Iron Chelation Therapy as a Modality of Management

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KEYWORDS

• Thalassemia major • Thalassemia intermedia • Transfusion-dependent thalassemia • Non-transfusion dependent thalassemia • Chelation • Liver iron concentration • Cardiac iron • Serum ferritin

KEY POINTS

- The monitoring of MRI-assessed liver and heart iron by using validated and standardized techniques has been the standard of care in management of iron chelation therapy in transfusion-dependent thalassemia and non-transfusion-dependent thalassemia.
- The transfusional iron intake, existing iron burden, and known compliance with chelation in a particular patient are crucial in response to prescribed chelation therapy.
- The accessibility of iron chelator to the different iron pools and efficiency for removing excess iron should be taken into account in chelator choice, dosing, and regimen based on the objective of iron chelation therapy.

INTRODUCTION

Iron chelation therapy is considered an essential component of thalassemia management. Body iron accumulation rate and distribution differ based on whether it develops as a consequence of the regular transfusion regimen that occurs in thalassemia major (TM),[1] or because of increased intestinal iron absorption and release of recycled iron from the reticuloendothelial system that occurs in thalassemia intermedia (TI).[2] It is estimated that 100 mL of pure concentrated packed red blood cells (with a hematocrit of 100%) contains 108 mg of iron, which is approximately 35 to 100 times more than the daily requirement.[3] Such extreme iron efflux by repeated transfusions in patients with transfusion-dependent thalassemia (TDT) results in an overwhelming carrying capacity of transferrin and the generation of harmful iron species, such as non-transferrin-bound iron and labile plasma iron (LPI) that is cleared preferentially by the liver, myocardium, and endocrine glands and that catalyses the formation of

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free radicals leading to oxidative damage in these tissues.[4,5] In fact, when adequate transfusion regimens became the norm, transfusional iron overload became evident very early in the transfusion history, and iron-induced cardiac deaths replaced anemia as the most common cause of mortality in TM.[6] Although deferoxamine (DFO) chelation became the standard management modality in thalassemia and markedly improved prognosis of disease, since the 1980s,[7–9] iron-induced heart disease, including heart failure and arrhythmia, continued to be the leading cause of death in TM until 1999.[10] The improved efficiency of iron chelation therapy with the introduction of new oral iron chelators, in addition to the documentation of organ-specific siderosis by MRI technologies and appropriate intensification of iron chelation treatment, alongside other improvements in clinical care increased the probability of complication-free survival with normal life expectancy in the modern era.[10–12] On the other hand, iron overload resulting from increased intestinal iron absorption has been recognized as an important clinical challenge in patients with non-transfusion-dependent thalassemia (NTDT) beyond the ages of 10 to 15 years.[13,14] In never or minimally transfused TI patients, MRI assessed liver (R2) and cardiac (T2*) iron demonstrated no evidence of cardiac iron overload, whereas there may be significant hepatic iron accumulation,[15] predisposing patients to develop fibrosis[16] and hepatocellular carcinoma.[17] However, the use of frequent transfusion therapy within the wide severity range of TI likely predisposes to cardiac iron deposition as well. Therefore, iron levels should be regularly assessed, and iron chelation therapy should be initiated where appropriate in NTDT patients.

Quantifying Iron Overload

Although the same tools that are available for the assessment of iron burden are used in both TDT and NTDT, monitoring of iron loading should be initiated after 6 to 8 transfusions in newly diagnosed patients with TDT, whereas it can be postponed to up to 10 years of age by considering the slow kinetics of iron loading in NTDT.

Serum ferritin (SF) is the most commonly used measure for the diagnosis and monitoring of iron overload and still remains the only tool in many countries. Traditionally, iron chelation therapy is started when SF exceeds 1000 μg/L, and maintenance of SF between 500 and 1000 μg/L may be associated with additional beneficial effects on complication-free survival in TDT.[9,18] It has demonstrated that liver iron concentration (LIC) can reliably measure total body iron stores.[19] Although SF generally correlates with body iron stores, TM patients with identical SF show highly variable LIC.[20] Furthermore, the studies in TDT have consistently demonstrated that the predictive value of SF trends to forecast changes in LIC was not strong enough,[21,22] although it seems stronger when SF was less than 4000 (r^2 0.51) compared with greater than 4000 μg/L (r^2 0.37).[22] In the modern management of iron overload, noninvasive quantification of LIC by MRI is considered the standard of care where available and may be used on patients as young as 4 to 5 years of age without sedation. LIC exceeding 3 mg Fe/g dry weight (dw) has been recommended as an indication to start chelation therapy. Although the suggested LIC range, derived from clinical observations in genetic hemochromatosis, is between 3 and 7 mg Fe/g dw,[8,23] the long-term efficacy and safety of chelation regimens, that was carefully titrated to normalize LIC less than 1.5 mg Fe/g dw, have been reported in adult patients with thalassemia.[24] The ability of cardiac T2* MRI as a validated technique to assess myocardial siderosis has demonstrated little predictive value of LIC (as well as SF) for cardiac iron deposition in previously chelated patients[25,26] and has provided insights into the different kinetics of iron loading/unloading in liver and heart.[27] In fact, cardiac iron clearance was found to be nearly 4 times slower compared with hepatic iron removal.[28] In light of these