

3. Iron Overload and Chelation Therapy

Principles

- To be aware of complications of iron overload, to monitor routinely and accurately for iron overload, and to reduce iron accumulation using iron chelators with the goal of preventing organ damage and dysfunction.
- To reduce body iron load quickly in patients with iron overload and end organ toxicity.
- To monitor for and treat adverse side effects of iron chelators.

Recommendation

- Transfusional iron loading and body iron stores should be monitored routinely.
- Chelation therapy should be started early in children receiving regular blood transfusion to prevent iron-related toxicities. The chelating agent used should be tolerable and effective in reducing iron load. Intolerability of a chelating agent leads to poor compliance, which results in increased iron overload, subsequent end organ complications, and overall increased morbidity and mortality.
- Deferasirox is the preferred chelator for most patients.
- Regular monitoring for specific chelator-related toxicity should be carried out and the appropriate action taken if toxicity is found.
- The effectiveness of chelation should be routinely monitored and appropriate dose and drug adjustments made when required.
- Patients and families should receive age-appropriate education and access to an experienced multidisciplinary team to provide support in the practical and psychological aspects of chelation therapy and to promote independence and motivation in managing chelation therapy.
- Patients should receive adequate monitoring to identify early signs of inadequate adherence to chelation therapy. If adherence is problematic they should be provided with appropriate culturally sensitive counseling or therapy to aim for improved treatment outcomes.

Background

Iron Overload Overview

Red cell transfusion is the mainstay of treatment for thalassemia major; however, over time this therapy results in significant iron overload. Beyond tissue iron storage as ferritin or hemosiderin, control of Non-transfusion bound iron (NTBI) is critical to preservation of cardiac function.¹¹⁰ Once the body's ability to store iron is exceeded, free iron accumulates and participates in the formation of reactive hydroxyl radicals, which cause denaturation of proteins, mitochondrial dysfunction, and membrane damage. Iron overload, mainly from blood transfusions and, to a lesser degree, from increased gastrointestinal absorption, is the major cause of morbidity and mortality in transfused thalassemia patients. If untreated, it is fatal in the first or second decade of life. Major complications of iron overload, including cardiac, liver and endocrine toxicities, can be avoided or ameliorated by early detection and treatment.¹¹⁷⁻¹¹⁹

Assessment of Iron Overload

In the current era of MRI iron assessment, there is nowadays no role for using surrogate markers such as serum ferritin.¹¹¹ There are several indirect and direct methods for iron load assessment. Serum ferritin, a simple indirect measure of iron stores, is associated with increased risk of cardiac complications when over 1000 or 2500 ug/l.¹¹⁸ However, ferritin is an acute phase reactant and may be falsely elevated in liver disease, infection, or inflammatory processes. The prediction of iron loading from ferritin is poor and hence it should not be used to track chelation efficacy unless it has been shown over multiple timepoints that ferritin correlates with LIC for an individual patient.¹¹² Regardless, there is poor correlation

between serum ferritin and myocardial iron. In non-transfused dependent thalassemia, the serum ferritin often underrepresents the LIC.¹¹³

Assessment of liver and cardiac iron using MRI has been shown to affect chelation therapy choices and improve outcomes in TM.¹¹⁴⁻¹¹⁶

MRI evidence of cardiac iron is also suggestive of diabetes and hypogonadism risk^{117-125,145} Chelation therapy should be started in patients with a ferritin over 1000 ug/l; however, once chelation has been initiated, the aim of therapy should be to normalise body iron stores and suppress NTBI.

Liver iron concentration (LIC) measured on ultrasound-guided liver biopsy is invasive and can be associated with morbidity and rarely mortality. In addition, there may be sampling error if iron deposition is patchy, and poor reproducibility if the sample is small or fibrotic.⁴⁴ Previous LIC thresholds of 7 or 15mg/g DW^{117,110,111} are no longer applicable when the heart can be imaged directly. Calibration curves for MRI R2 and R2* (inverse of T2 and T2*) signals for the liver have been developed and show a curvilinear relationship between liver iron estimated by R2 or R2* and by biopsy and validated across platforms.^{118, 123,156,159}

Transient elastography (fibroscan) may have a role in the assessment of liver fibrosis, but is not well validated in children and adults with and without concomitant HCV infection.¹¹⁹⁻¹²¹

Pancreatic MRI (obtained at the the same time as liver) can be used to assess iron in the pancreas, but its clinical utility is currently uncertain due to a lack of correlation with diabetes and pancreatic iron deposition.¹⁴² However, it may be useful as a tool to risk stratify those patients at greater risk of cardiac iron deposition.¹⁴³

Cardiac iron can accumulate by the age of 6 years in chronically transfused TM patients.¹²⁸ Therefore, cardiac MRI should be performed at this age, or earlier if possible with sedation/anesthesia. Iron concentration in the myocardium of the interventricular septum is inversely related to cardiac MRI T2* signal.^{123 131} There is no adequate surrogate for assessment of cardiac MRI, and all patients in Canada should have access to cardiac MRI iron assessment.^{134,135} Myocardial T2* values less than 25 ms (normal >42ms) are associated with a progressive and significant decline in left ventricular ejection fraction.^{122, 123,158,160,161} Cardiac MRI is non-invasive and allows concurrent determination of cardiac function. Early diagnosis of cardiac iron overload and dysfunction may allow for earlier intervention and better outcomes. At the present time there is no consensus on whether a single mean T2* value or multiple regional values is more useful.¹²⁴⁻¹²⁷ Currently, CMR T2* is validated on 1.5T magnets, but investigation is ongoing to validate 3T and higher magnets, as well as different iron protocols.¹³⁸⁻¹⁴⁰ The clinician must be satisfied that the MRI technique used in their centre has been validated and results are reproducible.¹³⁶ Assessment of cardiac fibrosis resulting from iron deposition is not yet well defined.

Where cardiac MRI is not possible due to technical reasons such as implanted non-compatible or interfering device, it is reasonable to use tissue Doppler imaging or strain analysis by ECHO as a surrogate of iron depiction as in interval assessment.¹²⁹ ECHO can also be used to detect early diastolic dysfunction or pulmonary hypertension.¹³⁷ proNT BNP may correlate with cardiac iron levels but not with cardiac function until late stage of disease.¹⁴¹

Initiation of Chelation Therapy

i. Deferoxamine (DFO)

Deferoxamine was the first iron chelator available. Its use has resulted in decreased end organ dysfunction and improved long-term survival. Its main disadvantage is that it must be administered parenterally using an infusion device.¹⁴⁴ However, recent data demonstrates less cardiac deaths with use of oral chelators.¹⁴⁵

The dose of deferoxamine is adjusted according to body iron load and age, and ranges from 20 – 40 mg/kg/day for children and up to 50 mg/kg /day for adults given for 8 – 12 hours for 5 – 7 nights per week. More aggressive chelation therapy is required for patients with significant iron loading.^{118, 158} Aggressive chelation therapy consists of a 24-hour continuous

infusion of deferoxamine to the maximum daily dose.¹⁴⁶ While an increase in the dosage of deferoxamine can increase the amount of iron chelation, the chelation efficiency of the same dose of drug is significantly increased by prolonging the duration of infusion, likely decreasing the organ damage due to non-transferrin bound iron. The constant presence of chelator decreases damaging reactive radical formation. Deferoxamine toxicity needs to be watched for when doses are high in the presence of low ferritin levels. The mean daily dose may be adjusted based on ferritin level in order to keep the therapeutic index below 0.025 (i.e. the mean daily dose (mg/kg) of Desferal divided by the serum ferritin level (micrograms/L) should be below 0.025. The therapeutic index is a valuable tool in protecting the patient from excess chelation, but it is not a substitute for careful clinical monitoring.

Side effects of deferoxamine include local skin reactions, predisposition to infection with *Yersinia enterocolitica* and other siderophoric organisms, severe allergy, divalent ion deficiency (e.g., zinc) and dose-related complications. Dose-related toxicities include auditory problems, including high frequency bilateral sensory neural loss, tinnitus, and deafness. High doses of deferoxamine increase the likelihood of night blindness, impaired color vision, impaired visual fields, and decreased visual acuity. The incidence of these side effects is increased if TI is >0.025. For intravenous therapy at high doses, renal dysfunction, hypotension and interstitial pneumonitis have been noted. Growth retardation can occur especially in children under 3 years and on high doses. Excessive doses of deferoxamine in patients with low iron loading can cause skeletal changes including vertebral demineralization and flattening of vertebral bodies.

ii. Deferiprone (DFP)

Deferiprone, the first oral iron chelator, was approved by Health Canada in February 2015. It is licensed for treatment of iron overload in patients with thalassemia syndromes when alternative chelation is inadequate.^{163, 164} Typical dosage is 75-100 mg/kg/d in 3 divided doses with higher doses preferred when used as monotherapy. Deferiprone reduces iron stores, as measured by ferritin or LIC, in thalassemia major patients receiving transfusions.¹⁵⁵⁻¹⁶⁵ It causes less iron excretion compared to deferoxamine on a molecule-to-molecule basis. Because of its small size and lipophilic nature, deferiprone is able to penetrate cells better and chelate iron from organs such as the heart more effectively.¹⁶⁶⁻¹⁶⁸ Myocardial T2* values and left ventricular ejection fraction (LVEF) improve more rapidly in deferiprone-treated patients compared to deferoxamine-treated patients.

While deferiprone clearly has selectivity for cardiac iron, deferoxamine chelates iron more efficiently from the liver. A systematic review demonstrated greater efficacy by deferiprone to improvement in cardiac and endocrine function but with insufficiently powered or too few studies to demonstrate efficacy for cardiac and liver iron control.¹⁴⁷ Given the clinical benefit of improvement in LVEF, this makes Deferiprone the preferred cardiac chelator.¹⁴⁸

The most serious complication of deferiprone is agranulocytosis (neutrophils < 0.5 x 10⁹/L), which occurs in less than 2% of patients and most likely in the first 6 months of treatment.¹⁶⁵⁻¹⁷² Milder neutropenia (0.5 – 1.5 x 10⁹/L) occurs in 8% of patients. Common side effects of deferiprone include arthropathy, transient elevation in ALT, and gastrointestinal upset.

iii. Deferasirox (DFX)

Deferasirox Dispersible Tablets (DT) (EXJADE) was approved in 2006 as an oral iron in Canada. It has been approved for the treatment of chronic iron overload in patients with transfusion-dependent anemias aged 6 years or older and in those patients aged 2 – 5 years who cannot be adequately treated with deferoxamine. Dosing is adjusted based on the patient's transfusion rate and trend of iron load; treatment ranges from 10 – 40 mg/kg/day. It is the most widely used chelator in North America.¹⁴⁹

A phase III trial (EPIC) demonstrated the efficacy of deferasirox DT and its non-inferiority to deferoxamine at doses of over 20 mg/kg/day when used by thalassemia major patients.¹⁵⁰ Non-inferiority at lower doses of deferasirox DT was not established and may have been due to study design. An extension study of CORDELIA has demonstrated its efficacy for improving cardiac T2* independent of LIC.¹⁵¹ Individualized assessment of total iron load and a tailored dosing regimen may be needed to achieve optimal iron chelation. There is growing body of data to support its efficacy in chelating the myocardium, though data is lacking for improvement of a previously low LVEF.^{152, 153}

Deferasirox DT has also been shown to control liver iron in non-transfusion dependent thalassemia (ESCALATOR study).¹⁵⁴

Side effects of deferasirox include gastrointestinal symptoms (26%), skin rash (7%), cytopenias, and an increase in serum creatinine and other renal adverse effects (34%). Toxicity is more common at low iron burden.¹⁵⁵ Side effects may be modifiable and efficacy increased by using a BID dosing regimen.¹⁵⁶ Administration with food can also increase drug absorption.¹⁵⁷

Deferasirox film-coated tablets (FCT) (JADENU) were approved by Health Canada in 2016. Public drug plan reimbursement criteria vary by province. There were very limited studies with the new formulation prior to approval though it does appear to have improved gastrointestinal side effect profile compared to DT for Oral Suspension (EXJADE). This may have a positive impact on patient adherence. A useful conversion tool is provided on the manufacturer's website for assisting in switching patients from EXJADE to JADENU formulation of Deferasirox.

Combination chelation therapy

The most commonly reported combination regimen utilises oral Deferiprone with parenteral Deferoxamine. Numbers are small and the dose and scheduling varies widely between studies, making analysis challenging.¹⁵⁹⁻¹⁶² Combination treatment with deferoxamine and deferiprone is increasingly being used to remove total body iron. Combination treatment reduces myocardial iron load, lowers ferritin and improves LVEF in thalassemia major patients with mild to moderate cardiac iron loading as defined by T2* values of 8 — 20 ms.¹⁶⁹⁻¹⁷²

The combination of Deferasirox and Deferoxamine has shown to improve liver and cardiac iron, though with small numbers.¹⁶³ More recently, there has been interest in combining two orally available chelators, Deferiprone and Deferasirox.⁴⁷⁵ However, coverage for this approach is highly variable among provinces in Canada.

iv. Iron Chelators Under Investigation

Other oral chelating agents are undergoing clinical trials, though with no recent success. There is growing interest in the development of, not only new chelators, but novel agents that target other pathways, such as calcium channel antagonists, hepcidin agonists, apo-transferrin, and silymarin.^{166,167}

v. Chelating Agents Summary

The ideal chelating agent should be highly efficient at binding iron, and be able to penetrate cells effectively and remove intracellular iron. It should be easy to administer orally, have a long half-life, and lack significant side effects. Lastly, the ideal chelating agent should be inexpensive and accessible. Although three therapeutic options now exist for iron-overloaded patients in Canada (see table 4), each agent at the present time has benefits and limitations.

Properties	Deferoxamine (DFO)	Deferiprone (DFP)	Deferasirox (DFX)
Molecular weight (daltons)	560	139	373
Route of Administration	Subcutaneous or intravenous	Oral	Oral
Half-life of iron free drug	20-30 minutes	3-4 hours	12-16 hours
Primary route of iron excretion	Urine and stool	Urine	Stool
Iron chelating efficacy	High (hexadentate)	Low (bidentate)	Moderate (tridentate)
Side Effects	<ul style="list-style-type: none"> • Local skin reactions • Sensorineural hearing abnormalities • Retinopathy and visual changes • Growth retardation • Bone changes • Potential renal and lung toxicity 	<ul style="list-style-type: none"> • Severe neutropenia • Gastrointestinal discomfort • Mild neutropenia • Arthralgias 	<ul style="list-style-type: none"> • Rash • Gastrointestinal discomfort • Renal impairment
Dosage	<ul style="list-style-type: none"> • 20-50mg/kg/day 3-7 times/week • Children's dose up to 30mg/kg 	75-100 mg/kg/day	<ul style="list-style-type: none"> • 10-40 mg/kg/day (Exjade) • 7-24mg/kg/day (Jadenu)
Contraindications	<ul style="list-style-type: none"> • Hypersensitivity • First trimester of pregnancy 	<ul style="list-style-type: none"> • Previous agranulocytosis • Pregnancy and lactation 	<ul style="list-style-type: none"> • Hypersensitivity • Creatinine clearance <60ml/min • Pregnancy and lactation

Table 4: Properties of Iron Chelators Available in Canada

Monitoring

- Every patient should have serial serum ferritin levels assessed every 3 months. Chelation therapy should be initiated for a persistently elevated ferritin > 1000 mg/ml or LIC >5mg/gm dry weight.
- Target serum ferritin is between 500 – 1000 mg/ml. Health care providers should recognize that serum ferritin may not be accurate in assessing iron overload independent of LIC and myocardial iron.
- LIC should be determined by a validated MRI technique after approximately 10 – 20 transfusions, prior to initiation of chelation therapy, and every 6–24 months, as clinically indicated.^{110,111}
- Cardiac function and iron should be monitored every 6–24 months using cardiac MRI T2*. Due to the non-linear scale of T2* changes over time should be evaluated using the cardiac iron concentration or by transforming the data.⁴⁷³

Treatment

- Young children needing chelation therapy should be started on subcutaneous infusion of Deferoxamine or oral chelation with Deferasirox or Deferiprone. To help with adjustment, the drug can be administered less frequently and increased to the target dose over 1 year.
- The target dose of deferoxamine should be 20 – 30 mg/kg/day for children, and up to 50 mg/kg/day for adults, given over 8 – 12 hours for 5 – 7 days/week.
- The treating thalassemia specialist should have access to the different drug options for chelating iron and should be able to tailor the use of the drugs based on specific individual patient requirements and evidence from clinical trials.

Toxicity

- For patients on deferoxamine, investigations should include yearly audiometry and ophthalmology examinations, bi-annual growth assessments for children, and regular screening x-rays for bone complications. Baseline assessments for the above should be done prior to initiating chelation.
- For patients on deferasirox, serum creatinine and urinalysis, liver enzymes, and blood counts should be monitored prior to commencement of the drug, and then monthly thereafter. Once stabilized, serum creatinine, liver enzymes, and ferritin should be monitored every 1–3 months depending on degree of iron overload, blood test stability and patient compliance. Complete blood count should be performed monthly. Audiometry and ophthalmic testing should be done annually or earlier, if clinically indicated.
- For patients on deferiprone, complete blood counts with differential should be performed weekly and ALT measurements done monthly for 3 – 6 months, and every 3 months thereafter. Summary for toxicity monitoring is provided in table 5.

Properties	Deferoxamine (DFO)	Deferiprone (DFP)	Deferasirox (DFX)
CBC and differential	Baseline Monthly	Baseline Weekly (neutrophils)	Baseline Monthly
Creatinine, UA	Baseline Monthly	Baseline 3 months	Baseline Two weekly (for one month) Monthly
Liver enzymes	Baseline Monthly	Baseline Monthly (for 3-6 months) Every 3 months thereafter	Baseline Monthly Every 3 months if stable
Audiometry	Every 2 years (if stable)	Every 2 years (if stable)	Annual
Ophthalmic testing	Every 2 years (if stable)	Every 2 years (if stable)	Annual
Growth assessment	Bi-annually (Children)	Not required	Not required

Table 5: Recommended Toxicity Monitoring for Available Iron Chelators

Support

- Patients and families should be educated on the role and importance of iron chelation therapy and the rationale for the treatment regimen.
- Deferoxamine infusions are burdensome and therefore compliance is poor. Every effort should be made to provide education for patients and their families. Issues such as drug preparation, choice of infusion site, types of needles and infusers used, and strategies for treatment of local reactions should be addressed. Children should be encouraged to participate in part of the routine of drug administration at an early age. This should be encouraged by the team based on the development level of the child, the family structure, and the cultural ideas of the family around the illness and treatment. The importance of chelation therapy should be reinforced at every clinic visit.¹⁶⁸ A study comparing QoL on Deferoxamine or Deferasirox or both showed no difference in a Chinese population.¹⁶⁹ Deferasirox has been shown to provide better QALY than Deferoxamine, though less than Deferiprone.¹⁷⁰⁻¹⁷¹ A randomized, open-label, Phase III trial evaluated Patient-Reported Outcomes (PROs) at the end of one year and found that significantly more patients on deferiasirox as compared to those on deferoxamine reported treatment satisfaction (89% vs. 41%, respectively) and treatment convenience (93% vs. 11%).¹⁵⁸ Of those previously treated with deferoxamine, 97% of those in the deferiasirox arm indicated a preference for deferiasirox and 86% indicated a willingness to continue treatment as compared to 14% of those assigned to the deferoxamine group. All of these findings suggest a greater likelihood of compliance with deferiasirox therapy
- All patients and families should have access to a multidisciplinary team to provide support in the practical and psychological challenges arising from daily chelation therapy and regular transfusions.
- The satellite clinic and specialist centre should have similar treatment and monitoring protocols. Good communication between the patient, family, local clinic, and specialist centre should be maintained to optimize patient care.

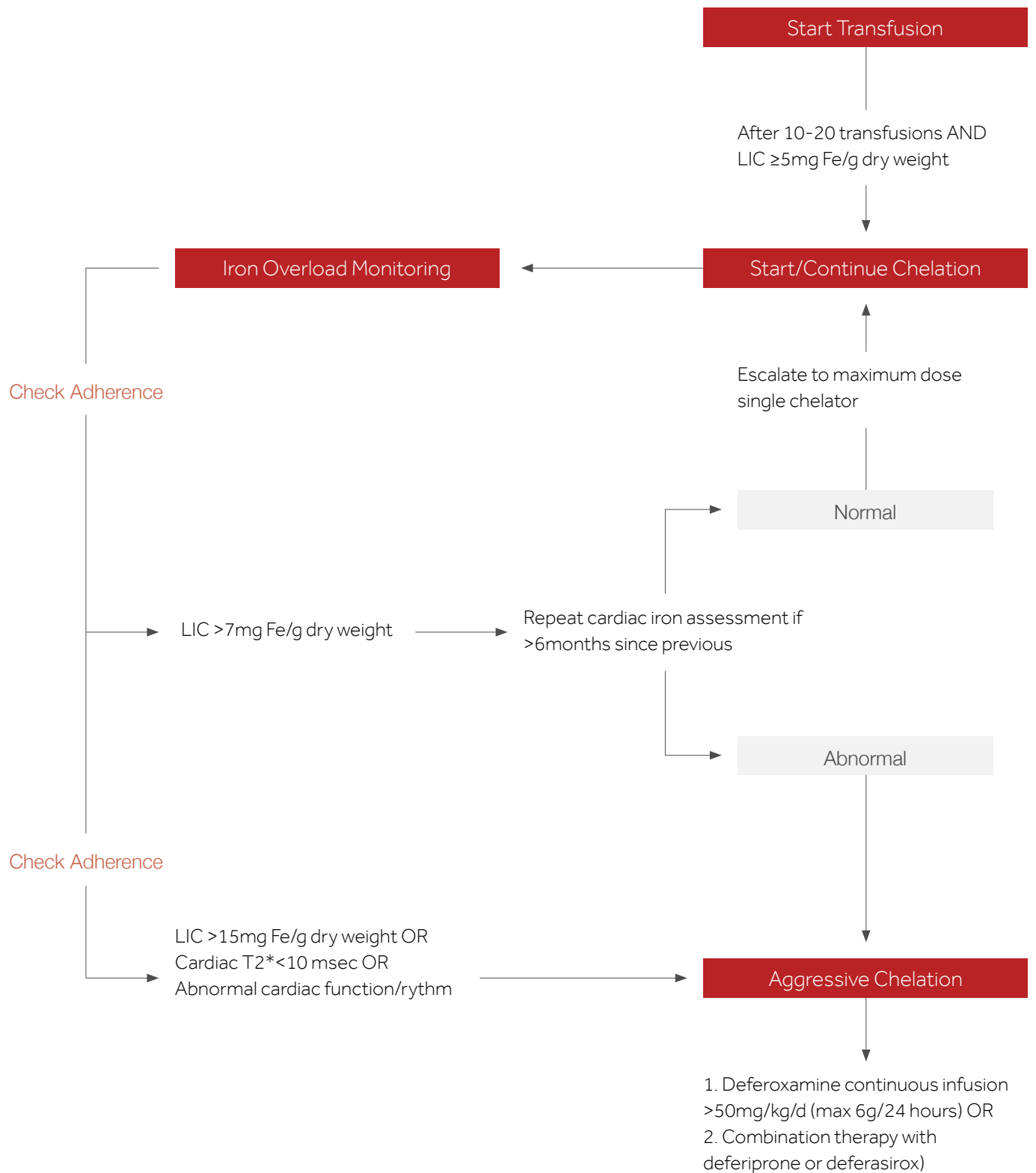


Figure 2: Iron Overload Assessment and Management in TDT patients