced by clinicians in patients with hyperferritinemia concerns the identification of those subjects with iron overload at risk of iron-related complications, and the appropriate use of invasive investigations such as liver biopsy. A serum ferritin threshold (>1000 μg/L) has been established in HFE-hemochromatosis to define the risk of iron-related liver damage unless coexistent hepato-toxic factors are present.[3] Defining this risk in other conditions is even more challenging as serum ferritin often overestimates LIC.[4] The coexistence of factors other than iron, such as heavy alcohol intake, metabolic alterations, and fatty liver, if present, should be corrected before the assessment of LIC as serum ferritin levels are partially responsive to lifestyle modifications. Quantification of LIC by magnetic resonance imaging can help in choosing the best therapeutic approach for these patients, e.g., life-style modifications, iron depletion, or both. Indeed, it is important not to underestimate iron overload as a cause of liver damage, but neither to overestimate it at the expense of other pathological conditions that may be equally or more relevant than iron in some patients. Thus, several studies have attempted to define the threshold value of LIC for the risk of iron-related complications. Based on liver biopsy and T2*- or R2*-weighted relaxometry, the LIC threshold has been set at 7 mg/g in transfusion-dependent thalassemia and even higher in hemochromatosis.[5]

As highlighted by Busti *et al.*,[1] the therapeutic approach to remove iron excess in βTT patients with iron overload can be challenging as they cannot afford the classical hemochromatosis phlebotomy regimen because of anemia, and because oral iron chelators are formally approved only for transfusion- and non-transfusion-dependent thalassemia, and other transfusion-dependent anemias. Accordingly, they proposed a pragmatic approach based on a low-intensity venesection program: 'mini-phlebotomies' (150-350 mL) every 2 to 3 weeks to treat βTT with liver iron overload. They found ferritin normalization after 6 to 36 months, depending on the severity of the iron overload. However, due to the reduced hemoglobin (100 to 135 g/L) and the small amount of blood removed, the amount of iron removed at each session was small and the time to reach iron depletion could be very long. In addition, during phlebotomy treatment, the erythropoietic drive would be further enhanced, hepcidin suppressed, and iron absorption increased, further reducing the efficiency of the treatment.[6,7] Although this regimen was well tolerated, we reasoned whether it should be limited to those subjects with the highest hemoglobin level and LIC who may truly benefit from iron depletion in a suitable time. As an alternative to phlebotomies, subcutaneous bolus injection of deferoxamine proved to be efficient in removing iron overload in both transfusional and non-transfusional iron overload.[8] This approach can be less demanding than 8-12 hours infusion and can be manageable at home but requires adequate training and can be less efficient in subjects with less iron overload. The oral iron chelator deferasirox can also be indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and older (European Medicines Agency - *https://ema.europa.eu*). Despite these limitations, low-dosage deferasirox has been proven to be highly efficient in removing iron overload in subjects with hemochromatosis.[9] The association of βTT with clinically relevant iron overload is a rare condition that has received little attention, although previous and recent publications have emphasized the risk to patients.[1,10] These patients have

the same problems as those with iron-loading anemias for whom therapeutic choices are also limited due to the strict indication of oral chelators by the drug authorities. Although the option of mini-phlebotomy and subcutaneous desferrioxamine may be considered in these patients, it would be appropriate to give them the opportunity to have easier access to effective and manageable home treatment with low-dosage oral iron chelators.

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Contributions

AP and RM contributed equally to writing this Comment.

References

1. Busti F, Castagna A, Marchi G, et al. A case series of patients with β-thalassemia trait and iron overload: from multifactorial hepcidin suppression to treatment with mini-phlebotomies. Haematologica. 2025;110(5):1226-1231.
2. Jones E, Pasricha SR, Allen A, et al. Hepcidin is suppressed by erythropoiesis in hemoglobin E β-thalassemia and β-thalassemia trait. Blood. 2015;125(5):873-880.
3. Bloomer SA, Brown KE. Iron-induced liver injury: a critical reappraisal. Int J Mol Sci. 2019;20(9):2132.
4. Olynyk JK, Gan E, Tan T. Predicting iron overload in hyperferritinemia. Clin Gastroenterol Hepatol. 2009;7(3):359-362.
5. Reeder SB, Yokoo T, França M, et al. Quantification of liver iron overload with MRI: review and guidelines from the ESGAR and SAR. Radiology. 2023;307(1):e221856.
6. Williams R, Manenti F, Williams HS, Pitcher CS. Iron absorption in idiopathic haemochromatosis before, during, and after venesection therapy. Br Med J. 1966;2(5505):78-81.
7. Piperno A, Girelli D, Nemeth E, et al. Blunted hepcidin response to oral iron challenge in HFE-related hemochromatosis. Blood. 2007;110(12):4096-4100.
8. Franchini M, Gandini G, de Gironcoli M, et al. Safety and efficacy of subcutaneous bolus injection of deferoxamine in adult patients with iron overload. Blood. 2000;95(9):2776-2779.
9. Cançado R, Melo MR, de Moraes Bastos R, et al. Deferasirox in patients with iron overload secondary to hereditary hemochromatosis: results of a 1-yr phase 2 study. Eur J Haematol. 2015;95(6):545-550.
10. Piperno A, Mariani R, Arosio C, et al. Haemochromatosis in patients with beta-thalassaemia trait. Br J Haematol. 2000;111(3):908-914.