How I treat transfusional iron overload

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INTRODUCTION

Iron overload is a major concern in patients with congenital and acquired anemias for whom regular transfusions are needed (Table 1). Under normal conditions, iron absorption and loss are balanced at approximately 1 mg/day. Transfused blood contains 200-250 mg of iron per unit. Hence, patients with β-thalassemia major (TM) or other refractory anemias receiving 2-4 units of blood per month have an annual intake of 5000-10,000 mg of iron or 0.3 – 0.6mg/kg/day. The body has no mechanism for excreting this excess iron. Moreover, patients with TM and other anemias characterized by ineffective erythropoiesis, absorb excess iron despite iron overload because of production of GDF15 and possibly other proteins (eg TWSGI) from erythroblasts, which inhibit hepcidin synthesis (1).

Untreated transfusional iron load results in damage to the liver, endocrine organs and most importantly to the heart. In TM, without effective iron chelation, death occurs from cardiac failure or arrhythmia, usually in late childhood or in the teenage years. Most studies of iron chelation therapy have been carried out in TM for which all patients need transfusions and iron chelation. As discussed later, the exact indication for iron chelation and the cost/benefit is much less well established for patients with sickle cell disease (SCD), myelodysplasia (MDS) and other refractory anemias.

We first highlight the available techniques used for assessing iron status. We then review the efficacy, side effects and how we monitor treatment with the three currently licensed iron chelators deferoxamine (DFO), deferiprone (DFP), deferasirox (DFX) alone or in combination. We then describe how we commence iron chelation in adults and children with TM and transfusional iron overload in conditions other than TM. The overall management of TM has already been superbly
reviewed in this series of ‘How I Treat’ (2) and recent excellent reviews of iron chelation therapy have been published (3,4)

**ASSESSMENT OF IRON OVERLOAD**

Calculation of iron intake recording the number of units of blood transfused is cost-effective, precise and can predict the total iron that will accumulate in the body.

**Serum ferritin**

Serum ferritin measurement may be the only available method of assessing iron burden in developing countries. It is useful for close and frequent patient monitoring to indicate changes in iron burden. More accurate measurements of iron stores (described below) are performed at less frequent intervals. Although serum ferritin has been used for deciding when to start chelation therapy, it is now known to be an inaccurate indicator of cardiac iron or of total body iron burden. Serum ferritin also fluctuates in response to inflammation, abnormal liver function, and ascorbate deficiency. Despite these reservations, there is an association, albeit weak, between the level of serum ferritin and prognosis in TM (8 -12).

**Liver iron concentration:**

Liver iron concentration (LIC) accurately predicts total body iron stores (13). When possible it should be measured annually in patients undergoing regular transfusion therapy. Normal LIC values are up to 1.8 mg Fe/g dry weight [dw], with levels of up to 7 mg/g dw seen in carriers of genetic hemochromatosis without apparent adverse effects. Several studies have linked very high LIC (above 15mg/g dw) to worsening prognosis (10,14), liver fibrosis progression (15) and liver function abnormalities (16). It is likely that very high liver iron concentrations are associated with high plasma
non-transferrin bound iron (NTBI) since the liver is the main organ for removing free iron from plasma. NTBI is damaging to the organs which are also affected by iron deposition.

Liver biopsy provides a direct measurement of LIC, being quantitative, specific and sensitive. Biopsy is an invasive procedure but in experienced hands it has a low complication rate (15). Inadequate sample size (< 1 mg/g dw or <4 mg wet weight or <2.5cm core length) or uneven distribution of iron, particularly in the presence of cirrhosis, may give misleading results (17). LIC can also be measured accurately by superconducting quantum interference device (SQUID). However, only four such machines are available worldwide: they are expensive to purchase and maintain, and require dedicated trained staff. The results correlate well with chemical estimation of LIC unless fibrosis is present.

MRI is more widely available and it offers noninvasive estimation of LIC. MRI scanners generate images of organs in which the signal seen depends on iron concentration. Iron causes the organ to darken more rapidly (Figure 1). T2* is the time needed for the organ to lose approximately 2/3 of its signal and is measured in milliseconds (ms). T2* shortens as iron concentration increases. Its reciprocal, 1000/T2*, is known as R2* and is measured in units of inverse seconds (S⁻¹).

MRI scanners can also measure T2 and R2 rather than T2* and R2* although technically this is slower and less straightforward. The results of R2* and R2 for liver iron are similar (18). The technique demonstrates an average sensitivity of > 85% and specificity of > 92% up to an LIC of 15 mg/g dw, and has been registered in the EU and USA. For calibration, the MRI machine must use a Phantom supplied by the company, while the data acquired are sent via internet for analysis by dedicated Ferriscan software (payment per scan analysed). It can be applied with little training, at any centre
with an up-to-date MRI machine. T2* MRI for liver iron quantification is also widely used. Liver T2* calibration using a clinically relevant MRI sequence has been published (18). T2* measurement of LIC is reproducible between centres using a clinical grade MRI sequence (19). We prefer the T2* technique to T2 as it offers measurement of both cardiac and hepatic iron overload at the same time (see below). T2 or R2 for measuring cardiac iron are less robust but widely used.

**Cardiac iron**

Estimation of myocardial iron using T2* MRI requires expertise in its use and standardization. Good correlation between different centers and machines has been shown (19), and the technique has been recently validated as a true measure of cardiac iron, correlating with chemical measurement on post-mortem cardiac biopsies (20). A shortening of myocardial T2* to <20 milliseconds (ms) (implying increased myocardial iron above normal) is associated with an increased likelihood of decreased left ventricular ejection fraction (LVEF) whereas patients with T2* values >20 ms have a very low likelihood of decreased LVEF (4). T2* values of 10-20 ms indicate a 10% chance of decreased LVEF; 8-10 ms an 18% chance; 6 ms a 38% chance; and T2* values of 4 ms a 70% chance of decreased LVEF (7).

Cardiac T2* therefore identifies those patients at risk of a fall in LVEF whose chelation treatment should be intensified (5,12,21,22). Improved survival in patients with TM in the UK has been attributed to the introduction of cardiac MRI T2* monitoring with intensification of chelation if indicated as well as the availability of the oral iron chelator DFP (23).
Cardiac T2* does not correlate with serum ferritin concentration or liver T2* in patients receiving chelation therapy in a cross-sectional analysis, although longitudinal studies may imply a significant relationship (4-6). The discrepancy between cardiac iron and LIC in many TM patients may be partly due to the differences in response to DFO therapy which removes liver iron more effectively than cardiac iron (24,25). However, even in the absence of DFO therapy, TM patients may develop a cardiac T2* <20msec with LIC concentrations in the range of 1.2 – 9.0mg/g/dw (26). Thus, cardiac MRI T2* measurement is needed in all TM patients irrespective of their LIC or serum ferritin level. We recommend that patients undergo cardiac MRI T2* measurement at least yearly if they have abnormal values (<20 ms) or more frequently if with diagnosed heart disease; and once every two years in those with values >20ms and normal cardiac function. All patients should have cardiac T2* measured if cardiac symptoms develop.

Other measurements:

Other tests of iron status cannot be recommended for regular monitoring of iron overload or response to chelation therapy. Measurement of non-transferrin bound iron (NTBI) is carried out only in a few research laboratories. Urine iron excretion after a single dose of a chelator gives some measure of total iron stores in the case of DFP but not for DFX or DFO where iron excretion is totally or partly by the fecal route. Measurement of the degree of saturation of the plasma iron binding capacity gives a rough idea of iron burden but is affected by recent iron chelation therapy or inflammation. Values over 100%, however, suggest inadequate chelation and the need for cardiac and liver iron determination.
Available Chelators

Deferoxamine (DFO)

DFO is the drug for which there is the longest experience in treating transfusional iron overload (Table 2). It is usually self-infused on at least 4 days a week over 8-12 hours. The usual dose is 40mg/kg body weight but higher doses up to 60 mg/kg have been used in patients with high body iron stores. Even higher doses have caused pulmonary and neurotoxicity and should be avoided. Vitamin C (maximum 200mg daily) may be given to correct deficiency and to enhance iron excretion. Some units give intravenous DFO (from a separate bag) with blood transfusion eg. 1g DFO for each unit of blood but we do not recommend this in children or in adults unless non-compliant and inadequately chelated.

The drug has transformed life expectancy for many patients with TM and other refractory anemias. It has also reduced endocrine and hepatic complications. Many patients with TM are not satisfactorily chelated by it, however, and then may develop a fatal cardiomyopathy. The reasons for these ‘failures’ of DFO therapy include cost of the drug, pump and tubing, poor compliance (8), allergy, toxicity, local problems at the site of the infusions, lack of 24 hour binding of NTBI (27) and Yersinia infection (not a complication of the oral chelators). Even among patients apparently complying with DFO infusions at least 5 times a week and with serum ferritin levels <1000ug/l, some may develop cardiac iron overload and failure (28). About 20% of patients receiving DFO alone in UK, Italy and Cyprus have cardiac T2* levels <10m sec (29).

Safety monitoring

This has been the subject of several excellent reviews and is only briefly discussed here (3,30,31). The main side-effects occur with high doses of the drug in patients, particularly children, with low iron
stores. These consist of damage to the retina (night blindness, visual field loss, retinal pigmentation and changes on electrical tests) and high tone sensory neural hearing loss. Growth and bone defects may also occur in children, with rickets-like bone lesions, metaphyseal changes and spinal damage with loss of sitting height. A therapeutic index can be calculated as follows: mean daily dose (mg/kg) / current serum ferritin (ug/l). If this is below 0.025 at all times, these side-effects of DFO do not occur (32).

Regular checks are needed for visual or auditory defects, in children six monthly and adults annually. In children, checks of growth, particularly sitting height compared to total height, detect early spinal growth defects.

Deferiprone (DFP, L1, 1,2dimethyl, 3 hydroxy, pyrid-4-one, Ferriprox)

This bidentate iron chelator is rapidly absorbed with a peak blood level about 45 minutes after ingestion. It is cleared rapidly from plasma with 85% conversion in the liver to a glucuronide derivative. Differences in the speed of this conversion partly accounts for a variation in efficacy between patients (33). It is usually given three times daily to achieve maximum iron chelation. The usual starting dose is 75mg/kg/day but, provided it is well tolerated, doses up to 100mg/kg/day can be given to enhance iron excretion (34,35). Patient compliance is excellent compared with DFO (33).

DFP has the lowest molecular weight of the three chelators and penetrates cells to chelate iron from intracellular compartments such as lysosomes and mitochondria (36). DFP has emerged as superior to DFO at reducing cardiac iron levels. Comparison of 359 Italian patients attending 7 centers between
the years 1995-2003, treated with DFO alone or for the 157 switched to DFP showed a clear superiority of DFP. In Italy, whereas no cardiac deaths and no new cardiac events (arrhythmias or cardiac failure needing drug therapy) occurred in a DFP group, 10 cardiac deaths and 42 non-fatal cardiac events occurred in a DFO group (37). Four retrospective studies in which cardiac iron in TM patients was assessed by T2* MRI suggested that DFP was more effective than DFO at removing cardiac iron. The patients receiving DFP had higher left ventricular ejection fractions (LVEF’s) than those receiving DFO, although for liver iron, the two drugs appeared equally effective (38-41).

Prospective randomized trials have confirmed the superiority of DFP alone compared with DFO at usual therapeutic doses, at removing cardiac iron, improving left ventricular function and preventing death (42,43). This was shown initially for patients with normal cardiac function and moderate cardiac siderosis (T2* 8-20ms) (42). In a subsequent large observational study, DFP improved all degrees of cardiac iron burden including those with T2* <8msec (43). In this study DFP also seemed superior to DFX at lowering cardiac iron, although non-prospective limited data were included.

Safety monitoring

The established side-effects of deferiprone were described within two years of the first clinical trials (33) and their incidence determined in large clinical trials (43-45) (Table 4a). The most frequent are gastro-intestinal (GI) such as nausea, vomiting and abdominal pain. A new liquid formulation has been reported to give fewer GI adverse reactions (46).

The most serious side effect of DFP is agranulocytosis—a neutrophil count of less than 0.5 x 10^9/l in two consecutive blood tests. It occurs in about 1% of patients, most frequently in the first year of
treatment, but it has been described in the second year or rarely, later. It is reversible but some deaths have occurred. The median duration of agranulocytosis is 9 days with a range 3-85 days.

Agranulocytosis has appeared to be most frequent in patients with the Blackfan-Diamond anemia (47,48). The mechanism is unclear. Granulocyte colony stimulating factor (G-CSF) may be given. It does not shorten the period of agranulocytosis but speeds recovery once this has begun. Rechallenge with the drug should be avoided and because of the risk of agranulocytosis, patients receiving DFP should be warned to report immediately any fever or sore throat. We recommend blood tests every week for the first year of therapy and at least every two weeks thereafter.

Lesser degrees of neutropenia, neutrophils 0.5-1.5x 10/9/l, occur more frequently (Table 4a). This is more common in patients with intact spleens, and reversible on stopping the drug. Rechallenge is worthwhile since neutropenia may not recur or the neutrophils may settle at a safe, albeit subnormal, level.

An arthropathy affecting mainly large joints, especially the knees, occurs in a proportion of patients. The arthropathy usually resolves after stopping the drug and often the drug can be successfully reintroduced at the same or a lower dose. Patients may also develop pains in the muscles which resolve without interrupting therapy.

Transient rises in liver enzymes occur in about 7% of patients but these usually fall to normal without stopping the drug. In 1% of patients the rises persist and the drug is then discontinued. The drug does not cause liver fibrosis (reviewed in ref 33).
Zinc deficiency was first reported to occur in diabetic TM patients receiving DFP and this was associated with increased urine zinc excretion (44). In large trials there has been a small overall fall in plasma zinc levels but few below the normal range (44). The deficiency is easily detected by measuring serum zinc levels and corrected with zinc supplements without diminishing iron chelation efficacy.

Combined Therapy: DFO and DFP

DFP given on each day of the week and subcutaneous DFO infusions given on some or all of these days was introduced in 1998 for patients inadequately chelated by maximum tolerated doses of DFP (34). The effect of the combined drugs on iron excretion has been found on the basis of urine iron excretion and iron balance studies to be additive or even synergistic (34,50). This has been explained as a shuttle mechanism with DFP entering cells and removing iron which is then passed on to DFO for excretion in urine or feces (51) (Figure 2). The DFP may re-enter cells and extract more iron. In addition recent studies show that DFP is capable of rapidly accessing NTBI fractions in plasma and transferring this iron to DFO (52). Shuttling of iron from DFP to DFO also applies to iron removed from transferrin (53).

Combination protocols have differed widely with doses of DFP ranging from 50-100 mg/kg and DFO doses from 20-60 mg/kg given in addition from one to seven days each week (54). For patients in cardiac failure, DFP is given daily with DFO continuously (Table 3).

Combined chelation can be intensified or reduced by changing the dose of either drug or by varying the number of days each week DFO is infused. Patients comply better with self-administered DFO when this is only needed on one or two days each week. Also the dose of both drugs may be adjusted
sufficiently low to avoid side-effects of either drug but to still give effective chelation. This has enabled the successful use of combined therapy in children in India (55).

Combined therapy with DFO and DFP has been found effective at improving cardiac iron assessed by T2* MRI, left ventricular ejection fraction (LVEF) and endothelial function (56,57) reviewed by Galanello et al (54.) In Cyprus where combination therapy with DFP and DFO was introduced for all patients at high risk of heart failure, there was a significant fall in mortality (58). In Italy a multicentre prospective randomized trial over 7 years in 265 patients found no deaths occurred in patients receiving DFP alone or in combination with DFO whereas 10 deaths occurred in those receiving DFO alone (59). Lai et al (60) confirmed the superiority of combined therapy over DFO alone in treating established iron-induced cardiac disease.

In patients who tolerate combined therapy over several years, it is possible to reduce total body iron burden in TM to normal, assessed by serum ferritin and T2* measurement of cardiac and liver iron and to improve endocrine function (61). Improvements in glucose metabolism and gonadal function in both sexes have been achieved (61). This contrasts with single agent chelator therapy for which there are no reports of significant reversal of endocrine damage. Side-effects from the combined therapy have been the same as with either drug alone. There has been no increase in the incidence of agranulocytosis, and no new toxicity.
Alternating therapy: DFP and DFO

The regimen of giving the two drugs on different days each week has been termed alternating or sequential therapy. It is aimed at improving compliance with both drugs and at giving some form of chelation every day. In the largest prospective study (59,62) in the sequential arm the patients received DFP 75mg/kg on 4 days a week and DFO 50mg/kg on 3 days. Follow up was a minimum of 5 years. One death from cardiac arrhythmia occurred. In view of the efficacy of and usual compliance with combined DFO and DFP therapy, we have not found it necessary to resort to alternating therapy.

Deferasirox (DFX)

DFX is the most recently introduced iron chelator except in North America where DFX was licensed before DFP. In contrast to DFP, iron excretion is via the fecal route (Table 2). As DFX has a long half-life in plasma, levels are maintained within the therapeutic range over a 24-hour period (Table 2). It can therefore provide 24-hour chelation cover and binding of NTBI with only once daily administration.

To date, DFX clinical experience extends over nine years, with more than 8,000 patients investigated across several transfusion-dependent anemias. In a randomized phase 3 trial in 586 patients with TM, a DFX dose of 30 mg/kg/day significantly reduced LIC and serum ferritin. The efficacy of DFX doses of 20 or 30 mg/kg/day was comparable with that of 40-60 mg/kg/day of DFO infused 5 days/week (63). DFX was also shown to be effective at reducing iron burden in patients who were heavily iron overloaded at baseline (64) and who eventually required dose escalation to >30 mg/kg/day (65). DFX has demonstrated long-term (5 year) dose-dependent efficacy in both adult and pediatric patients (66) and was recently shown to be associated with improvement in iron-related hepatic pathology (67).
DFX has been associated with greater patient satisfaction and adherence to therapy, and increased time available for normal activities when compared to DFO (68).

DFX has been found effective in removing iron from the heart in patients with baseline T2* 5-10 ms (severe) and T2* 10-20 ms (mild-to-moderate iron loading) (69-71). Among 71 patients with varying degrees of cardiac siderosis, cardiac T2* significantly improved from a mean of 12.0 to 17.1 ms over a 3 year period (72). LVEF in these patients was normal at the start of the study and did not change. Another study (US04) showed that monotherapy with DFX was effective in chelating cardiac iron in patients with mild to moderate hepatic iron stores but was borderline significant for removal of cardiac iron in patients with severe hepatic iron burden (73).

A small number of patients have been treated with twice daily DFX apparently increasing tolerability and efficacy (74). Until the results of larger studies have been reported, this interesting approach cannot be recommended.

**Safety monitoring**

In general, DFX has shown a favorable safety profile at high doses (>30 mg/kg/day), and in patients achieving serum ferritin levels <1000 µg/l (65, 75-81) (Table 4b). As for DFP, side-effects do not appear more frequent or severe at low iron levels but we recommend reduction in dose or discontinuation of both drugs when the serum ferritin is <500 µg/l.

The most common adverse events attributed to DFX therapy are GI disturbances and skin rash (Table 2). Diarrhoea is more common in the elderly. Mild, non-progressive increases in serum creatinine and
liver enzyme levels have also be noted. Recommendations for their monitoring and management are summarized in Table 4b. A boxed warning was added to the US DFX prescribing information, although this amendment has not been adopted by the European Health Authority or applied globally. The warning indicates that ‘DFX may cause renal and hepatic impairment, including failure, and gastrointestinal hemorrhage. In some reported cases, these reactions were fatal’. However, these reactions were observed in patients with advanced age, high-risk MDS, and those with underlying renal or hepatic impairment or low platelet counts. DFX is contraindicated in patients with renal and hepatic failure (82).

**Combined or alternating therapy: DFX and DFO**

As yet, there are no reports of large studies and we do not recommend these protocols except in a clinical trial setting. In one study published by abstract only, 15 TM patients with LIC >15mg/kg or with lower LIC concentration but evidence of iron related organ damage were treated with DFX 20-30mg/kg daily combined with DFO 35-50mg/kg SC on 3-7 days each week (83). Liver iron improved significantly after a mean of 29 weeks. No excessive toxicity was seen. As both DFO and DFX primarily remove liver iron, their combined effects may not be additive as they may compete for the same iron pool. This was so in a gerbil model (84).

Sequential therapy of these chelators has been suggested as an attractive option. In a small study of seven iron-overloaded TM patients, patients received 20 to 30 mg/kg/day of oral DFX for four consecutive days, then a subcutaneous infusion of 20 to 40 mg/kg/day of DFO for 8 to 12 hours on the next 3 consecutive days (85). All of the patients showed a decrease in serum ferritin without any side-
effects. This protocol, warrants further evaluation in larger patient numbers but currently we do not recommend it.

**Combined therapy: DFP and DFX**

Three studies of combined chelation with the two oral chelators DFP and DFX have been reported. In the largest, 16 patients were treated with DFP 75-100 mg/kg /day in three divided doses together with DFX 20-25 mg/kg each day (86). There was a fall in total body iron measured by serum ferritin, liver iron and cardiac iron measured by T2* MRI. Improvements occurred in LVEF, gonadal function and glucose metabolism. Compliance was excellent and quality of life improved for the patients who stopped using DFO infusions. Side-effects were no different from those when the drugs are used as mono-therapy. In two other reports, a total of 4 patients also showed improvement in cardiac iron, cardiac function with excellent compliance and no unexpected side-effects (87,88). Further long term studies in a larger number of patients are needed before this combined, attractive (to patients), oral chelation strategy can be recommended.

**FBS0701**

FBS0701 is a novel, orally-available member of the desazadesferrithiocin class of siderophore related tridentate chelators currently in clinical development. In pre-clinical studies, FBS0701 bound Fe(III) with very high affinity and selectivity and demonstrated a >4-fold higher no-observable-adverse-effect level compared to DFX, suggesting a favorable clinical safety profile, especially with respect to gastrointestinal and renal toxicity (89). Multi-dose safety and pharmacokinetic studies in iron-overloaded patients established the acute safety of FBS0701 and the feasibility of once-a-day dosing (90) and a phase 2 study has now been reported confirming these observations (91).
GENERAL PRINCIPLES OF IRON CHELATION THERAPY

Initiating therapy

Prior to initiation or change of iron chelation therapy, TM patients should be evaluated for the rate of transfusional iron loading (Table 3) and previous chelation. Serum ferritin, LIC, and cardiac T2* MRI and cardiac, hepatic, renal and endocrine (thyroid, parathyroid, pancreatic, gonadal and pituitary) function also need to be tested (2, 92, 93). Potential for pregnancy and the growth and development in children are also assessed (2). The overall prognosis in the chronic anemias other than TM must be assessed. If this is poor eg in high risk myelodysplasia patients, it may not be necessary to institute iron chelation. The same clinical and laboratory tests should be used for initiating and monitoring efficacy of chelation therapy, as for TM.

For patients already satisfactorily chelated on one or other chelator, no change in chelation is needed. Patients in North America and the European Community starting chelation as adolescents or adults have to choose initially between DFO or DFX. After the advantages and disadvantages of the two drugs have been explained, most opt for DFX. In some countries eg Turkey DFP is also approved as first line treatment. It is licensed in the European Community ‘for the treatment of iron overload, in patients with thalassaemia major when deferoxamine therapy is contraindicated or inadequate’. In the USA the indication is ‘for the treatment of patients with transfusional iron overload due to thalassaemia syndromes when current chelation therapy is inadequate’. Efficacy at tolerable doses, comorbidities, drug side-effects, compliance often related to patient preferences, and special patient populations and clinical trials require favoring the use of one regimen over another. These considerations also determine on which chelation regimen the patient is continued. In North America where DFP was only licensed in 2011, DFX is the most widely used but in the UK and other parts of the world eg. India
and the Far East where DFP has been licensed for 10 years or more, DFP alone or in combination with DFO is used by a substantial proportion of patients (91).

In TM, we recommend initiating chelation therapy as soon as transfusions have caused enough iron excess to potentially cause tissue damage. Usually in TM, this is at the age of two years or older. Current practice is to start after first 10-20 transfusions, when the serum ferritin level is >1000 µg/l, or when LIC is >7 mg Fe/g dw. Dosing should be tailored according to transfusional iron take to achieve levels below these thresholds and a cardiac T2* >20ms. A discussion with the parents will be needed explaining the advantages and disadvantages of the different drugs.

**Maintenance therapy**

Maintenance therapy is adjusted to prevent tissue damage due to iron overload (36,92,93). A LIC >15mg/g/dw, serum ferritin >2500µg/l or cardiac T2* MRI <20m sec indicate inadequate chelation. If cardiac iron overload is present (T2* <20msec), cardiac iron removal becomes the primary goal of therapy (Table 3). As discussed earlier, not all patients are satisfactorily chelated on DFO, DFP or DFX alone. In many the dose or frequency of DFO infusions must be revised or the patient switched to another chelator or switched to combined therapy, eg of DFO with DFP. The iron intake from blood can also be reduced in TM patients by splenectomy if blood requirements are unusually high (>200-220ml packed red cells /kg/year).

**Monitoring for side-effects**

This is carried out at appropriate intervals relevant to the chelator or chelators being used (see earlier and Table 4). Depending on the severity of side effects, reduction of dose, switching to another
chelator or use of combined therapy may be needed. In general, side-effects with DFO are most frequent at low iron burdens whereas for DFX and DFP side effects appear to be equivalent at different levels of iron burden.

**Monitoring efficacy**

*Cardiac siderosis*

Intensification of chelation is needed for all patients with a cardiac T2* <15ms, whatever the serum ferritin or LIC. Fall in LVEF due to cardiac siderosis, or cardiac failure or arrhythmia is best treated by the combination of DFO intravenously (or subcutaneously) at doses of 40-60mg/kg/day and deferiprone orally 75mg/kg/day.

*Liver iron*

This should be monitored by MRI. Levels >15mg/g/dw indicate commencement or intensification of chelation is indicated. Chelation should be tailored as far as possible to achieve a LIC <7mg/g/dry weight.

**Special Populations**

*Pediatric patients*

Chelation strategies described above in the adult TM population can be applied in children with special considerations as follows. Initially in children a dose of DFO 20-30mg/kg/day is used to avoid toxicity with a maximum dose of 40mg/kg in children whose growth has ceased (2, 92). Close monitoring of growth and bone development are needed if DFO is started at age <3 years. In USA (FDA) DFX can also be used to initiate treatment in children as young as 2 years, commencing at a dose of 20mg/kg. In Europe (EMEA) DFX is only approved as a second line drug for children less than 6 years. Compliance in young children may be better to DFO infusions than to oral DFX but most parents
choose DFX. DFX has also had no reported adverse effect on children’s growth or on adolescent sexual development in both patients with TM and SCD (66, 81). However, monitoring for renal toxicity in children is particularly important (95). A recent study of DFP therapy found that with the newly introduced liquid formulation, the efficacy and safety profile in 100 children aged 1-10 years was similar to that in older children or adults (46). In developing countries cost and compliance considerations may make DFP a first choice for children.

**Pregnancy**

DFO is the only chelating drug that can be used in pregnancy. It should be interrupted during the first trimester and can be used in the second and third trimesters. A continuous intravenous infusion of DFO (50 mg/kg over 24 hours) can be given prior to a planned pregnancy (92). DFP and DFX should be stopped in pregnancy and during breast feeding. Sexually active patients receiving DFX or DFP should use contraception (92).

**Congenital Anemias**

Non-transfusion dependent thalassemia (NTDT)

Chelation in this disease has been discussed at length in a special supplement (96). NTDT describes patients with genetic disorders of hemoglobin synthesis who are not sufficiently severe to warrant regular blood transfusions but are more severely anemic than patients with β- or α-thalassemia trait. Many different genotypes underlie NTDT, β-thalassemia intermedia, hemoglobin E/β thalassemia, haemoglobin H and hemoglobin E/β thalassemia being the most common.
The patients become progressively iron loaded with increasing age mainly through increased iron absorption. In some patients, transfusions often given at times of infections, during pregnancy or to avoid bone complications, contribute to iron loading. Direct assessment of LIC by biopsy or by MRI is recommended because serum ferritin underestimates iron load in this patient population (97). Chelation is usually started with DFO but switched to one or other oral chelator in those unable or unwilling to comply with DFO (98). In some studies on E/β-thalassemia iron chelation with DFP has resulted in an improvement in erythropoiesis and hemoglobin levels (99). Clear guidelines are not available but we use an LIC >7mg/g/dw as an indicator to start iron removal (100). Preliminary data show DFX is safe and removes iron in TI patients (100,101). A large 1 year randomized, double blind, placebo-controlled phase 2 prospective study on 166 NTDT patients reported DFX to be both safe and efficacious (102). We do not recommend venesections to reduce iron burden since these may aggravate bone abnormalities by increasing anemia.

Blackfan Diamond Anemia (BDA)

The indications for commencing iron chelation therapy in BDA are similar to those in TM. The first report of agranulocytosis with DFP was in an adult patient with BDA (47) and the drug should be avoided in this condition (48). There have been no unexpected side-effects in chelating DBA patients with DFX and it was effective at lowering LIC and serum ferritin, although less so than in myelodysplasia (103). We recommend to try DFX in patients inadequately chelated on DFO or with hypersensitivity to it.
Aplastic Anemia

The British Society for Haematology Guidelines recommended DFO as first line chelation therapy for both congenital or acquired aplastic anemia (104). Particular problems may arise because of infections or bleeding at the site of the injection. We recommend DFX as second line chelator and reserve DFP/DFO for patients with a cardiomyopathy or a T2* <10msec. A recent subgroup analysis of 116 patients treated in the EPIC trial with DFX for 1 year found significant reduction in serum ferritin in both chelation naïve and previously treated patients. Serum creatinine rose in 25% of the patients especially in those receiving cyclosporin (68). There were no drug related cytopenias. A separate study showed that DFX was equally effective as assessed by serum ferritin and labile plasma iron in production or hemolytic anemias (102).

Congenital sideroblastic anemia

The indication for chelation and drugs to be used are similar to those in TM.

Sickle cell disease

Blood transfusions have been used in sickle cell disease (SCD) for patients at risk of cerebrovascular accidents or with frequent life threatening crises. An increasing range of indications have now been identified so that many patients with SCD have received multiple transfusions by adulthood (106).

All national guidelines recommend iron chelation in chronically transfused patients with SCD, mainly to avoid liver damage. This is supported by an 11.3% incidence of cirrhosis due to raised total iron burden in an analysis of 141 adult SCD patients over a 25 year review (107).

Assessment of SCD-specific populations has demonstrated that elevated iron levels are associated with an increased frequency of acute events, hospitalization, and death. Prospective trials are needed to
determine whether the increased iron levels are simply an indicator of the more severely affected patients or increase susceptibility to these other complications. Some studies have shown that patients with SCD with high serum ferritin levels and with a similar number of transfusions to those in TM, had normal cardiac T2* values (5, 108,109) and less endocrine damage (110).

The indications for iron chelation therapy in patients with SCD are, however, similar to those as outlined for adults with TM (Table 3). DFO remains the most widely used drug but compliance with it is particularly poor in SCD patients. A recent study on long-term safety and efficacy of DFX for up to five years showed a clinically acceptable safety profile, including maintenance of normal renal function with appropriate DFX dosing, iron burden was substantially reduced (82). Serial measurement of the glomerular filtration rate as well as of serum creatinine are indicated during DFX safety monitoring (82, 95). Oral therapy with DFP may be preferred if renal damage is present. A recent review of 14 trials found that among 502 patients, treatment with DFO alone (SC or IV), DFP alone, DFX alone, or combined treatment with DFO and DFP had been used. Only two randomized trials had been reported. The authors concluded that the use of chelation in SCD has been based on little efficacy or safety evidence and the cost: benefit ratio had not been fully explored (111). Further prospective studies are clearly needed.

**Acquired Anemias**

Aplastic anemia has already been discussed. Iron-mediated organ damage may occur in multiply transfused, low risk myelodyplasia (MDS) patients with several reports highlighting that mortality rate is greater in heavily iron-overloaded MDS patients developing hepatic and cardiac dysfunction (112-
114). These and other studies have shown an association between high iron levels and increased mortality in MDS treated conventionally or after stem-cell transplantation (115,116). It is difficult to be certain, however, how far the iron loading in all these studies directly reduces survival or is a marker for those patients with a poor prognosis because of the length and severity of the MDS (113,117-119). An early T2* MRI study in 11 patients showed that cardiac function and MRI T2* tended to remain normal for a long latent period in MDS patients even with hepatic iron loading (120). A more recent study in 43 multiply transfused MDS patients found 16.8% with a cardiac T2* <20msec (121).

Leitch (119) has critically reviewed published data on the benefits and risks of iron chelation therapy in MDS. Some studies, often retrospective, have shown improved survival or reduced transformation to acute myeloid leukemia (119,122). A recent matched pair analysis of 188 iron loaded MDS patients in which 94 patients received long term chelation with DFO or DFX and 94 did not, found median survival significantly longer in the chelated group (123). These data support the hypothesis that iron overload plays a role in decreasing survival in multiply transfused low risk MDS. Emerging data also suggest that iron chelation may be beneficial for overall survival in multiply transfused high risk MDS and in those selected for stem cell transplantation.

Several studies have shown improvement in white cell and platelets in MDS treated with DFO or DFX (124,125). An improved hemoglobin level, in some cases obviating the need for transfusions has also been described in MDS patients treated with DFO or DFX (119, 124,126-128). This effect may be at least partly due to removal of excess iron from the iron and oxygen dependent prolyl hydroxylase in the renal oxygen sensing system for erythropoietin production (129,130). Reduction of oxidative stress which may inhibit hematopoiesis has also been suggested (125). Prospective randomized trials currently in progress will help to determine which patients with MDS will benefit from chelation
therapy whether for leukemic transformation, overall survival, for hepatic or endocrine complications, for transfusion requirements and for other hematological parameters.

We recommend that transfusion dependent patients with an otherwise good prognosis (life expectancy >1 year) in whom chelation therapy is considered necessary should generally be managed as outlined for TM (Table 3). Various national and international guidelines have been published recommending starting chelation in low and intermediate-1 risk MDS (defined by an international prognostic score) after 20-30 units of blood have been transfused and with serum ferritin levels >1000ug/l in some, >2500ug/l in other guidelines. Liver and cardiac iron concentrations are also useful in deciding whether or not to start chelation therapy.

Choice of chelation for patients with MDS, chronic myelofibrosis, red cell aplasia, paroxysmal hemoglobinuria and other severe acquired anemias may not be easy. DFO and DFX are licensed for first line therapy. DFO may be difficult to administer because of excessive bruising or infection at the infusion site due to cytopenias. On the other hand extra caution should be used in treating elderly MDS patients or patients with myelofibrosis or other refractory anemias with DFX because of the greater frequency of decreased hepatic, renal, or cardiac function, not related to iron overload, and of concomitant disease or other drug therapy (117-119). DFP is not advisable because of the risk of agranulocytosis but the incidence of this in MDS is probably no higher than in TM (33). The relative costs of the drugs may influence choice many countries (Table 2).
FUTURE PROSPECTS:

The outlook for patients with TM and other transfusion dependent anemias has improved substantially with the availability of three iron chelating drugs and the use of T2* MRI to detect cardiac siderosis before cardiac symptoms develop. Combined therapy with DFO and DFP has proved particularly effective at treating a previously fatal iron induced cardiomyopathy. In the UK, infection rather than iron induced cardiomyopathy is now the main cause of mortality in TM (23). It seems likely that patient preference and compliance will result in the increased use of the oral chelators and corresponding reduced use of subcutaneous DFO. Randomised trials of oral chelators against DFO may become more difficult to perform because of patient preference. This will be particularly so if a third orally active iron chelator becomes clinically available. With each drug alone, however, a proportion of patients, perhaps 20%, will be inadequately chelated because of lack of efficacy or because the drug dosage has to be reduced or stopped because of side-effects. Switching chelators and combination therapy of the oral chelators is likely to increase in use so a randomized trial of the two oral chelators DFP and DFX in combination against alternative chelation regimens is urgently needed.

For developing countries, the oral chelators are particularly attractive if the costs can be kept low. Clinical trials are taking place of DFP, which alone of the three chelators can cross the blood brain barrier (131), in conditions such as Friedrich’s ataxia and Parkinson’s disease with excess iron deposits in the brain. Treatment of diseases, where iron overload is localized to a single organ, will need to be the subject of a future ‘How I Treat’ review.
Acknowledgment

We thank Professor Dudley Pennell for helpful comments on the sections of the manuscript dealing with measurement of cardiac and liver iron by MRI.

Author Contribution

All three authors AVH, AT and MDC contributed equally to reviewing the relevant literature and writing the manuscript.

Conflict of Interest

AVH - None declared

AT 1. I receive research funding from Novartis
   2. I am a member of Novartis Speakers Bureau

MDC 1. Member of Novartis Speaker Bureau,
      1. Member of Genzyme Advisory Board
      2. Member of Shire Advisory Board

REFERENCES:


Table 1

Refractory anemias for which blood transfusions and iron chelation may be needed

<table>
<thead>
<tr>
<th>CONGENITAL</th>
<th>ACQUIRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassemia major</td>
<td>Aplastic anemia</td>
</tr>
<tr>
<td>Thalassemia intermedia</td>
<td>Red cell aplasia</td>
</tr>
<tr>
<td>Aplastic anemia (Fanconi)</td>
<td>Myelodysplasia</td>
</tr>
<tr>
<td>Blackfan Diamond anemia</td>
<td>Chronic myelofibrosis</td>
</tr>
<tr>
<td>Sideroblastic anemia</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td></td>
</tr>
</tbody>
</table>

Rarely in some cases of congenital hemolytic anemia eg pyruvate kinase, glucose-6-phosphate dehydrogenase deficiency
Table 2  Comparison of Deferoxamine, Deferiprone and Deferasirox*

<table>
<thead>
<tr>
<th></th>
<th>Deferoxamine (DFO)</th>
<th>Deferiprone (DFP)</th>
<th>Deferasirox (DFX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>560</td>
<td>139</td>
<td>373</td>
</tr>
<tr>
<td>Chelator: iron</td>
<td>1:1 (hexandentate)</td>
<td>3:1 (bidentate)</td>
<td>2:1 (tridentate)</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Subcutaneous or intravenous</td>
<td>Oral tablets or liquid</td>
<td>Oral suspension</td>
</tr>
<tr>
<td>Iron excretion</td>
<td>urine, fecal</td>
<td>urine</td>
<td>Fecal</td>
</tr>
<tr>
<td>Plasma half life</td>
<td>20 min</td>
<td>1-3 hour</td>
<td>8-16 hour</td>
</tr>
<tr>
<td>Usual dose</td>
<td>40mg/kg/day</td>
<td>75-100mg/kg/day</td>
<td>20-40mg/kg/day</td>
</tr>
</tbody>
</table>

- **Licensed**: Licensed for treatment of chronic iron overload due to transfusion dependent anemia. In Europe, North America, Asia For treatment of iron overload in thalassemia major where DFO is contraindicated or inadequate. In USA, licensed for treatment of transfusional iron overload in patients 2 years or older. In Europe, approved for treatment of transfusional iron overload in thalassemia major, 6 years and older and when DFO is contraindicated and inadequate, in patients with other anemias, patients 2-5 years old and in non-transfusion dependent thalassemia.

- **Cardiac iron removal**: Compliance problem; not effective in all compliant patients. Continuous infusion more effective. Most effective of the three chelators. Used with continuous deferoxamine in cardiac failure. Reduces liver iron concentration and improves liver pathology. Reduces cardiac iron in 3 year study.

- **Annual cost (54kg body weight)**
  - (UK NHS)
  - Not applicable at the same rate in all countries

<table>
<thead>
<tr>
<th></th>
<th>40mg/kg/5 days = £4788**</th>
<th>75mg/kg/day = £4505</th>
<th>100mg/kg/day = £6007</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20mg/kg/day = £13,245</td>
<td>30mg/kg/day = £19,865</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40mg/kg/day = £26,490</td>
<td></td>
</tr>
</tbody>
</table>

- **Main side-effects**: Local reactions, auditory, retina, allergy, bone abnormalities. Gastrointestinal, neutropenia/agranulocytosis, arthralgia, liver enzyme rise, zinc deficiency***. Gastrointestinal, rash, renal, liver***.

- **Advantages**: 36 years experience. Best for cardiac iron removal. Once daily administration.

- **Disadvantages**: Mode of administration, lack of compliance. Weekly blood count monitoring in first year. Cost.

*Modified from Kwiatkowsky J.L (3)  **Add cost of treating, needles pump  *** See also Table 4
<table>
<thead>
<tr>
<th>T2* ≥20 ms</th>
<th>DFO**</th>
<th>DFP</th>
<th>DFO+DFP combination</th>
<th>DFX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron intake &lt;0.3 mg/kg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIC ≥15 mg Fe/g dw</td>
<td>40-50 mg/kg/d, 8-10 hr/d, 6 or 7 d/wk, SQ</td>
<td>75-100 mg/kg/d</td>
<td>DFO 40 mg/kg/10-12h/2d + DFP 75 mg/kg/d</td>
<td>30-40 mg/kg/d</td>
</tr>
<tr>
<td>LIC 7 to &lt;15 mg Fe/g dw</td>
<td>40-50 mg/kg/d, 8-10 hr/d, 5 d/wk, SQ</td>
<td>75-100 mg/kg/d</td>
<td>DFO 40 mg/kg/10-12h/1-2d + DFP 75 mg/kg/d</td>
<td>20-30 mg/kg/d</td>
</tr>
<tr>
<td>LIC 3 to &lt;7 mg Fe/g dw</td>
<td>40-50 mg/kg/d, 8-10 hr/d, 5 d/wk, SQ</td>
<td>75 mg/kg/d</td>
<td>DFO 40 mg/kg/10-12h/1-2d + DFP 75 mg/kg/d</td>
<td>20-30 mg/kg/d</td>
</tr>
<tr>
<td>LIC &lt;3 mg Fe/g dw</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron intake 0.3-0.5 mg/kg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIC ≥15 mg Fe/g dw</td>
<td>40-50 mg/kg/d, 8-10 hr/d, 6 or 7 d/wk, SQ</td>
<td>75-100 mg/kg/d</td>
<td>DFO 40 mg/kg/10-12h/2d + DFP 75 mg/kg/d</td>
<td>30-40 mg/kg/d</td>
</tr>
<tr>
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<td>75-100 mg/kg/d</td>
<td>DFO 40 mg/kg/10-12h/1-2d + DFP 75 mg/kg/d</td>
<td>30-40 mg/kg/d</td>
</tr>
<tr>
<td>LIC 3 to &lt;7 mg Fe/g dw</td>
<td>40-50 mg/kg/d, 8-10 hr/d, 5 d/wk, SQ</td>
<td>75 mg/kg/d</td>
<td>DFO 40 mg/kg/10-12h/1-2d + DFP 75 mg/kg/d</td>
<td>Suspend</td>
</tr>
<tr>
<td>LIC &lt;3 mg Fe/g dw</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron intake &gt;0.5 mg/kg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIC ≥15 mg Fe/g dw</td>
<td>40-50 mg/kg/d, 8-10 hr/d, 6 or 7 d/wk, SQ</td>
<td>75-100 mg/kg/d</td>
<td>DFO 40 mg/kg/10-12h/2d + DFP 75 mg/kg/d</td>
<td>30-40 mg/kg/d</td>
</tr>
<tr>
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<td>20-30 mg/kg/d</td>
</tr>
<tr>
<td>LIC &lt;3 mg Fe/g dw</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Modified from Brittenham G.M (2)

**Vitamin C-dose limited to 200 mg/day given orally at the time of infusion.

†Therapeutic index = mean daily dose (mg/kg) (Mean daily dose = actual dose of each infusion x doses/7 days)/ferritin (mg/l). Keep index <0.025 at all times.

DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox; LIC, liver iron concentration; dw, dry weight; d, day; wk, week; SQ, subcutaneous infusion; IV, intravenous infusion.
Table 4a   Deferiprone-related adverse effects and their management

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Incidence in core trials(%)</th>
<th>Monitoring and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>33 in first year</td>
<td>Mild: continue drug or reduce dose. If severe, discontinue drug temporarily and restart at lower dose. Try liquid formation. 5% of patients discontinue drug permanently</td>
</tr>
<tr>
<td>(nausea, vomiting, abdominal pain)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8.5</td>
<td>Monitor blood count weekly for first year, fortnightly in second and subsequent years. Stop drugs for a few weeks. Rechallenge and continue drug if neutrophils at safe level of &gt;1.5 x 10⁹/l</td>
</tr>
<tr>
<td>(neutrophils &lt;1.5 x 10⁹/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>1</td>
<td>Stop drug, treat with intravenous antibiotics if febrile. Give G-CSF if neutropenia prolonged and/or febrile</td>
</tr>
<tr>
<td>(neutrophils &lt;0.5 x 10⁹/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rise in transaminases</td>
<td>7</td>
<td>Continue to monitor without stopping drug. Enzymes usually fall to normal. If persistently raised &gt;2 times upper limits of normal (about 1% of patients) discontinue drug.</td>
</tr>
<tr>
<td>Arthropathy</td>
<td>3.9 – 41</td>
<td>Related to degree of iron overload in some series. Stop drug temporarily and restart at lower dose About 2% of patients stop drug permanently because of arthropathy.</td>
</tr>
<tr>
<td>Zinc deficiency</td>
<td>Rare:</td>
<td>Give zinc supplements</td>
</tr>
<tr>
<td></td>
<td>Mainly in diabetes</td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>Incidence in core trials (%)</td>
<td>Monitoring and management</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8.8</td>
<td>Patients should take an antidiarrheal for up to 2 days, and keep hydrated. Deferasirox could be taken in the evening rather than the morning. Products such as Lactaid (if the patient is lactose intolerant) or probiotics (acidophilus or lactobacillus) could be added to the diet.</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5.0</td>
<td>Patients should sip water or other clear fluids, and avoid solid food for the first few hours. Avoid narcotic pain medications and non-steroidal anti-inflammatory drugs. Deferasirox could be taken in the evening rather than the morning.</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>14.3</td>
<td>Patients should drink small, steady amounts of clear liquids, such as electrolyte solutions, and keep hydrated.</td>
</tr>
<tr>
<td><strong>Skin rash</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild-to-moderate</td>
<td>4.3</td>
<td>Likely to resolve spontaneously. Deferasirox should be continued without dose adjustment.</td>
</tr>
<tr>
<td>Severe</td>
<td>0.4</td>
<td>Deferasirox should be interrupted and reintroduced at a lower dose. Patients should take low-dose oral steroids for a short period of time.</td>
</tr>
<tr>
<td><strong>Renal changes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;33% above pretreatment values at two consecutive visits (not attributed to other causes)</td>
<td>11</td>
<td>Deferasirox dose should be reduced by 10 mg/kg.</td>
</tr>
<tr>
<td>Progressive increases beyond the ULN</td>
<td>0</td>
<td>Deferasirox should be interrupted, then reinitiated at a lower dose followed by gradual dose escalation if the clinical benefit outweighs the potential risks.</td>
</tr>
<tr>
<td>Pediatrics, &gt;33% above pretreatment values and above the age-appropriate ULN at two consecutive visits</td>
<td>11</td>
<td>Deferasirox dose should be reduced by 10 mg/kg.</td>
</tr>
<tr>
<td>Changes in liver function (elevation in transaminases)</td>
<td>2</td>
<td>Liver function should be monitored monthly. Following any severe or persistent elevations in serum transaminase levels, dose modifications should be considered. Deferasirox therapy can be cautiously re-introduced once transaminase levels return to baseline.</td>
</tr>
<tr>
<td><strong>Auditory and ocular alterations</strong></td>
<td>&lt;1</td>
<td>Auditory and ophthalmic function should be tested before initiating therapy and annually thereafter</td>
</tr>
</tbody>
</table>

ULN, upper limits of normal.

*Vichinsky E (81)
Figure 1.

Cardiovascular magnetic resonance T2* images showing the heart and liver from 3 different patients at the same echo time (10.68ms): A. Normal appearance with a bright myocardial and liver signal indicating that there is no significant cardiac or hepatic iron loading (myocardial T2* 29ms, liver T2* 22ms). B. Dark myocardial signal indicating severe myocardial siderosis (heart T2* 6.2ms) but no liver iron (liver T2* 18ms). Note that the spleen (asterisk) also has high signal, suggesting that there is no significant splenic iron loading. C. Normal myocardial signal (heart T2* 24ms) but dark liver consistent with severe hepatic iron overload (liver T2* 1.8ms). Images courtesy Dr JP Carpenter.
Figure 2.

The ‘shuttle’ mechanism by which deferiprone (DFP) given orally binds iron from transferrin (TF), non-transferrin bound iron (NTBI) and from intracellular compartments and transfers some of this iron to deferoxamine (DF0). The free DFP is then available to bind more iron. Some DFO also enters cells to bind iron directly.
How I treat transfusional iron overload

A. Victor Hoffbrand, Ali Taher and Maria Domenica Cappellini