Overview of current chelation practices

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Abstract

Deferoxamine (DFO) is reference standard therapy for transfusional iron overload since the 1980s. Although it is a highly effective iron chelator, the compliance problem to subcutaneous administration of DFO remains as the major problem. The oral chelator Deferiprone (DFP) has no marketing licence in North America, however, it has been licensed in India since 1994 and the European Union (EU) granted marketing approval for DFP in 1999, specifically for patients with thalassemia major when DFO is inadequate, intolerable or unacceptable. There are still limited data available on the use of DFP in children between 6 and 10 years of age, and no data on DFP use in children under 6 years of age. Subsequently the oral chelator Deferasirox (DFX) was approved by FDA and EMA for the treatment of patients with transfusional iron overload -older than 2 years of age- as first line therapy, in 2005 and 2006 respectively. The primary objective of iron chelation is to maintain body iron at safe levels at all times but once iron is accumulated, the objective of iron chelation is to reduce tissue iron to safe levels which is a slow process. The chelation regimen, dose and frequency of administration, of the chelator(s) are mainly determined based on body iron burden, presence of myocardial iron and the transfusional iron loading rate. A proper monitoring of chelation is of importance for measuring the response rate to a particular regimen and providing dose adjustments to enhance chelation efficacy and to avoid toxicity. Efficacy of a chelation regimen may exhibit individual variability resulting from factors such as absorption and metabolism of the chelator. Tolerability and compliance are also individual variables effecting the response to chelation. Understanding of advantages and limitations of chelators, accurately determining chelation needs

of patients with iron overload and designing individualized chelation regimens with less toxicity but optimum efficacy, should provide long-term survival and quality of life for patients with iron loading anemias. The goal of this review is to summarize current concepts in iron chelation therapies based on the considerable amount of prospective data obtained by clinical studies.

Introduction

It is estimated that globally, 300 000 children are born each year with either sickle cell anemia or a form of thalassemia and almost 100 000 patients undergo transfusions.¹ Regular transfusions in patients with thalassemia major (TM) from infancy have resulted in iron induced liver disease and endocrine complications and are inevitably followed by death from iron induced cardiomyopathy if untreated.² In patients with thalassemia intermedia (TI), increased intestinal iron absorption leads to considerable amount of iron accumulation which is ultimately needed iron chelating therapy.³ Gradually increasing number of patients with sickle cell disease (SCD) is also being treated with long-term red cell transfusions and requiring chelation therapy.^{4,5} The purpose of this review is to focus on the chelation practices on transfusional iron overload in mainly patients with TM.

Objectives of iron chelation therapy

The primary objective of iron chelation is to maintain body iron at safe levels at all times but once iron is accumulated, the objective of iron chelation is to reduce tissue iron to the safe levels, which is a slow process particularly in heavily iron loaded subjects.^{6,7} Uncertainties also exist about how quickly total body and tissue iron levels can be safely removed and optimal balance would be established between removal of body iron and avoiding chelator toxicity for varied chelation regimens.

The chelator and dosing regimens (especially if the chelator is DFO) are mainly determined based on body iron burden, the presence of myocardial iron and the transfusional iron loading rate. A proper monitoring of chelation is of importance for measuring the response rate to a chelation regimen and providing dose adjustments to enhance chelation efficacy as well as to avoid toxicity. Efficacy of a chelation regimen may show individual variability resulting from factors such as absorption and metabolism of the chelator. Tolerability and compliance with the chelator are also individual variables effecting response to chelation. Understanding of advantages and limitations of chelators, assessing the iron burden of patients accurately and designing individualized chelation regimens with less toxicity but optimum efficacy may provide long-term survival and quality of life for patients with iron loading anemias.

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Properties of iron chelators

Three chelators are currently in use for the purpose of preventing and removing transfusional iron overload. DFO is a reference standard therapy since the 1980s and was the only approved chelator until 1999 in Europe, when European Union (EU) granted marketing approval for oral chelator DFP specifically for patients with TM when DFO is inadequate, intolerable or unacceptable. There are still limited data available on the use of DFP in children between 6 and 10 years of age, and no data on DFP use in children under 6 years of age.⁸ Subsequently, DFX as once daily oral chelator was approved by FDA and EMA for the treatment of patients with transfusional iron overload -older than 2 years of age- as first line therapy.⁹

DFO must be administered by prolonged subcutaneous infusion due to its rapid metabolism in plasma ($t_{1/2}$ =20-30 min). It is extremely important to comply with adequate dose of DFO (20-60 mg/kg/d) at least 5 days a week. Labile plasma iron (LPI) chelated with DFO is eliminated predominantly by the kidneys.¹⁰ Hepatocytes efficiently take up DFO, which then chelates hepatocellular iron and feroxamine is excreted in the bile.¹¹ High molecular weight (MW 559) of hydrophilic DFO retards its access into the labile cell iron (LCI) pool.¹² However clinical data showed that siderotic heart failure is reversible with 24 hours intravenous DFO infusion via indwelling catheter and myocardial T2* improves in concert with function during recovery.^{13, 14}

Oral chelator DFP is a widely used regimen of 75 mg/kg per day at three divided doses, up to 100 mg/kg. Moderate plasma half life ($t_{1/2}$ =2-3 h) is required, therefore its administration is at least 3 times a day. Although, LPI is removed by DFP, rebound between doses may occur.¹⁰ DFP, probably because of the rapid inactivation by glucuronidation within the liver,¹⁵ shows less impressive effect on liver iron concentrations.¹⁶ However, it readily enters cells as a small (MW 139) and lipophilic molecule and may access intracellular iron more effectively than DFO.^{17, 18} A randomized prospective study suggests that DFP has superior access to myocardial iron stores compared with DFO, which accords with in vitro data.¹⁹ DFP is excreted predominantly by urine.

DFX at doses of 10 to 40 mg/kg per day is administered once daily dosing providing 24-h protection from LPI.¹⁰ DFX forms complexes with plasma iron and DFX-iron complexes are eliminated predominantly through a hepatobiliary route. Hepatocytes also readily take up deferasirox, which chelates hepatocellular iron. The DFX-iron complexes are then excreted in the bile.²⁰ In vitro studies confirm its rapid access to labile cell iron pools.^{17, 18} Continued reduction and normalization of cardiac iron was observed in a long term prospective study of DFX.²¹ DFX is excreted by feces (Table 1).

Table 1. Properties of iron chelators.

Properties Chelator iron complex	Deferoxamine Hexadentate (1:1)	Deferiprone Bidentate (3:1)	Deferasirox Tridentate (2:1)
MW, hydro/lipophilic	559, hydrophilic	139, lipophilic	373, lipophilic
Usual dose	20-60 mg/kg/d	75-100 mg/kg/d	10-40 mg/kg/d
Route	s.c., i.v. 8-12 h, 5 days/week	oral, tid	oral, od
Half-life	20-30 min	2-3 h	8-16 h
Excretion	urinary, fecal	urinary	fecal
Depletion of LPI ¹⁰	yes (continuous infusion)	yes (rebound between doses)	yes
Removal of hepatocellular iron	yes ¹¹	less impressive ¹⁶	yes ¹³
Accessing LCI pool	Retard ¹²	rapidly penetrate and bound ^{17,18}	rapidly penetrate and bound ^{17,18}
Clinical data; extracting LCI in cardiomyocytes	benefits of 24h i.v. infusion ^{13,14}	higher than standard DFO ¹⁹	in comparison vs DFO

When should chelation be started and what are the safe levels of body iron burden?

The primary objective of iron chelation therapy is to maintain body iron at safe levels at all times. This has been traditionally determined based on experience with DFO chelation in which intensive chelation at or close to the time when a transfusion program was initiated in effort to prevent iron toxicity resulted with chelator toxicity which particularly appears as impaired growth and skeletal changes. Following this observation, chelation has been started following 10-20 red cell transfusions and when serum ferritin exceeds 1000 ug/L.²² Although this traditional threshold is currently applied to other chelation practices, there is uncertainty whether chelation can be safely started earlier with other chelators or this should be desired.

Chelation therapy should aim to maintain an LIC of about to 3.2-7 mg iron/g d.w. (normal ranges 0.6-1.2 mg iron/g d.w.) which was associated with normal survival without complications of iron overload in subjects with non transfusional iron overload.^{24, 25} Maintenance of normal liver iron levels might decrease the likelihood of complications of iron overload but increase chelator toxicity. Although, the serum ferritin levels corresponding to the targeted LIC have not been clearly defined, in practice, serum ferritin is maintained at between 500 and 1000 ug/L.^{23, 24} It has also been described that most of the toxic effects of DFO are more likely related with prescribing relatively higher doses of DFO while body iron stores are low. Based on this observation, it has been suggested that a therapeutic index obtained from the ratio of the mean daily dose of DFO (mg/kg) divided by the serum ferritin (ug/L) identifies patients at risk of sensorineural hearing loss, if the ratio is greater than 0.025.²⁵ Thereafter, the therapeutic index has been implemented carefully to avoid DFO toxicity. However, it is unknown whether chelator toxicity of DFP or DFX also occurs as low body iron levels fall.

Removal characteristics of excess iron

The secondary objective of iron chelation therapy is to reduce tissue iron to the safe levels once it is accumulated. The questions are; how quickly total body & tissue iron levels can be safely removed and normalized?

How optimal balance would be established between effectiveness in removal of excess iron and toxicity of chelator?

Impact of transfusional iron loading rate, chelator dose and regimen on iron removal

Negative iron balance is defined as excess of iron excreted over that received in form of transfused red cells. In a prospective randomized study comparing DFX with DFO, it has been shown that transfusional iron loading rate has a major impact on the success of a chelator and the percentage of patients achieving negative iron balance, by using any chelator dose, decrease with increasing transfusional iron intake. Further, at an average transfusional iron intake of 0.3-0.5 mg/kg/d, it has been shown that negative iron balance was achieved in 75% of patients receiving standard doses of subcutaneous DFO (35-49 mg/kg/d) 5 days a week, whereas it was achieved in 86% of patients at greater doses of DFO. DFX at a dose of 20 mg/kg was able to achieve negative iron balance in 55% of patients but at dose of 30 mg/kg, negative iron balance was achieved in 83% of patients (Table 2).²⁶

The success of DFP in achieving negative iron balance was also examined in short term iron balance studies. It has been shown that DFP at a dose of 75 mg/kg achieved negative iron balance in 46% of patients whereas at dose of 100 mg/kg, negative iron balance was achieved in 86% of patients.^{27,28} In line with the observation of iron balance study with DFP, in a randomized prospective study, 62% of TM patients treated with DFP at the dose of 75 mg/kg showed a decrease in LIC during the study period of one year. However, the addition of subcutaneous standard dose DFO (40-50 mg/kg) only twice weekly to daily DFP therapy resulted with decrease in LIC in almost 90% of patients which was comparable with those achieved by standard DFO infusions 5 days a week (Table 3). In this study, mean transfusional iron intake was measured as 0.25 mg/kg/d in patients randomized to DFP and combined therapy arms and 0.20 mg/kg/d in those randomized to DFO arm.²⁹ It has also been shown that combined therapy of daily DFP and twice weekly DFO resulted with higher ratio of iron excretion to iron intake (negative iron balance) compared to DFP monotherapy or standard DFO therapy given subcutaneously 5 days a week.^{30,31}

The prescribed doses of DFX have been selected based on transfusional iron intake in addition to baseline body iron burden in following clinical trials of DFX. The 1 year EPIC study was the largest trial conducted for an iron chelator to evaluate whether fixed starting doses of DFX, based on transfusional iron intake, with dose titration guided by serum ferritin, provides acceptable chelation practice in patients with transfusional iron overload. More than a 1000 TM patients were recruited to the study. At the end of the study, patients receiving higher DFX doses of above 30 mg/kg at lower transfusional iron intake reflected in significant reduction in serum ferritin, whereas lower DFX doses at higher transfusional iron intake was consistent with maintenance of serum ferritin levels (Table 4).³²

The 1 year ESCALATOR study in heavily iron loaded patients with TM also confirmed the importance of timely dose adjustments based on serum ferritin trends monitored at monthly intervals for achieving therapeutic target of maintenance or reduction in iron burden by

means of LIC in pediatric and adult patients with TM.³³ Long-term efficacy and safety of DFX has also been evaluated in TM patients aged ≥ 2 years. Patients who completed a 1-year, Phase III, randomized trial comparing DFX vs. DFO³⁴ entered a 4-year extension study, either continuing on DFX (DFX cohort) or switching from DFO to DFX (crossover cohort). Initial DFX doses were assigned to the patients in both cohorts based on LIC values. During the extension study, dose adjustments of 5 to 10 mg/kg/day were allowed every 3 months based on trends in serum ferritin and safety parameters. At the EOS, 51.0% and 42% of patients in DFX and crossover cohorts achieved serum ferritin levels below 1000 $\mu\text{g/L}$ after at least 4 years of DFX, of whom only 13 and 17% had serum ferritin below 1000 at baseline. DFX treatment had a dose-dependent effect on LIC with the largest reduction in patients assigned to starting dose of 30 mg/kg/day at the end of study.³⁵

Impact of iron chelators on survival of patients with thalassemia major

Implementation of DFO chelation at the end of 1970s resulted with a significant improvement in survival of patients with TM who has born after 1970 in a large Italian cohort. However, almost 10% of patients, who has born after 1970, inevitably developed heart disease which was remained as the most common cause of the death, occurring in more than half of the patients. Compliance problem with the

Table 2. Percentage of patients achieving negative iron balance based on transfusional iron loading rate and chelator dose (Data from Cohen A, *et al.* Blood 2008; 111:583-7).

DFO (mg/kg) X5/ week	Transfused iron (mg/kg/d)		
	<0.3	0.3-0.5	>0.5
35-49	76%	75%	52%
>50	100%	86%	89%
DFX (mg/kg/d)	Transfused iron (mg/kg/d)		
	<0.3	0.3-0.5	>0.5
10	29%	14%	0%
20	76%	55%	47%
30	96%	83%	82%

Table 3. Changes in LIC with different chelation regimens in TM (Data from Aydinok *et al.* Blood 2006; 108(11): abstract 557).

LIC (mg Fe/g d.w.)	DFP (n=29) n (%)	DFP+DFO (n=24) n (%)	DFO (n=19) n (%)
decrease	18 (62)	21 (87.5)	17 (90)
maintained	4* (14)	2* (8.5)	1* (5)
increase	7 (24)	1 (4.0)	1 (5)

*LIC maintained below 7 mg Fe/g d.w. at 1 of 4 in DFP and all in DFP+DFO and DFO arms

Table 4. Change in serum ferritin from baseline by mean accrual dose of DFX (Data from Cappellini MD, *et al.* Haematologica 2010; 95(4): 557-66).

Deferasirox doses	<20 mg/kg (n=231)	≥ 20 –<30 mg/kg (n=732)	≥ 30 mg/kg (n=141)	All patients (n=1104)
Median SF at baseline	(462–20788)	(480–22320)	(1326–16944)	(462–22320)
at EOS	2356	3160	5093	3188
Change in SF	2311	3067	4167	3025
	– 45	– 93	– 926	– 163
P-value	0.67	0.56	<0.0001	0.0001
Mean iron intake (mg/kg/day)	0.38	0.46	0.35	0.43

cumbersome DFO infusions is considered as a major factor in mortality and morbidity.³⁶

In fact, as late as 1999, 50% of UK patients died before the age of 35 years and iron induced heart disease was responsible for 71% of the deaths in TM. Since 1999, there has been 71% reduction in annualized death rate from iron overload. This marked improvement in survival can be attributed to introduction of cardiac T2* to identify myocardial siderosis and appropriate intensification of iron chelation treatment.³⁷

Impact of chelator regimens on cardiac iron content

Iron induced cardiac failure and arrhythmia is responsible for most of the deaths in TM.^{36,37} Assessment of cardiac iron by using magnetic resonance technique (T2*) demonstrated that there was a progressive and significant decline in left ventricular ejection fraction below a myocardial T2* of 20 ms.³⁸ Further, it was demonstrated the impact of cardiac T2* for prediction of cardiac complications. Cardiac T2* was found superior to serum ferritin and liver iron in identifying patients at high risk of developing heart failure and arrhythmia from myocardial siderosis in TM.³⁹ Assessment of cardiac iron by the magnetic resonance procedure and management of TM patients by considering cardiac risks is strongly recommended in clinical practice.

From that point of view, a prospective randomized study comparing standard doses of DFP and DFO, a significant reduction in cardiac iron content achieved by both chelation regimens while iron reduction in the liver was only significant in DFO group (Table 5).⁴⁰

In another randomized prospective 1 year study, the higher doses of DFP were compared with standard dose of DFO in TM patients with moderate cardiac siderosis. Although, LIC fell less impressively with DFP compared to DFO, the improvement in myocardial T2* and LVEF at 12 months was significantly greater in the patients taking DFP rather

than DFO (Table 6).⁴¹ It is assumed that transfusional iron initially fills the liver and cardiac iron may not decrease until liver iron is lowered. In contrast, based on this observation, it could be suggested that, DFP may lower cardiac iron with less reduction in liver iron.

Since DFP is less effective in removing liver iron than DFO, for simultaneously focusing on liver and heart iron combined therapy of daily DFP 75 mg/kg/d plus DFO 35 mg/kg/d 5 days a week has been compared in a randomised placebo control study with standard DFO monotherapy (43 mg/kg/d x 5d/w; equivalent 30mg/kg/d for 7d/w) in TM patients with moderate cardiac siderosis. Myocardial T2* and liver T2* showed a significantly larger improvement in the combined group compared with the DFO group (p<0.02 and p<0.001 respectively) (Table 7).⁴²

Clinical studies have shown that myocardial iron removal is a slow process compared to faster removal of iron from the liver. The EPIC cardiac sub-study was designed to assess the efficacy of DFX over 3 years treatment in reducing myocardial iron in patients with TM with mild, moderate and severe myocardial siderosis as well as severe liver iron (28.4 ± 9.7 mg/g dw). Patients were initiated on 30 mg/kg/d DFX and dose adjustments were allowed based on serum ferritin trends and 6 monthly cardiac T2* assessments. At end of study, 42% of patients have been receiving DFX doses of at or above 40 mg/kg/day indicating that DFX doses of above 30 mg/kg are required for cardiac iron removal. There were no deaths during the 3 year study. A continuous and significant improvement in myocardial T2* from baseline was observed in TM patients with mild to moderate and severe cardiac iron loading (p<0.001), along with a significant decrease in liver iron with a manageable safety profile over 3 years at these higher doses of DFX. It was notable that 68.1% of patients with mild to moderate myocardial siderosis at baseline (cardiac T2* 10-<20) had normalized myocardial iron content (≥20 ms) whereas myocardial iron in 50% of patients with severe cardiac siderosis (cardiac T2*>5-<10 ms) improved to mild to moderate range after 3 years.⁴³

Table 5. Changes in liver iron and cardiac iron content with standard doses of DFP vs DFO (Data from Maggio A, *et al.* Blood Cells, Molecules, and Diseases 2002; 196–208).

Chelators Doses	DFP group (n=60) 75 mg/kg/day			DFO group (n=66) 50 mg/kg/d x 5 days / week		
	Baseline	EOS	Difference	Baseline	EOS	Difference
Liver MRI (SIR)	0.83±0.21	0.90±0.26	-0.07±0.38	0.87±0.34	1.02±0.33	-0.15±0.27 [#]
Heart MRI (SIR)	1.08±0.19	1.19±0.31	-0.11±0.33*	0.96±0.26	1.09±0.28	-0.13±0.31 [#]

*p>0.05, [#]p<0.01 compared to baseline, SIR; signal intensity ratio

Table 6. Descriptives of study group at baseline and the change in LIC, myocardial T2* and LVEF at the end of study (Data from Pennell, D. J. *et al.* Blood 2006;107: 3738-3744).

Chelators Dose	DFP (n=29) 92 mg/kg/d	DFO (n=32) 43 mg/kg/d X5,7/w (35mg/kg/d)
Compliance (%)	94 ± 5.3	93 ± 9.7
Transfusion (ml/kg/y)	152 ± 43.4	144 ± 44.4
Baseline heart T2* (ms)	13	13.3
Baseline LIC (mg/g dw)	6.16 ± 6.0	6.32 ± 5.8
Change in LIC at EOS (%)	-10.1	-24.4
Change in T2* at EOS (%)	+27	+13
Absolute change in LVEF	3.1% ± 3.6%	0.32% ± 3.4%

Table 7. Description of the study group at baseline and the change in liver and myocardial T2* at the end of study (Data from Tanner MA, *et al.* Circulation. 2007; 115:1876-84).

Chelators Dose (DFP) Dose (DFO)	Combined (n=32) 75 mg/kg/d 35 mg/kg/dX5,7/w	DFO (n=33) - 43 mg/kg/d X5 /w (30mg/kg/d)
Transfusion (ml/kg/y)	133.4 ± 34.9	130.2 ± 38.6
Baseline heart T2* (ms) [>20]	11.7	12.4
Baseline liver T2* (ms) [>19]	4.9	4.2
Change in liverT2* at EOS (ms)	+5.8	+0.8
Change in heart T2* at EOS (ms)	+6	+3.3

How quickly can cardiac iron levels be safely removed and normalized?

The best improvement in cardiac T2* was achieved by continuous iv DFO chelation at a mean dose of 43 mg/kg/day which was given over 24 h, 7 day a week. In this study, all patients had T2* below 10 ms associated with impaired left ventricular ejection fraction at baseline. The cardiac T2* increasing on average by 4.9% per month was observed during DFO infusion of 12 months. Further, a progressive and significant improvement in LVEF over the course of intravenous treatment was also observed.⁴⁴ In another prospective study, combined therapy of daily DFP (73.9 ± 4.0 mg/kg/d) and s.c. DFO (38.0 ± 10.2 mg/kg/d 5.3 days a week) has been prescribed to TM patients with similar characteristics to that reported in previous study. In this study, the improvement in cardiac T2* was almost similar with 24h DFO infusion.⁴⁵ Combined therapy of DFP and DFO was also resulted with similar improvement in cardiac T2* in patients with mild to moderate myocardial iron loading.⁴² Overall improvement rates of cardiac T2* were comparable in other monotherapies with DFO, DFP and DFX.^{41, 42, 43}

Potential chelation regimens for removing cardiac iron faster than monotherapies

It has been shown that treating heavily iron-loaded patients with intensive chelation of 24h DFO infusion or combined therapy of DFP & DFO may rapidly decrease cardiac iron burden, thereby reducing their risk status quicker.^{44, 45} It would be suggested that the shuttle mechanism between DFP and DFO,⁴⁶ is also likely to occur for the combination of DFX and DFO. Preliminary data showed that this combination is well tolerated in patients with TM.⁴⁷ A prospective study combining DFX & DFO in patients with severe cardiac siderosis has recently been started to see whether this combination would achieve faster removal of cardiac iron to relatively safe levels of >10ms. Few short term observations have been reported for the tolerability and efficacy of combination of DFX & DFP.^{48, 49} However, more controlled studies are needed to investigate alternative chelation regimens.

Impact of chelator regimens on endocrine tissues

Despite therapeutic progress on survival and significant reduction in death from iron overload in the new millennium,⁴⁸ endocrine complications remained as the most common cause of significant morbidity and impaired quality of life.⁴⁹ Growth and pubertal failure are the earliest consequences of iron toxicity and are usually due to pituitary dysfunction. In pediatric patients prone to growth retardation due to severe iron overload, long-term DFX treatment for up to 5 years was found effective in maintaining normal growth progression and sexual development in parallel to continued and significant reduction in median serum ferritin levels over 5 years in all age groups.⁵⁰ Normal growth and sexual maturation may be achieved by properly monitoring of iron loading and the timely starting and maintaining of iron chelation to prevent iron toxicity in TM. In a recent study, it has been suggested that intensified chelation with daily DFP (75-100 mg/kg/d) plus subcutaneous DFO (20-60 mg/kg/d) may prevent and even reverse endocrine complications including impaired glucose metabolism, hypothyroidism and hypogonadism with a positive impact on patients' quality of life. In this study, intensive combination therapy was maintained until liver

and cardiac iron assessed by MRI has been normalized. Once this purpose was achieved, dose and frequency of DFO was adjusted to avoid potential chelator toxicity.⁵¹

Adverse events with current chelators

The safety profile of the chelators is acceptable and manageable however appropriate monitoring of adverse reactions should be maintained since almost all of the side effects are reversible if determined at early stages.

Most of the toxic side effects of DFO on impaired growth and skeletal changes are observed in children when treatment started early (<2 years), at low body iron burden (serum ferritin <1000 µg/L) and at relatively higher doses of chelator (>40 mg/kg).^{52, 53} DFO related retinopathy (loss of visual acuity, field defects, and defects in color vision) and ototoxicity (symmetric and high-frequency sensorineural hearing loss) are also observed at higher doses of chelator at lower serum ferritin levels.⁵⁴ *Yersinia enterocolitica* infections should be suspected in patients on DFO chelation with enterocolitis and fever that prompt antibiotic therapy might prevent life threatening sepsis and shock.⁵⁵

Agranulocytosis is the most serious side effect of DFP therapy and close monitoring (7-10 daily control of WBC & ANC) is required. The incidence of agranulocytosis (neutrophils <0.5x 10⁹/l) occurred in 0.5% of patients (an incidence 0.6 per 100 patients' year) during in a one year prospective study⁵⁶ and no new cases of agranulocytosis developed during extension study for a further 3 years.⁵⁷ Although most cases of agranulocytosis have occurred in the first few months of therapy, agranulocytosis in the second year of therapy has also been reported. Agranulocytosis is always reversible with discontinuation of DFP and reintroduction of DFP after an initial episode of agranulocytosis is not recommended.⁵⁸ Gastrointestinal disturbances including nausea, vomiting and abdominal pain are met mainly at the first few weeks and months of the therapy and generally resolved by reducing dose, taking drug with meals and temporary supportive (anti-emetic) therapy. After resolving the symptoms, the dose is slowly increased to the target levels. Arthropathy affecting more frequently knees and ankles resolves after temporary discontinuation of the drug or reduction of the dose, at a median time of 12 days. Transient fluctuating increase in liver enzyme levels is generally normalized without any intervention.⁵⁹ Some patients complain from increased appetite and weight gain with DFP chelation.

DFX has been investigated regarding safety during clinical studies which have been conducted with more than 3000 patients and some of these studies have been extended up to 5 years. Generally transient mild to moderate gastrointestinal disturbances (nausea, vomiting, abdominal pain, diarrhea and constipation) were observed in 15% of patients. Skin rashes affecting almost 10% of patients are observed in first few weeks of DFX and generally transient. Transient fluctuations in liver enzymes have also occurred. During the first months of DFX treatment, mild, dose dependent, non-progressive increase in serum creatinine has been observed in one-third of patients. These creatinine increases remained within normal ranges, or resolved spontaneously with dose reduction.³⁴ Cases of acute kidney injury have also been reported in the post-marketing surveillance of DFX in patients with advanced age, myelodysplastic syndromes, or other types of anaemia associated with severe co-morbidity like renal and hepatic impairment^{60, 61} but have not observed in patients with TM. High frequency hearing loss and lenticular opacities are also observed less frequently. It is recommended monthly monitorization of serum creatinine, urine protein and liver enzymes and annual auditory and ophthalmic examinations.

Summary and Conclusions

Current chelation practices are mainly based on the transfusional iron loading rate, the existing body iron burden and the tolerability of chelator and dosing regimen aimed to maintain or reduce body iron to the safe levels by monitoring iron measures. However, uncertainties still exist about how low sustained levels of body iron should be maintained since the beginning to guarantee a lifelong complications free survival? How far body iron levels can be reduced without increasing chelator toxicity particularly in patients whose liver iron and ferritin have been depleted while cardiac siderosis remains?

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