Iron overload in thalassemia: different organs at different rates

Ali T. Taher[1] *and Antoine N. Saliba*[2]

[1]*Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon; and* [2]*Department of Medicine, Indiana University School of Medicine, Indianapolis, IN*

Thalassemic disorders lie on a phenotypic spectrum of clinical severity that depends on the severity of the globin gene mutation and coinheritance of other genetic determinants. Iron overload is associated with increased morbidity in both patients with transfusion-dependent thalassemia (TDT) and non–transfusion-dependent thalassemia (NTDT). The predominant mechanisms driving the process of iron loading include increased iron burden secondary to transfusion therapy in TDT and enhanced intestinal absorption secondary to ineffective erythropoiesis and hepcidin suppression in NTDT. Different organs are affected differently by iron overload in TDT and NTDT owing to the underlying iron loading mechanism and rate of iron accumulation. Serum ferritin measurement and noninvasive imaging techniques are available to diagnose iron overload, quantify its extent in different organs, and monitor clinical response to therapy. This chapter discusses the general approach to iron chelation therapy based on organ involvement using the available iron chelators: deferoxamine, deferiprone, and deferasirox. Other novel experimental options for treatment and prevention of complications associated with iron overload in thalassemia are briefly discussed.

Learning Objectives

- Understand that iron overload is associated with increased morbidity in patients with transfusion-dependent thalassemia (TDT) and non–transfusion-dependent thalassemia (NTDT)
- Learn serum ferritin measurement and noninvasive magnetic resonance imaging techniques available to diagnose iron overload, quantify its extent in different organs, and monitor clinical response to therapy
- Learn different chelation strategies that can be used with the currently available chelators deferoxamine, deferiprone, and deferasirox, as well as the novel therapies being developed to alleviate iron loading

Thalassemia: a state of ineffective erythropoiesis and iron overload

Thalassemia is an inherited disease with multiple genetic forms, including α-thalassemia, β-thalassemia, hemoglobin E/β-thalassemia, and others. Molecular defects in the α-globin gene cluster on chromosome 16 or the β-globin gene cluster on chromosome 11 result in defective hemoglobin synthesis. Thalassemic disorders lie on a spectrum of severity with different clinical phenotypes, complications, and strategies for treatment. Imbalance in the relative quantity of α-globin and β-globin chains results in early apoptosis of maturing nucleated erythroid cells with hematopoietic expansion in an attempt for potential compensation, a state often referred to as ineffective erythropoiesis leading to chronic hemolytic anemia without significant reticulocytosis and an array of secondary pathophysiologic mechanisms. The degree of transfusion dependence is one of the elements considered in a recent classification of thalassemic disorders into transfusion-dependent thalassemia (TDT) and non–transfusion-dependent thalassemia (NTDT). Iron overload develops from increased intestinal iron absorption signaled by ineffective erythropoiesis, while it can also be secondary to regular transfusions, which have been conventionally used to manage severe forms of the disease. In view of the varying mechanisms and rates of iron loading, the extent of accumulation in various organs may vary within and between patients. This is also further impacted by the type of iron chelator eventually used to manage iron overload, as some have been characteristically known to chelate iron in some organs better than others.

Pathophysiology of iron overload in TDT vs NTDT

The human body lacks a physiological mechanism for removal of the excess iron load resulting from blood transfusion. Each unit of transfused packed red blood cells contains 200 to 250 mg elemental iron. In TDT, transfusional iron usually amounts to 0.3 to 0.6 mg/kg per day with an assumed monthly transfusion rate of 2 to 4 U packed red blood cells. Senescent transfused red blood cells are phagocytized by the reticuloendothelial macrophages. As a result, labile cellular iron is released into the plasma to bind transferrin.[1] After transferrin binding is saturated, non–transferrin-bound iron is readily transported through calcium channels into the liver (hepatocytes), heart (cardiac myocytes), and endocrine glands. The accumulation of iron in different organs leads to the different clinical complications of iron overload. Reactive oxygen species produced by the metabolism of non–transferrin-bound iron contribute to the cellular dysfunction, apoptosis, and necrosis in target organs. Transferrin is the main iron transport protein, and it can bind 2 molecules of Fe^{3+}. Transferrin

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Table 1. Distribution of complications related to iron overload in both TDT and NTDT

	Complications*	
	TDT	NTDT
Cardiovascular	Cardiac siderosis, left ventricular heart failure	Pulmonary hypertension, right ventricular heart failure, venous thrombosis
Liver	Liver fibrosis, liver cirrhosis, viral hepatitis	Liver fibrosis, liver cirrhosis, hepatocellular carcinoma
Endocrine	Hypothyroidism, hypoparathyroidism, growth retardation, hypogonadism, osteoporosis, diabetes mellitus	Osteoporosis
Other		Leg ulcers, gallstones, extramedullary hematopoietic tumors, silent cerebral ischemia

*All complications can happen in both TDT and NTDT. This table mentions the distribution of the more commonly prevalent complications in each group based on available studies.

then binds to transferrin receptor 1 (TfR1) and transferrin receptor 2 (TfR2). Transferrin is then endocytosed. The acidic environment of the lysosomes, Fe^{3+} is released from transferrin, is reduced to Fe^{2+}, and then reaches the cytosol through divalent metallic transporter 1. While TfR2 is uniquely expressed in the liver and intestine, TfR1 is expressed in most tissues, including erythroid precursors, the liver, and the myocardium. The affinity of TfR1 for iron is higher than that of TfR2 by ~25 times. TfR2 lacks an iron responsive element, and iron loading continues to happen in the liver in the face of high liver iron concentration (LIC), while TfR1 is downregulated with elevated transferrin saturation. Historically, the most important clinical complication of iron overload has been cardiac siderosis, which is at the origin of arrhythmias and heart failure and has been a major cause of mortality in TDT. Hepatic and endocrine dysfunction due to iron overload are also commonly observed in TDT patients.[2] In fact, the decline in cardiac mortality with improved iron overload diagnosis and management has shed further light on increased relative mortality from hepatic failure as noted in European registries.[3] The ability to detect iron using noninvasive techniques, as will be outlined in later sections, allowed better understanding of the rate of iron overload in different organs in TDT. Studies have highlighted geographical variation in the prevalence of iron overload in different thalassemia populations.[4] For instance, cardiac siderosis seems to affect >25% of patients with thalassemia major in Southeast Asia while affecting 15% to 20% of patients in Europe and the Middle East.[5] Translational studies correlating the variation in geographical distribution of cardiac siderosis and environmental or genetic differences are lacking. This variation may also be reflective of geographical variation in iron chelation therapy (ICT) prescription.[6]

As NTDT has increasingly been examined and studied over the past few decades, it was noticed that iron overload differentially involves the liver rather than the myocardium in patients who are not dependent on regular red blood cell transfusion. This was evident from observational studies that showed absence of cardiac siderosis even in patients with severe liver iron overload.[7] Whether this is attributed to the mechanism of iron overload in NTDT or to slower iron loading remains unclear. It is known that iron overload in NTDT is related to increased intestinal iron absorption that is driven by hepcidin suppression and erythron expansion. Every 1 mg/g dry weight (dw) increase in LIC is associated with higher odds of thrombosis, pulmonary hypertension, hypothyroidism, osteoporosis, and hypogonadism in NTDT.[7] NTDT patients with iron overload are also at higher odds of developing renal dysfunction. Hepcidin synthesis by the liver normally suppresses the release of iron from erythroid precursors, hepatocytes, basolateral membranes of hepatocytes, and macrophages by binding to ferroportin, which mediates iron export.[1] Therefore, hepcidin suppression secondary to ineffective erythropoiesis leads to the upregulation of the transport of absorbed iron through the enterocyte basolateral membrane into the systemic circulation. It has been suggested that erythropoietic stimulation leads to erythroferrone production by the bone marrow and spleen erythroblasts. Erythroferrone, a 340-amino-acid soluble protein produced by the bone marrow and spleen erythroid precursors, directly acts on the liver leading to the inhibition of hepcidin production.[8] Other erythroid factors, including growth differentiation factor and twisted-gastrulation 1, have been previously considered but have not been shown to be upregulated in murine models of β-thalassemia.[9]

Table 1 describes the distribution of complications related to iron overload in both TDT and NTDT. TDT has been associated with multiple comorbidities, including heart failure secondary to cardiac siderosis and the chronic state of anemia, cardiac arrhythmia, liver fibrosis, chronic viral hepatitis, and endocrine disease (hypothyroidism, hypoparathyroidism, growth retardation, hypogonadism, bone disease, and diabetes). The OPTIMAL CARE study revealed the association of NTDT with a similar yet distinct array of complications.[10] The most common NTDT-related complications include osteoporosis, extramedullary hematopoiesis, hypogonadism, pulmonary hypertension, liver disease, and leg ulcers. Hypothyroidism, heart failure, and diabetes mellitus are less commonly observed in NTDT as compared with TDT. Unlike patients with TDT, who present early in their life with clinical iron overload after 10 to 20 transfusions, patients with NTDT tend to develop iron overload later at ~10 to 15 years of age.

Diagnosis and quantification of iron overload

Magnetic resonance imaging

Magnetic resonance imaging (MRI) using R2 or T2* techniques has replaced liver biopsy as the gold standard for the quantification of LIC given its safety and reliability. Direct histological examination of hepatic tissue obtained by biopsy is highly sensitive and specific for the diagnosis of iron overload. As compared with MRI, liver biopsy remains more invasive, although it has low complication rates.[11] Estimation of LIC by MRI in milligrams of iron per gram of liver dw reliably correlates with total body iron stores.[12,13] MRI is also being used for the quantification of the cardiac iron concentration using T2* technique, in milliseconds. T2* gets shorter as myocardial iron concentration increases. Most guidelines for the management of thalassemia now rely on noninvasive monitoring using MRI to diagnose iron overload and tailor ICT.

Specific LIC and cardiac T2* thresholds have been associated with morbidity in TDT and NTDT. LIC values >5 mg/g dw are associated

Table 2. Recommended strategies for assessment and follow up of iron overload and its related complications

	TDT	NTDT
Baseline	Serum ferritin Liver MRI for LIC Cardiac T2* MRI Echocardiography Bone mass densitometry Testing for endocrinopathy (free T4, TSH, calcium, phosphate, 25-OH vitamin D, FBS)	Serum ferritin Liver MRI for LIC Echocardiography Bone mass densitometry Testing for endocrinopathy (free T4, TSH, calcium, phosphate, 25-OH vitamin D, FBS)
Every 3 mo	Serum ferritin Safety labs for ICT monitoring	Serum ferritin Safety labs for ICT monitoring
Yearly	Serum ferritin Liver MRI for LIC* Cardiac T2* MRI† Echocardiography Bone mass densitometry Testing for endocrinopathy (free T4, TSH, calcium, phosphate, 25-OH vitamin D, FBS)	Serum ferritin Liver MRI for LIC* Echocardiography Bone mass densitometry Testing for endocrinopathy (free T4, TSH, calcium, phosphate, 25-OH vitamin D, FBS)

FBS, fasting blood sugar; TSH, thyroid-stimulating hormone.
*If LIC is normal, MRI can be spaced out in frequency to every 2 years; if LIC >15 mg/g dw, consider repeating MRI more frequently (every 6 months).
†If T2* <10 ms or if cardiac dysfunction is present, consider repeating MRI more frequently (every 6 months).

with increased morbidity in NTDT. LIC values >7 mg/g dw are used to indicate increased risk for complications related to iron overload in TDT. LIC values >15 mg/g dw are predictive of advanced liver fibrosis, mortality, and increased risk of cardiac disease in TDT.[14,15] Cardiac T2* values <10 ms predict a higher risk of symptomatic heart failure and mortality, while values between 10 and 20 ms are associated with lower left ventricular ejection fraction (LVEF) and arrhythmias in patients with TDT.[5] Recommended strategies for assessment and follow-up of iron overload are summarized in Table 2.

Serum ferritin assessment

One of the significant limitations to the use of MRI for the quantification of iron overload remains the relative unavailability and higher costs, especially in areas of the world where the disease is most prevalent. Those areas include many countries in the developing world spanning sub-Saharan Africa, the Mediterranean region, the Middle East, India, and Southeast Asia. This has prompted the identification of serum ferritin levels that correlate with hepatic iron overload in both TDT and NTDT. Cutoffs of <300 ng/mL for the absence of iron overload and >800 ng/mL for the presence of clinically significant iron overload in NTDT have been suggested.[16] However, recent reevaluation found a significant number of patients with serum ferritin levels between 300 and 800 ng/mL to have iron overload requiring management.[17] Generally, the same LIC tends to correlate with lower serum ferritin in NTDT as compared with TDT.[18] Serum ferritin has limited ability to predict cardiac iron overload in TDT but can reliably predict cardiac siderosis and endocrine disease when it is >2500 ng/mL.[19] In TDT, we tend to use a serum ferritin threshold of >1000 ng/mL to indicate the need for initiation of ICT. Serum ferritin levels <1000 ng/mL are associated with lower morbidity and mortality in TDT.[2,20] The association between serum ferritin and cardiac T2* seems to be less robust than the association between serum ferritin and LIC.[21] Serum ferritin levels >4000 ng/mL tend to be more variable and less predictive of the extent of iron overload. Serum ferritin is an acute phase reactant that fluctuates with inflammatory, infectious, and other stress states. Therefore, its reliability for the assessment of iron overload remains limited. Clinicians must use well-informed medical judgment before using serum ferritin as the sole tool to assess iron overload. Nevertheless, serum ferritin measurements may be the only tool available for the clinician in resource-limited settings. Most guidelines recommend measurements of serial serum ferritin and basing decisions about ICT on trends rather than individual measurements. We reiterate that, when available, imaging techniques to quantify organ-specific iron load are preferred over serum ferritin assessment.

Impact of ICT on survival trends in thalassemia

The relative impact of thalassemia is expected to increase over the coming decades as mortality from infectious disease and malnutrition progressively decreases in areas of the world where thalassemia is prevalent. In addition, the waves of migration from those areas with higher prevalence of thalassemia to North America and Northern Europe are also expected to change the worldwide distribution of the disease.[22] Large randomized controlled trials using organ-specific siderosis outcomes assessed by imaging techniques previously described showed the safety and efficacy of oral ICT agents in decreasing cardiac and hepatic siderosis. Deferoxamine (DFO) as a continuous infusion, augmented by deferiprone (DFP), remains the strategy of choice for treatment of acutely decompensated cardiac disease secondary to iron overload. Being cheaper, DFO may be the only option available to patients in resource-limited settings.[23] The introduction of effective ICT has been shown to correlate with improvement in survival, enhancement of quality of life, and reversal of hepatic and cardiac functional complications in patients with TDT.[23,24] In large industry-driven clinical trials that were not specifically designed to assess endocrine disease, long-term ICT has not been shown to reverse endocrine disease, including diabetes and hypothyroidism, secondary to iron overload. It is, however, clinically evident that endocrinopathy may improve with chelation, but the response remains unpredictable.[25] Improvement in the ability to quantify organ-specific siderosis using MRI techniques has played a substantial role in guiding the need for

Table 3. Strategy for safety monitoring and follow up for ICT

	DFX	DFP	DFO
Adverse effects	Gastrointestinal disturbances	Gastrointestinal	Auditory
	Gastrointestinal bleeding	Neutropenia/agranulocytosis	Ophthalmologic (retinal)
	Increase in serum creatinine	Arthralgia	Reactions at site of infusion
	Rash	Increase in liver enzymes	Delay in bone growth
	Increase in liver enzymes	—	*Yersinia* infection
	Liver failure	—	—
	Renal insufficiency	—	—
CBC with differential	Baseline and monthly	Baseline and weekly*	Baseline and monthly
Serum creatinine†	Baseline, weekly during the first month of therapy, then monthly	—	Baseline and monthly
Serum electrolytes	Baseline and every 1-3 mo	—	Baseline and every 1-3 mo
Urinalysis	Baseline and every 1-3 mo	—	—
Urine protein/creatinine	Baseline and monthly	—	—
Serum ALT, AST, and bilirubin	Baseline, every 2 wk during the first month, then monthly	Baseline and monthly	Baseline and monthly
Ophthalmic plus auditory examination	Baseline and yearly	—	Baseline and yearly

*Daily if the absolute neutrophil count is $<1500/mm^3$.
†Consider more frequent monitoring if baseline kidney disease is present or in case of concomitant use of nephrotoxic medications.

ICT, avoiding underchelation or overchelation, and, consequently, optimizing care for patients with thalassemia.[26]

Management of iron overload in thalassemia

Iron chelation therapy: an organ-based approach

The aims of ICT include maintenance of safe iron body stores to help counterbalance the excess iron loading, remove iron already deposited in tissues, and prompt reversal of heart failure. Three iron chelators have been approved by most regulatory agencies for ICT in thalassemia: DFO, DFP, and deferasirox (DFX).

General guiding principles. Assessment of iron overload should be pursued after the transfusion of 10 U packed red blood cells in patients with TDT and at age of 10 years in patients with NTDT.[2,27] Serum ferritin is used in early childhood before patients can tolerate liver and myocardial MRI without sedation. Around age 8 to 10 years, consideration should be given to assessment of myocardial and hepatic iron load using noninvasive imaging techniques. Table 3 delineates the proposed strategy for safety monitoring and follow up for ICT. The clinician should adopt an individualized approach when choosing ICT based on general iron overload profile, organ predominance of iron deposition, transfusion requirements, likelihood of adherence to therapy and follow-up, and profile of comorbidities. Oral ICT and novel formulations of previously approved agents may be better choices for patients with poor compliance. Our approach is to start DFO or DFX therapy for children with TDT older than 2 years of age. DFP serves as second line therapy, as experience with it has been the most limited.[28] We also recommend close follow-up for early detection of nonadherence or intolerance to therapy, which would warrant considering alternative agents and strategies. Long-term ICT was associated with better control of iron burden when therapy was appropriately and promptly adjusted for transfusional iron intake and patient weight based on set therapeutic goals.

Approach to hepatic siderosis. DFO was the first iron chelator to be made available in the clinical realm. It is administered intramuscularly, subcutaneously, or IV. DFO therapy has consistently been shown to be associated with a significant decrease in LIC in patients TDT. An average DFO dose of 51 mg/kg administered at least 5 days a week resulted in an average LIC decrease of 6.4 mg/g dw in β-thalassemia major patients with LIC >14 mg/g dw.[29] DFX, an oral iron chelating agent, was shown to significantly decrease LIC by 3.1 to 7.8 mg/g dw in patients with TDT.[30] DFX doses >30 mg/kg per day were needed to achieve optimal improvement in LIC in patients with heavy iron loading in the context of TDT.[31] DFX monotherapy and DFP monotherapy have been shown to improve hepatic siderosis.[32-34] It is important to recognize that deaths due to cardiac complications have been decreasing while the proportion of deaths secondary to hepatic complications, including liver cirrhosis and hepatocellular carcinoma, has been on the rise.[3] Managing concomitant conditions, such as chronic hepatitis B and C, and avoiding alcohol and other hepatotoxic medications remain of utmost importance. All 3 iron chelators available exhibit a dose–response relationship; some studies have been flawed by the use of suboptimal doses of DFX or DFP. There is no head-to-head trial comparing DFX and DFP at optimal doses. Based on the most robust data available, we recommend monotherapy with DFX, at a dosage of 20 to 30 mg/kg or higher per day, or combination therapy with DFO and DFX for the treatment of hepatic siderosis in TDT.[30,35,36] Combination DFX and DFO has been shown to result in rapid and dramatic reduction in LIC in patients with high baseline LIC.[36]

Approach to cardiac siderosis. For patients with normal LVEF and severe cardiac siderosis (T2* <10 ms), monotherapy with DFX at higher doses, monotherapy with DFO at higher doses, or combination DFO and DFX therapy is recommended in patient with TDT and LIC >7 mg/g dw. Combination DFO and DFP therapy remains the strategy of choice in TDT patients with lower hepatic iron burden. In TDT patients with mild-to-moderate cardiac siderosis (T2* 10-20 ms), monotherapy with DFX or monotherapy with DFO is recommended if LIC >7 mg/g dw. Monotherapy with DFP or combination DFO and DFP therapy may be preferred alternatives if LIC <7 mg/g dw. In TDT patients with no evidence of cardiac siderosis (T2* >20 ms), DFX or DFO monotherapy is recommended. DFP monotherapy may alternatively be used if hepatic iron burden is low.[37] DFO has been the agent of choice for treatment of cardiac siderosis in patients with acute heart failure related to iron overload. DFX has been also shown to be associated with improvement in myocardial T2* that was noninferior to DFO in patients with normal heart function but allowed a higher proportion of patients to move

Table 4. Alternative strategies for ICT when MRI technology is not available in TDT

LVEF	Strategy
Normal	
SF >4000 ng/mL	DFX or DFO high dose, DFO and DFX, or DFO and DFP
SF 1500-4000 ng/mL	DFX or DFO
SF <1500 ng/mL	DFX, DFO, or DFP
Abnormal	24-hour IV DFOorDFO and DFP

DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox; LVEF, left ventricular ejection fraction; SF, serum ferritin.

to lower cardiac risk categories.[38,39] In a meta-analysis, DFO and DFP were found to improve myocardial siderosis by comparable amounts.[40] The addition of DFP to DFO has been shown to enhance myocardial T2* in patient with mild-to-moderate myocardial overload.[41] Continuous DFO therapy and combination DFO and DFP therapy have been shown to be associated with improvement in cardiac T2* and LVEF.[42,43] Based on the available evidence, our approach is to use 24-hour continuous DFO IV or combination DFO and DFP therapy in TDT patients with compromised LVEF regardless of the cardiac T2*. Randomized controlled trials have shown superior efficacy of DFP versus DFO, the superiority of combined DFP and DFO vs DFO monotherapy, and the equivalence of DFX vs DFO in control of cardiac siderosis.[44] Well-designed head-to-head clinical trials of the available agents to study long-term safety and efficacy remain needed. Alternative strategies for ICT in the absence of MRI technology are shown in Tables 4 and 5.

Approach to iron overload in the patient with NTDT. DFX is the most widely studied and only approved iron chelating agent in NTDT patients 10 years or older. As previously mentioned, there is no evidence of significant cardiac siderosis in NTDT patients even in the presence of considerable hepatic iron overload. Treatment of NTDT patients with DFX at starting doses ranging between 5 and 10 mg/kg per day up to 20 mg/kg per day was associated with significant improvement in LIC after 12 months of therapy.[16] Higher doses of DFX reaching 30 mg/kg per day were also shown to achieve more significant and clinically relevant reductions in LIC with longer follow-up in patients with NTDT.[45,46] We recommend initiating therapy with DFX at a dose of 10 mg/kg per day in patients 10 years of age or older with an LIC ≥5 mg/g dw. It is recommended to interrupt DFX therapy for LIC <3 mg/g dw. DFP has not been extensively studied in NTDT. Single-arm, open-label studies with small sample sizes and a more recent randomized controlled trial showed significant decreases in serum ferritin and LIC with DFP therapy.[47] DFO has not been systematically studied in NTDT, although studies with small sample sizes and short durations have shown an increase in urinary excretion of iron and a decrease in serum ferritin.

Approach to iron overload in the pediatric patient. The goals of blood transfusion therapy in children with TDT includes correcting anemia, suppressing erythroid expansion, preventing splenomegaly and skeletal abnormalities, and ensuring appropriate growth and development. Growth retardation is thought to be mediated by iron deposition in the pituitary gland and the subsequent effect on the growth hormone-insulin-like growth factor axis. High doses of DFO in children with low iron load may be associated with growth retardation, which should be distinguished from growth retardation secondary to inadequate transfusion or iron overload.[48] It is recommended to check height and weight of children with TDT every 3 months.[2] DFX therapy is effective in TDT patients starting 2 years of age with no observed negative effects on growth or sexual development. DFP has not been well studied in patients younger than 6 years of age. Challenges in the treatment of thalassemia change with age. In early childhood, the clinician must ensure adequate support and therapy to optimize growth and development. In late childhood and adolescence, sexual development and transition of care are important areas of focus. As patients transition in to adulthood, the goals of therapy include preventing long-term complications related to anemia, iron overload, and hypercoagulability.[49]

Recent advances in ICT

Compliance with ICT is associated with effective control of iron overload and improved patient survival.[23,24,50] The importance of adherence to ICT has driven recent efforts to improve tolerability of oral ICT agents. A recent phase 2 study in TDT has shown the efficacy and safety of a film-coated tablet of DFX and suggested improved adherence with the novel formulation compared with dispersible tablets.[51] The ECLIPSE study used patient-reported outcome analyses and showed greater patient satisfaction, fewer concerns, and improved palatability of the medication with film-coated DFX tablets. The safety profile of DFX film-coated tablets was generally similar to the older dispersible tablet formulation.

Novel promising modalities targeting iron overload

Hitting a step earlier is one strategy that could potentially help prevent iron overload. Therapies that reduce the need for transfusions in TDT and suppress ineffective erythropoiesis in NTDT could be promising in that aspect. Gene therapy is a promising venue that is being currently explored. A few ongoing trials are recruiting patients (NCT03207009, NCT02453477, and NCT02906202). The potential improvement in normal hematopoiesis will preclude the need for regular long-term blood transfusions and will help prevent transfusional iron overload and its complications.[52] Genome editing involves the introduction of DNA breaks into targeted areas of the genome using enzymes such as clustered regularly interspaced short palindromic repeats/Cas9. Targeted disruption of factors, such as BCL11A, that silence the γ-globin genes may potentially allow faster and safer results in the treatment of β-thalassemia, whether transfusion dependent or non–transfusion dependent.[53] Trials in the area of allogeneic hematopoietic stem cell transplantation are under way to evaluate new conditioning regimens and other donor/recipient variables. Hematopoietic stem cell transplantation is particularly interesting, as iron overload may persist after transplantation. The effect of baseline iron load on outcomes of hematopoietic stem cell transplantation procedures has not been clearly elucidated. Another promising approach that is being currently evaluated in clinical studies is the utilization of modified activin receptor II fusion proteins (sotatercept and luspatercept) to enhance late-stage erythropoiesis

Table 5. Alternative strategies for ICT when MRI technology is not available in NTDT

Serum ferritin	Strategy
SF ≤300 ng/mL	None
SF 300-800 ng/mL	None, or use other measures indicative of iron overload state, or try to obtain MRI
SF >800 ng/mL	Initiate ICT with DFX

DFX, deferasirox; ICT, iron chelation therapy; SF, serum ferritin.

by acting as ligand traps for members in the transforming growth factor-β superfamily.[54,55] The aim of therapy with such agents is to increase hemoglobin levels in both NTDT and TDT and to decrease the transfusional requirements in TDT, and data from phase 2 studies have thus far been encouraging. The potential positive effects on iron overload are hypothesized to be mediated by the expected improvement in ineffective erythropoiesis and reduction in transfusional iron load. JAK2 inhibitors have been recently investigated in clinical trials in TDT based on improvement in ineffective erythropoiesis and splenomegaly in murine thalassemia models.[54] Studies in NTDT murine models showed that moderate transgenic hepcidin expression resulted in lower iron loading, longer erythrocyte life span, higher hemoglobin concentrations, and improved splenomegaly.[56] Long-acting hepcidin analogs (minihepcidins) have thus been developed to suppress iron absorption and are currently being investigated.[57] If and when minihepcidins reach the clinical realm, they could be potentially used alone or in combination with ICT to control iron overload. The downregulation of TMPRSS6, a metalloprotease, leads to the stimulation of endogenous hepcidin production.[58] Studies in preclinical iron overload models have shown that antisense oligonucleotides and small interfering RNAs targeting TMPRSS6 effectively stimulate hepcidin, decrease iron load, improve ineffective erythropoiesis, and prolong erythrocyte survival, thus showing merit for further clinical investigation of this approch.[59]

Correspondence

Ali T. Taher, Department of Internal Medicine, American University of Beirut Medical Center, Cairo St, PO Box 11-0236, Riad El Solh 1107 2020, Beirut, Lebanon; e-mail: ataher@aub.edu.lb.

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