Review Article

Deferasirox: Over a Decade of Experience in Thalassemia

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Abstract. Thalassemia incorporates a broad clinical spectrum characterized by decreased or absent production of normal hemoglobin leading to decreased red blood cell survival and ineffective erythropoiesis. Chronic iron overload remains an inevitable complication resulting from regular blood transfusions (transfusion-dependent) and/or increased iron absorption (mainly non-transfusion-dependent thalassemia), requiring adequate treatment to prevent the significant associated morbidity and mortality. Iron chelation therapy has become a cornerstone in the management of thalassemia patients, leading to improvements in their outcome and quality of life. Deferasirox (DFX), an oral iron chelating agent, is approved for use in transfusion dependent and non-transfusion-dependent thalassemia and has shown excellent efficacy in this setting. We herein present an updated review of the role of deferasirox in thalassemia, exploring over a decade of experience, which has documented its effectiveness and convenience; in addition to its manageable safety profile.

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Introduction. Thalassemia is characterized by genetic disorders leading to defective synthesis of the normal globin subunits of human hemoglobin.[1] Various mutations might affect one or both of the β-globin genes located on chromosome 11 causing β-thalassemia, and/or any of the four α-globin genes located on chromosome 16 leading to α-thalassemia.[2] The clinical spectrum of this condition is determined by the type of mutation which either causes a decrease in or absence of the affected globin chain, the number/type of genes involved; as well as the coinheritance of other genetic abnormalities, with cases ranging from asymptomatic to severe transfusion-dependent anemia. High incidence of thalassemia has been reported in the Mediterranean region, the Middle East, the tropical and subtropical regions of Africa among others, thus creating a significant heath burden.[3] The initial exploration of this disease identified the abnormal synthesis of one of the globin chains and the excess of the other, as the primary pathophysiological mechanism leading to shortened red blood cell (RBC) survival, ineffective erythropoiesis, associated with medullary and extramedullary erythroid proliferation.[2] Nonetheless, knowledge gained over the past few years has led to further understanding of the associated physiological and pathological alterations which result in significant morbidity/mortality in this population of patients. Among those, iron overload (IOL), related to blood transfusion; in addition to increased

intestinal absorption, further complicates the management of those patients and significantly affects their outcome. IOL leads to deposition of iron in different vital organs including the liver, heart, endocrine glands among others, leading to various clinical manifestations.[4] Multiple previous studies have documented cardiomyopathy related to IOL as a significant cause of mortality in β-thalassemia major patients.[5] Extensive evidence supports the initiation of iron chelation therapy (ICT) according to specific criteria, and the availability of oral chelator agents has further improved patients' compliance with this essential therapy. ICT has become an essential component in the management of thalassemic patients with a significant impact on their survival and quality of life. Multiple iron chelators have been utilized in this setting, including the parenteral agent deferoxamine (DFO) which has been the standard of care, in addition to oral deferiprone (DFP) and DFX that have led to better patients' compliance which might reflect into better efficacy. The choice regarding the optimal agent depends on the severity of iron burden, the organs affected, and patients' comorbidities. We herein present an updated overview of the role of DFX, an oral iron chelator, in the management of transfusion-dependent (TDT) and non-transfusion-dependent thalassemia (NTDT), discussing its pharmacological characteristics, efficacy; as well as safety.

Pathophysiology of IOL in Thalassemia. The predominant mechanisms underlying the development of IOL in thalassemia include increased iron accumulation secondary to transfusion therapy (main cause in TDT) and enhanced intestinal absorption secondary to ineffective erythropoiesis and hepcidin suppression (mainly in NTDT). Iron level is generally tightly controlled by multiple regulatory proteins which modify iron absorption and release as required to maintain a balance between iron influx (resulting from recycled erythrocytes or dietary absorption) and excretion. In plasma, iron is transported by transferrin which binds to its receptors (TFR1expressed in most tissues and TFR2 that is uniquely expressed in the liver and intestine).[6] Transferrin saturation is sensed by TFR1 and 2 to modulate the production of specific regulatory molecules such as hepcidin through complicated molecular pathways. In TDT,

transfusional iron usually amounts to 0.3 to 0.6 mg/kg per day (d) with a monthly transfusion rate of 2 to ≥ 4 units packed RBC (200 to 250 mg elemental iron per unit). Senescent transfused RBCs are phagocytized by the reticuloendothelial macrophages, leading to the release of cellular iron into plasma. The human body lacks a physiological mechanism for removal of the excess iron load resulting from blood transfusion.[7] So, iron accumulation occurs with increased transferrin saturation resulting in non-transferrin-bound iron (NTBI) which is readily transported through calcium channels leading to iron deposition in hepatocytes, cardiac myocytes, and/or endocrine glands, with variable clinical complications related to the production of reactive oxygen species (including the active labile plasma iron-LPI).[6,7] This accumulation results in cellular dysfunction, apoptosis, and necrosis at the level of affected organs.[7,8] Even in the absence of regular RBC transfusions, IOL develops in many patients with NTDT, indicating a role for increased absorption of iron in the development of hemosiderosis in thalassemic patients.[9] The conditions of anemia and hypoxia that result from ineffective erythropoiesis influence the level of the serum protein hepcidin, the main regulator of intestinal iron absorption.[10-13] Hepcidin negatively regulates iron absorption by reducing the expression of ferroportin, a transmembrane protein responsible for exporting intracellular iron into circulation at the level of the basolateral membranes of the intestinal epithelia, macrophages and sinusoidal surfaces of hepatocytes.[14] Hepcidin levels decline when iron sequestration for erythropoiesis increases,[12] and this, in turn, results in upregulated ferroportin which causes an increase in the release of iron from the reticuloendothelial system, leading to depletion of macrophage iron.[15,16] The downregulation of hepcidin in NTDT can also be mediated by elevated levels of growth differentiation factor-15 (GDF-15),[17] a member of the transforming growth factor-β (TGF-β) family,[15,18,19] and twisted gastrulation factor.[20] Recent studies have highlighted the role of GDF-15 in further exacerbating IOL in NTDT. GDF-15 is normally upregulated during ineffective erythropoiesis, causing the downregulation of hepcidin. The variability in the pathophysiological etiology of IOL across TDT and NTDT affects the rate of iron accumulation and explains the

associated variance in the deposition of iron in different vital organs.[6] Remarkably, it has been noted that iron accumulation preferentially occurs in the liver in patients with NTDT rather than the myocardium. This was established after observational studies showed the absence of cardiac siderosis even in patients with severely elevated liver iron content (LIC).[9]

Diagnosis and Quantification of IOL. Multiple noninvasive methods have become available for the evaluation and serial monitoring of IOL in thalassemic patients. These have largely replaced the initial standard method that included tissue biopsy for pathological examination. Each of those methods has its advantages and drawbacks. Nowadays, clinicians use a combination of serum ferritin (SF), LIC and cardiac iron evaluation as detected by magnetic resonance imaging (MRI), for the documentation of IOL; as well as clinical monitoring for patients started on chelation therapy. While SF evaluation is simple, widely available, and inexpensive, it might underestimate the actual iron load in many patients (specifically NTDT).[21,22] Given its reliability and reproducibility, measuring LIC using MRI is currently among the forefront strategies for the estimation of hepatic iron accumulation and has been validated against LIC detected by liver biopsy.[23] Myocardial T2* below 10 ms and 20 ms have been associated with an increased risk of heart failure and arrhythmia respectively.[24] SF has been shown to predict hepatic iron burden but does not correlate with cardiac iron trends.[25] In addition, the post-hoc analysis from one of the major chelation trials has documented decreases in LIC by > 1 mg/g dry weight in 52% of patients without a serum ferritin response, and a correlation between SF and LIC changes only when SF <4000 ng/ml.[26] The current recommendations thus include measuring SF every three months and LIC using MRI annually for both TDT and NTDT, in addition to yearly cardiac T2* MRI in TDT patients only.[27]

Pharmacokinetics of DFX. DFX binds iron in a 2:1 ratio (tridentate agent).[28] Its use is characterized by a convenient administration for all age groups, good oral bioavailability (reaching 70%), in addition to its high affinity and specificity to iron[29] DFX is characterized by a long half-life reaching around 8-16 hours[30] is metabolized in the liver[31] and leads to iron excretion mainly through the fecal route.[32] Pharmacokinetic parameters are unique in a specific population of patients, with dose adjustments recommended in hepatic impairment, or with concurrent uses of strong UDP-glucuronosyltransferase inducers and/or bile acid sequestrants, and continuous transfusion burden.[33] Long-term therapeutic outcomes are affected by the DFX to iron complex formation ratio, which has been recently suggested as an indicator of efficacy.[34]

Evidence in TDT. There has been an extensive evaluation of DFX in TDT patients, either as monotherapy or in combination with other chelator agents in cases of severe IOL or when single agents do not lead to adequate efficacy.

Monotherapy. DFX at 20 mg/kg/d had shown similar efficacy to DFO at 40 mg/kg/d in reducing LIC.[35] The prospective ESCALTOR trial reported sustained reduction in LPI levels in a group of β-thalassemia patients with significant IOL with a mean decrease in LIC by 3.8 mg iron/g dw, and SF by 517 ng/ml.[30,36] Two-year treatment with DFX leads to a reduction of iron levels in those whose baseline LIC ≥7 mg iron/g dw while maintaining iron levels in those with baseline LIC < 7 mg/g dw.[37] An initial phase II trial in pediatric patients with TDT had shown that low doses of DFX were associated with limited efficacy.[4] These results were also replicated in a large randomized phase III study including 586 pediatric and adult patients with β-thalassemia who achieved a significant reduction in SF and LIC with DFX at doses of 20-30 mg/kg/d, while doses of 10 mg/kg/d showed inadequate efficacy in regularly transfused patients.[38] Sustained improvements in iron burden were noted with follow up to 5 years, where 83% achieved SF ≤2500 ng/ml, 47.3% of patients reaching SF≤1000 ng/ml after 4 years, with more than half of patients receiving a final dose of DFX ≥25 mg/kg/d during the extension period.[39] While doses of 20 mg/kg/d have maintained an LIC below 7 mg/g dw, higher doses of around 30 mg/kg/d have been required to achieve a net reduction in iron levels in those with LIC ≥ 7 mg/g dw.[40,41] This large prospective trial included 1115 patients with β-thalassemia and showed a statistically significant decrease in SF with DFX therapy. In addition, it indicated the need to

choose a starting dose that correlates with the patient's transfusion requirements, and that needs to be titrated in a timely manner. At least three years of DFX lead to reversal or stabilization of liver fibrosis in TDT patients showing evidence of IOL.[42] A systematic review and meta-analysis including 1520 patients with TDT also showed increases in SF at lower DFX doses, but no significant difference in the change in SF with DFX at 30 mg/kg as compared to DFO.[43] JaiSwal et al. later reported a significant mean reduction in SF of 1207.11 ng/ml (32.38% decrease) after 12 months therapy with DFX at a mean dose of 38 mg/kg/d in 45 heavily transfused thalassemia patients.[44] A prospective observational study including 176 patients with TDT (total 267), reported long-term results in pediatric patients treated with DFX and documented a decrease in median SF of 575 ng/ml after five years of DFX therapy with a mean dose of 25.8 mg/kg/d.[45] A Cochrane review reported by Bollig et al. indicated similar efficacy of DFX as compared to DFO (depending on the ratio of DFX to DFO dose, generally showing similar results at a mean ratio of 1 mg of DFX to 1.8 mg of DFO).[46]

DFX has also been effective in the management of cardiac siderosis. Wood et al. have reported an improvement in myocardial T2* in patients with severe cardiac siderosis treated for 18 months with DFX at doses up to 40 mg/kg/d (13 patients).[47] DFX also led to normalization of cardiac T2* in 68% of patients with a baseline level of 10-20 ms, and sustained improvements with prolonged duration of therapy.[48] The phase II CORDELIA trial documented non-inferiority of DFX compared to DFO in the management of β-thalassemia major asymptomatic patients with cardiac IOL (T2* 6-20 ms), with a 12% increase in the geometric mean (Gmean) myocardial T2*.[49] On the other hand, the MILE study has shown that DFX at similar doses lead to a 10% relative improvement in myocardial T2*, with the most significant results noted in those with moderate cardiac siderosis and those with lower baseline LIC, while no significant changes were reported in cases of severe cardiac iron deposition.[50] Greater improvement in LIC and myocardial T2* were noted with higher doses of DFX (above 30 mg/kg/d). This study also showed statistically significant improvement in LIC, specifically those with baseline LIC ≥7 mg/g dw, with a statistically insignificant reduction in SF, and no major safety concerns. DFX has also resulted in the greatest improvement in the prevalence of endocrinopathy, in addition to a significant improvement noted on bone mineral density evaluation as compared to DFO, DFP and DFO combined with DFP in a retrospective study.[51]

Safety of DFX. Common adverse events (AEs) noted in trials evaluating DFX included gastrointestinal (GI) disturbances, skin rash, elevation in serum creatinine and/or liver transaminases among others.[52] Abdominal pain was reported in 4.8% of thalassemia patients in the EPIC trial, nausea in 3.8% and diarrhea in 7.8% of patients, while elevations in creatinine >33% above baseline were noted in 3.6% of the thalassemia cohort.[40] Most of the AEs occurred with higher doses of DFX (specifically >25 mg/kg/d) including increases in creatinine by ≥ 30% which has been reported in around 38% of patients.[38] DFX causes a short-term effect on renal hemodynamics with a reversible reduction in glomerular filtration rate.[53] Elevations in liver transaminases have been more commonly reported in TDT patients.[40,54] Porter et al. have related GI AEs to lower baseline LIC (<7 mg/g dw).[41] Similar AEs have been reported during prolonged follow up periods extending beyond five years.[39]

Less common AEs include ocular and visual disturbances, cytopenia, and Fanconi syndrome.[55] For pediatric patients, Vichinsky et al. reported AEs with suspected relation to DFX in 39.1% of patients with nine patients having a serious AE (3.4%), with a gradual decline in the incidence of AEs over time.[45] Osborne et al. recently reported the utilization and safety of DFX using an observational post-marketing study conducted in England. Beta-thalassemia was the second most frequent reason for prescribing DFX (26 patients; 21.3%), and increased creatinine was noted in only two patients out of 122 (1.6%).[56] The EPIC trial had reported a 0.6% of proteinuria after 1-year follow up.[40] Bayhana et al later evaluated the prevalence and need for monitoring of proteinuria in thalassemia patients on DFX therapy, where a retrospective single center analysis including 37 total patients (36 with thalassemia major), reported proteinuria in 7 patients (18.9%) at a mean follow up of 44 months, all of which resolved with follow up. This analysis identified younger age (below 23) and higher doses of DFX (above 29 mg/kg/d) as risk factors for the development of

proteinuria.[57] A retrospective chart review recently reported safety data for prolonged follow-up periods reaching 13 years, including 282 patients, with no significant or persistent nephrotoxicity noted and only non-progressive and reversible increases in creatinine.[58]

DFO and DFX. It has become more common over the past few years to utilize combination chelation therapy, whether sequentially or concurrently, especially in cases of severe cardiac IOL. A quasi-experimental study conducted in Iran included 32 patients with TDT with severe IOL not responding to monotherapy, who received DFX (30-40 mg/kg/d with DFO 40-50 mg/kg/d for 2 days per week, showing a significant reduction in mean SF from 4031±1955 to 2416±1653 ng/mL after 12 months of treatment, with no major safety concerns.[59] In an open label trial that included 18 patients, the combination of DFO (35-50 mg/kg for 3-7 days) and DFX (20-30 mg/kg/d) led to a statistically significant decrease in median LIC by 5.4 mg/g dw, with a statistically insignificant improvement of cardiac T2* by 2.7 ms in 6 patients with baseline T2* below 20 ms.[60] Cassinerio et al. have also reported improvements in ferritin level, hepatic and cardiac MRI T2* among seven patients receiving DFO at 32 mg/kg for 3-4 days/week with DFX at an initial dose of 20 mg/kg/d, after one year of treatment.[61] Aydinok et al. conducted a third trial combining DFO at 37.4 mg/kg/d for five days/week with DFX 29.6 mg/kg/d. They included 60 patients with T2* 5-10 ms but a left ventricular ejection fraction ≥56%, moreover, reported improvements in mean LIC from 33.4 to 18.2 mg/g dw at 24 months, and in cardiac T2* by 9% after one year, and to 9.5 ms at 24 months (baseline 7.2 ms).[62] These trials all showed the feasibility of combining DFO and DFX with no unexpected toxicity noted. Recently, a multiple treatment comparison network meta-analyses and sequential trial analysis included 32 clinical trials and noted that DFX with DFO led to better improvement in SF level compared to monotherapy or the combination DFO/DFP.[63]

DFP and DFX. Farmaki et al. initially reported significant improvements in SF level and hepatic iron in 16 patients with the low iron burden (baseline LIC 1.6±1.1mg/g dw) using DFP combined with DFX.[64] A significant reduction in SF by 3275 µg/l was also noted among 36 pediatric/young adult thalassemia patients who had shown suboptimal response to monotherapy with either DFP or DFX, after 1 year treatment with a combination of DFP and DFX, with AEs including GI disturbances, arthropathy and increases in creatinine.[65] They also reported transient elevations in liver enzymes by> 5 times the upper limit in 11% of patients. In a randomized controlled trial assessing the combination of DFP 72 mg/kg/d with either DFO or DFX at 23 mg/kg/d, Elalfy et al.[66] reported a significant reduction in LIC from 12.52 ± 2.28 mg/g dw to 10.17 ± 2.23 mg/g dw with an increase of cardiac T2* from 16.59 ± 1.85 ms to 19.75 ± 2.65 ms. A more rapid rate improvement in cardiac T2* was attained with DFX and DFP compared to DFO and DFP.[66] They noted arthropathy in 16.6% of patients, increases in alanine aminotransferase (ALT) in around 8% of patients, and in creatinine in 6.2% of patients. Karami et al reported results of combining DFP (mean dose of 53.9±22.2 mg/kg/d) with DFX (mean dose of 29.3±6.8 mg/kg/d) in 6 patients with TDT after failing monotherapy, and showed non-significant increases in SF with a significant effect on LIC (change by 7.59±3.16 mg/g dw).[67] Furthermore, 33 patients with TDT who failed monotherapy were evaluated in a prospective study at a single center in India, with 12 patients continuing the 2-year treatment with 75 to 100 mg/kg/d DFP (divided into three doses) and 20 to 40 mg/kg/d DFX.[68] This regimen showed a reduction in the mean SF by 44.67%±13.78% at two years and was well tolerated with GI disturbances noted in around 6% of patients, and elevations in creatinine >33% above the baseline on two consecutive occasions noted in around 85% of patients. Pinto et al. have recently reported successful iron chelation in 8 patients who were intolerant to mono or combination therapies, using alternating DFP (starting dose 75 mg/kg/day) and DFX (25 mg/kg/day).[69] With a median follow up of 52 months, this alternating regimen lead to decrease in the mean ferritin by 587 ng/ml, in addition to effective removal of excess cardiac and hepatic iron, with no moderate to severe AEs.

DFX in the Post-transplantation Setting. Hematopoietic stem cell transplantation (HSCT) remains the only widely available curative therapy for thalassemic patients. Inati et al.[70] conducted a prospective randomized trial comparing DFX (12

patients) versus phlebotomy (14 patients) in thalassemia patients with IOL post HSCT (LIC >3 mg/g dw or SF >300 µg/L), showing a median reduction in SF by 498 µg/L and a mean decrease in LIC by 5.8 mg/g dw after 1 year of DFX therapy. A significantly greater reduction in LIC was obtained with DFX compared to phlebotomy in those with baseline SF above 1000 µg/L.[70] Yesilipek et al. recently reported results from a phase II multicenter (in Turkey), single arm study including 27 patients with thalassemia who underwent HSCT within a period of 6 months to 2 years prior to enrollment, and had evidence of IOL (SF> 1000 µg/L, cardiac MRI T2* <20 ms, or LIC ≥5 mg/g dw). DFX was given at an initial dose of 10 mg/kg/d then increased to 20 mg/kg/d, and resulted in a significant and continued reduction in median LIC (from 8.6 to 4.1 mg/g dw), increase in median cardiac T2* from 26 to 28 ms over a 52 week period.[71] This trial reported serious AEs in only 11.1% of patients, none of which were related to DFX, with no evidence of hepatotoxicity or nephrotoxicity in this population of patients.

DFX in NTDT. All available iron chelators have proven their efficacy in TDT patients. However, having received Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval, DFX remains to be the only drug used in NTDT patients, mostly based on results from the THALASSA trial.[72,73] In this trial, 1-year treatment with DFX in NTDT patients > 10 years was shown to decrease LIC at a daily dose of 5 and 10 mg/kg, respectively, compared to placebo.[73] Further analysis showed that DFX at starting doses of 5 and 10 mg/kg/d led to consistent reductions in LIC across all patients, irrespective of baseline LIC, SF, splenectomy status, underlying NTDT form or demographics.[73] Greater reductions in LIC were also achieved in those patients that were dose-escalated at six months from 10 mg/kg/d starting dose to 20 mg/kg/d.[73] Furthermore, to assess a period of 2 years of DFX treatment, a 1-year extension phase was then carried out. Patients continued to respond and showed a decrease in SF and LIC over two years.[73] Moreover, data from the THETIS study later showed that a starting dose of 10 mg/kg/d of DFX is effective in reducing IOL in these patients and that a dose escalation up to 30 mg/kg/d should be considered starting at week four based on LIC response.[74] DFP has not been extensively studied

in NTDT. However, single-arm, open-label studies with small sample sizes and a more recent randomized controlled trial showed significant decreases in SF and LIC with DFP therapy.[75] Although DFO has not been systematically studied in NTDT, studies with short durations and small sample sizes have shown an increase in urinary excretion of iron and a decrease in SF upon DFO administration.

Guidelines with specific indications/thresholds have been established to determine the appropriate time for initiation, dose escalation, and termination of ICT in NTDT patients. DFX with an initial starting dose of 10 mg/kg/d should be started in patients ≥10 years of age if their LIC ≥ 5 mg iron/g dw, or if their SF concentration was found to be ≥ 800 µg/L (if LIC is not available due to MRI unavailability).[76] To monitor iron levels, LIC should be repeated six months after therapy initiation, with follow up every 6–12 months, and SF levels should be measured every three months.[76] If LIC levels at six months are still greater than 7 mg/g dw (or SF >1500 µg/L only if LIC is unavailable) with less than 15% reduction in baseline values, dose escalation should be considered up to 20 mg/kg/d.[76] DFX therapy can be safely discontinued when patients reach an LIC value of 3 mg/g dry weight (or SF level of 300 µg/L only if LIC is unavailable).[76] In the realm of NTDT, it is recommended to intensify ICT if the LIC after six months of treatment >7 mg/g dw, SF >1500–2000 ng/mL or in case of <15% decrease from baseline. Indications to stop ICT in NTDT include a SF < 300 ng/mL and/or LIC < 3 mg/g dry wt. liver.

Adherence to ICT. Compliance with ICT is often associated with effective IOL control and improved patient survival.[77,78] Moreover, adherence to long-term ICT is crucial in preventing IOL-related complications. Poor adherence to ICT is associated with shorter life expectancy and increased morbidity. There are several factors that might affect adherence to ICT including the fact that early iron overload is asymptomatic, the challenges related to the transition from childhood to adolescence, the possible inconvenience of administration of chelation therapy, the lack of subjective awareness of improvement by patients or recurrence of symptoms after discontinuing a chelator agent, in addition to the AEs associated with various

treatments. Adherence to ICT remains a challenge for thalassemia patients, and is a multidimensional issue, involving several factors including patient-related factors (attitudes and beliefs, perceptions of severity, expectations from treatment), disease-related factors (acute, chronic, physical state, emotional state), demographic factors (age, gender, culture, religion, socioeconomic status), and therapy-related factors (frequency of dosage, complexity of regimen, administration route, palatability, AEs).

DFO therapy, owing largely to its cumbersome administration, has a detrimental impact on multiple areas of patients' lives, including their emotional well-being, physical functioning, self-esteem, among others. Treatment with DFO is demanding. The drug has poor oral bioavailability and a short plasma half-life. Therefore, slow subcutaneous infusions are necessary 3–7 times weekly. Because of injection-site reactions and pain, the administration is inconvenient, and the necessary equipment is not available in many countries. These factors lead to poor compliance, which in turn leads to increased mortality.[6] Treatment satisfaction and adherence are generally greater with oral ICT than with parenteral infusion. One study showed that adherence to oral DFX monotherapy was significantly higher than DFO infusion (96% vs. 92%; p<0.001).[79] Adherence to oral DFX on DFO/DFX combination therapy was lower than that of monotherapy (90% vs. 96%; p<0.001). Adherence to DFO infusion on DFO/DFP combination therapy was non-significantly lower than that of monotherapy or DFO/DFX combination therapy (88% vs. 92%; p=0.25). Adherence did not significantly change over follow-up period except that an increase in adherence was seen after a change in chelation from DFO infusion to oral DFX (p=0.03, paired t-test). In a qualitative examination of the reported patient adherence over time after this iron chelator change, no evidence of a 'honeymoon' phase was seen, with temporary high adherence to the new chelator. In an open-ended comment section, many participants commented on the benefits of oral chelation and their improved adherence.[79]

Another study by Cappellini et al., compared patient-reported outcomes (PROs) during receipt of DFO infusions or once-daily DFX oral therapy.[80] PRO questionnaires were completed by patients, their parents or legal guardian at different time points: baseline, week 4, week 24, and end of study (EOS). Patients assessed their satisfaction level with study treatment (very satisfied, satisfied, neutral, dissatisfied, or very dissatisfied) and rated its convenience.[80] At baseline, 289 and 282 patients in the DFX and DFO groups, respectively, had previous experience with DFO (7 and 8 patients, respectively were DFO-naïve); of these patients, 45.3% and 45.0%, respectively, reported that they were very satisfied or satisfied with DFO treatment, while 32.5% and 33.0% reported being dissatisfied or very dissatisfied.[80] There were no significant differences in the satisfaction ratings between the groups at baseline. At week 4, week 24, and EOS, significantly more patients receiving DFX reported being very satisfied or satisfied with treatment compared with those receiving DFO (92.0% vs 50.4% and 89.6% vs 44.0%, respectively; P < 0.001).[80] At each time point, more patients receiving DFO reported being dissatisfied or very dissatisfied with treatment compared with those receiving DFX (28.0% vs. 0.7% and 31.2% vs. 2.4%).[80] When considering only those patients who responded to the question at EOS, the overall proportion of patients who were satisfied with treatment was 88.8% (246/277) for DFX and 40.5% (109/269) for DFO.[80] Results of this study suggested that DFX had a positive impact on patients' daily lives. A recent Cochrane review exploring the interventions needed for improving adherence to ICT in patients with thalassemia or sickle cell disease concluded that real-life data is required to assess specific adherence strategies and thus make recommendations in this setting.[81]

Recent Advances in ICT. The efficacy and safety of DFX dispensible tablet (DT) has been well portrayed through extensive clinical trial programs in patients with a variety of anemias, including thalassemia, sickle-cell disease, myelodysplastic syndromes (MDS), and other rare anemias,[4,35,38,82,83] and has been used widely used in clinical practice all over the world for over a decade. Nevertheless, barriers to optimal patient acceptance of treatment still exist with DFX-DT including preparation time, palatability, the need to take the drug in a fasting state, and drug-related side effects, notably GI tolerability.[84]

DFX film coated tablet (FCT). An improved FCT formulation of DFX has been therefore

developed for oral administration.[84] Both DFX FCT and DT are once-daily, oral iron chelators that are dosed based on body weight. DFX FCT contains the same active substance, dose-adjusted to achieve comparable exposure to that achieved with the DT. Because of the increased bioavailability of the FCT, doses required to achieve the same chelation effect are 30% lower than the DT. DFX DT has a chalky consistency and is taken on an empty stomach, at least 30 min before the next meal, and its administration requires careful dispersion of the tablets in a glass of water, orange juice, or apple juice.[84] DFX FCT, on the other hand, can be taken orally on an empty stomach or with a light meal, offering more convenient and simpler mode of administration, and potentially improved GI tolerability.

The open-label, phase II ECLIPSE study evaluated the overall safety profile, as measured by the frequency and severity of AEs and changes in laboratory values, and the pharmacokinetics (PK), and PROs of DFX FCT and DT formulations in patients aged ≥10 years with TDT or very-low-, low-, or intermediate-risk MDS, requiring ICT.[84] The overall incidence of AEs was similar between treatments, but there were fewer serious AEs with FCT. FCT recipients consistently reported better adherence, greater satisfaction, and fewer concerns, with a safety profile consistent with the known DT formulation.[84] Taking the dose conversion factor into account, which was required because the two formulations have differing bioavailability, patients received similar mean doses of the active ingredient in DFX. However, at the end of the 24-week trial period, FCT patients had a higher observed median absolute reduction in SF from baseline, suggesting a possible association between the treatment arm and observed efficacy.[84] A potential explanatory factor of this difference in efficacy could be better treatment adherence among the patients receiving FCT compared with DT. These findings suggest a preference in favor of the new formulation, with better patient satisfaction and adherence translating into reduced IOL-related complications.

Table 1 includes significant trials evaluating DFX in TDT and NTDT, and **figure 1A** and **B** includes recommendations regarding chelation with DFX and suggested monitoring and/or
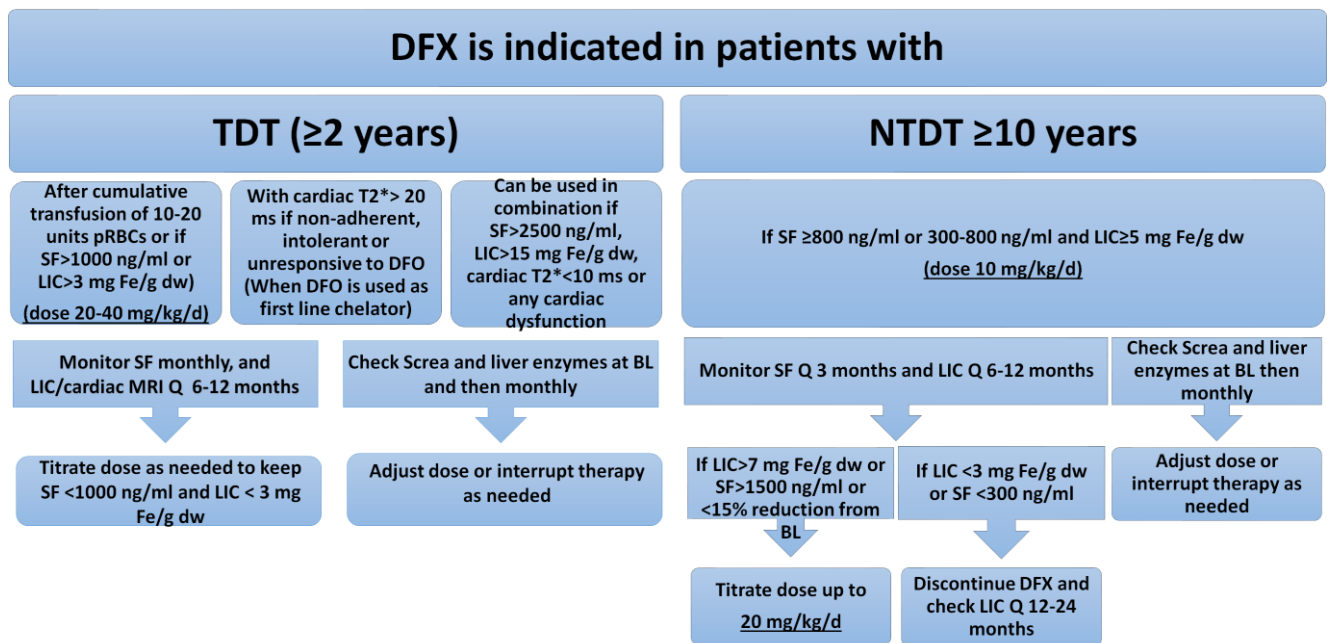
Table 1. Significant trials evaluating DFX in TDT and NTDT.

Trial/Design	Patient population	Treatments	Key findings
TDT			
Prospective Phase II randomized trial (with 4-year extension)[82]	Transfusion-dependent anemias with transfusional IOL (n=184; 85 with thalassemia)	DFX at doses 5-30 mg/kg/d (depending on baseline LIC)	Significant decreases in mean LIC (by 6.0 ± 7.8 mg Fe/g dw in patients with LIC ≥ 7) at doses of 20-30 mg/kg/d (changes were dose dependent)
Phase 3 trial comparing 1-year DFX with DFO (with 4-year extension)[38,39]	586 β-thalassemia patients n=296 (DFX cohort) n=290 (DFO cohort) 555 patients on extension (continuing DFX or switching from DFO to DFX-crossover)	DFX based on iron burden or response in the initial cohort (mean 21.6 mg/kg/d) DFO 20-50 mg/kg/d for 3-7 d/week (based on iron burden)	Failed to meet non-inferiority objective across all doses Significant and sustained reduction in SF and LIC with largest changes noted with higher DFX starting dose (30 mg/kg/d) Dose adjustment/ interruption in 36.8% and 33.1% with DFX and DFO respectively Mean LIC decreased by 7.8 ± 11.2 mg /g dw versus 3.1 ± 7.9 mg/g dw in the DFX and crossover cohorts respectively
EPIC Phase IIIb (1-year prospective trial)[40]	Patients with transfusion dependent anemias (n= 1,744 with 1,115 thalassemia patients)	DFX at 10-30 mg/kg/d (depending on iron burden)	Significant reduction in SF by 264 ng/ml with DFX (mainly with doses ≥30 mg/kg/d) GI disturbances noted in 28% of patients
EPIC prospective trial (cardiac sub study): 1 year then 2-year extension[48,85,86]	Asymptomatic β-thalassemia patients with myocardial T2* > 5 to < 20 ms (n=114) or T2*>20 ms (n=78-prevention)	DFX at 10-30 mg/kg/d (depending on iron burden) then increased up to 40 mg/kg/d	Significant improvement in mean myocardial T2* with maintained results after 3 years -68.1% of patients with baseline T2* 10 to <20 ms normalized

	At 2 years extension period n=71		- 50.0% of patients with baseline T2* >5 to <10 ms improved to 10 to <20 ms -Stabilization of T2* over 1 year in patients with T2*> 20 ms
The CORDELIA trial **Phase II multicenter randomized trial and its extension**[49,87]	Asymptomatic thalassemia patients who had received ≥50 transfusions with evidence of cardiac IOL (T2* 6-20 ms) and normal EF (n=197) 1-year extension (n=103)	DFX at 40 mg/kg/d DFO at 50-60 mg/kg/d 5-7 days/week	After 1 year, Geometric mean cardiac T2* increased by 12% with DFX and 7% with DFO-trend toward superiority of DFX; highest increases noted in patients with lower baseline LIC (<7 mg Fe/g dw) Sustained improvements in myocardial iron at 24 months irrespective of baseline myocardial or liver iron burden; myocardial T2* improved from 11.6 to 15.9 ms with DFX and from 10.8 to 14.2 ms with DFO
The MILE study **Phase IV single arm open-label trial**[50]	Patients with hemoglobinopathies among other anemias (including n=36 with TDT)	DFX up to 40 mg/kg/d	10% relative improvement in myocardial T2* (mainly in those with moderate cardiac siderosis, lower baseline LIC and with doses ≥30 mg/kg/d)
DFP combined with DFX **Prospective randomized controlled trial**[66]	TDT patients with severe IOL (n=96; 48 in each arm)	Arm 1: DFP 75 mg/kg/d with DFO 40 mg/kg/d over 10 hours for 6 days Arm 2: DFX 30 mg/kg/d with DFP 75 mg/kg/d	Both regimens were equally effective in reducing IOL DFP/DFX was superior in improving cardiac T2*, compliance and patients' satisfaction
DFX+DFO **Open label trial**[60]	TDT patients with severe IOL (n=18 completed 12 months treatment)	DFO at 35–50 mg/kg/d, 3–7days/week combined with DFX at 20–30 mg/kg/day	Statistically significant improvement in LIC by 5.4 mg/g dw
Open label trial[61]	TDT patients (n=7)	DFO: 32 ± 4 mg/kg for 3–4 days/week combined with DFX: 20 ± 2 mg/kg/d (initial dose)	Improvement in LIC from 11.44 to 6.54 mg/g dw and in cardiac T2* from 19.85 ± 12.06 to 26.34 ± 15.85 ms
Quasi-experimental study[59]	TDT patients with severe IOL not responding to monotherapy (n=32)	DFX at 30–40mg/kg/d and DFO at 40–50 mg/kg/d for 2 days/week	Significant reduction in mean SF from 4031±1955 to 2416±1653 ng/mL after 12 months of treatment
Open label trial[62]	TDT patients with severe myocardial IOL (n=60)	DFO at 37.4 mg/kg for 5 d/week with DFX 29.6 mg/kg/d	Improvements in mean LIC from 33.4 to 18.2 mg/g dw, and in cardiac T2* from 7.2 ms to 9.5 ms at 24 months
NTDT **THALASSA (Phase II prospective, randomized, placebo controlled study with 2-year extension)**[72,73]	NTDT patients with IOL (n=166)	DFX 5 or 10 mg/kg/d versus placebo	Significant and sustained decreases in LIC and SF with DFX (greater reductions in patients receiving starting doses of 10 mg/kg/d)
FCT **ECLIPSE trial (open label phase II)** [84]	Chelation-naïve or pre-treated patients with TDT (n=140) or low/intermediate MDS	DFX at 20 mg/kg/day with DT (n=86) or 14 mg/kg/day with FCT (n=87)	Similar safety profiles between DT and FCT FCT lead to an absolute reduction in median SF by 350 ng/ml (14% change) compared to 85.5 ng.ml (4.1% change) with DT FCT also led to better compliance and improved palatability

Legends: TDT: transfusion-dependent thalassemia; IOL: iron overload; DFX: deferasirox; d: day; LIC: liver iron concentration; Fe: iron; g dw: gram dry weight; DFO: deferoxamine; EPIC: Evaluation of Patients' Iron Chelation with Exjade; SF: serum ferritin; GI: gastrointestinal; EF: ejection fraction; DFP: deferiprone; NTDT: non-transfusion-dependent thalassemia; THALASSA: Assessment of Exjade in Non-Transfusion-Dependent Thalassemia; FCT: fil-coated tablet; MDS: myelodysplastic syndrome; DT: dispensable tablet
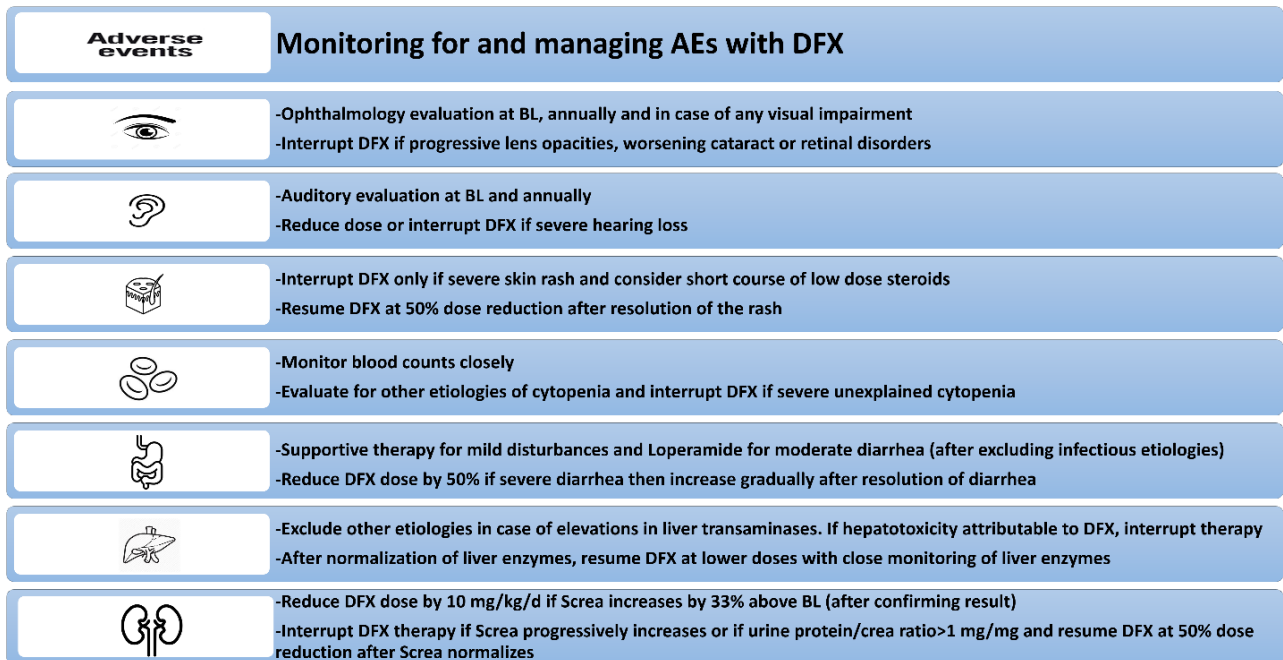
Figure 1 A. DFX in thalassemia.

DFX: deferasirox; TDT: transfusion-dependent thalassemia; NTDT: non-transfusion-dependent thalassemia; pRBCs: packed red blood cells; SF: serum ferritin; LIC: liver iron concentration; g dw: gram dry weight; DFO: deferoxamine; MRI: magnetic resonance imaging; Screa: serum creatinine; BL: baseline

Note that the DFX doses provided are for the dispersible formulation, for the film coated tablet the dosage is around 30% less and the conversion used is:

- 10 mg/kg/day DFX dispersible → 7 mg/kg/day FCT
- 20 mg/kg/day DFX dispersible → 14 mg/kg/day FCT
- 40 mg/kg/day DFX dispersible → 28 mg/kg/day FCT

Figure 1 B. Monitoring for and managing adverse events with DFX.

AEs: adverse events; DFX: deferasirox; BL: baseline; Screa: serum creatinine.

adjustments.

Conclusions. ICT has become a cornerstone in the management of thalassemia patients (TDT and NTDT). The choice of the optimal chelator agent and schedule depends on patients' characteristics and comorbidities; in addition to the burden of IOL, the organs affected and the presence of

symptoms. Over a decade of experience with DFX in thalassemia patients has documented its efficacy and manageable safety profile. Extensive evidence suggests the need to tailor the dose of DFX to the severity of IOL; as well as the frequency of ongoing transfusions. Recent advances with the oral formulation might lead to better results related to optimized compliance, awaiting results with longer follow up duration. Future trials exploring different combination or sequential chelating regimens are awaited. In addition, current and future efforts might lead to improvements in the management of the degree of anemia in thalassemia, thus reducing the needs for transfusion and further ameliorating the continuous exacerbation in IOL.

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