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Australian Guidelines for the assessment of iron overload and iron chelation in transfusion-dependent thalassaemia major, sickle cell disease and other congenital anaemias.

Short Title: Iron chelation in the haemoglobinopathies

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ABSTRACT

Iron overload is the most important cause of mortality in patients with thalassaemia major. Iron chelation is therefore a critical issue in the management of these patients and others with transfusion-dependent haemoglobinopathies and congenital anaemias. In recent years, significant developments have been made in the assessment of iron overload, including the use of MRI for measuring liver and cardiac iron. Advances in the modalities available for iron chelation, with the advent of oral iron chelators including deferiprone and deferasirox in addition to parenteral desferrioxamine, have expanded treatment options. A group of Australian haematologists have convened to formulate guidelines for managing iron overload on the basis of available evidence, and to describe best consensus practice as undertaken in major Australian Haemoglobinopathy units. The results of their discussions are

described in this article, with the aim of providing guidance in the management of iron overload in these patients.

Key Words: Thalassaemia, Haemoglobinopathy, Iron overload, Iron chelation

INTRODUCTION

The transfusion-dependent haemoglobinopathies and congenital anaemias are a significant problem in a country such as Australia with a population of diverse ethnic origins, where increasing numbers of patients with haemoglobinopathies such as thalassaemia and sickle cell disease are treated. While patients with beta-thalassaemia major are transfusion-dependent, a proportion of sickle cell disease patients also undergo regular transfusion to prevent severe complications such as recurrent, severe sickling crises. Iron overload is one of the most critical issues in these patients, and complications of iron overload remain the most important cause of mortality [1, 2] Iron chelation is therefore crucial in the management of these patients to prevent complications such as cardiomyopathy, the predominant cause of premature death, liver fibrosis and cirrhosis, and endocrinopathies including growth failure, abnormal sexual development and infertility, hypothyroidism and diabetes. An important factor in suboptimal iron chelation and poor prognosis is the lack of adherence.[2, 3]

For several decades, the only available iron chelator was desferrioxamine, for which there is the longest cumulative experience and evidence of efficacy.[4] Two oral chelators have come into the clinic in recent years - deferiprone and deferasirox. At the same time, advances have been made in the assessment of tissue iron load, especially with the development of MRI assessment of liver and cardiac iron, enabling the adjustment of therapy according to organ iron load.

It has been increasingly recognised that therapy should be tailored to specific patient needs, within the context of standard recommendations and consensus best practice. This has highlighted the benefit of compiling guidelines on iron chelation in this group of patients. As a result, a group of Australian haematologists and paediatricians involved in the care of haemoglobinopathy patients has convened to discuss clinical protocols, to try to define “best practice” in Australia; and where there are uncertainties due to the lack of evidence, to define consensus practice according to extensive collective experience.

A range of guidelines have been published by national, international and institutional groups.[5-10] The Australian panel reviewed these recommendations as a background to describing our practice and formulating the following consensus opinion.

A. Measurements of iron load and pathophysiological significance

Parameters used to monitor iron load include serum ferritin, liver biopsy, MRI assessment of liver and cardiac iron, in conjunction with functional testing such as echocardiography and measures of endocrine function. Dual energy CT for measurement of liver iron has also been performed in some centres.[11] Each of these parameters has a different role. While serum ferritin is valuable due to its ease of measurement and wide availability, it has significant limitations as the levels can reflect confounding factors such as inflammation. In contrast MRI technology has enabled accurate and specific measurement of organ iron load, providing a more efficacious means of tailoring therapy to individual risk, but availability is currently restricted and should be improved.

I. Serum Ferritin

Serum ferritin is the most commonly used parameter for monitoring iron overload. It correlates with cardiac impairment and survival,[4] but can be elevated by many confounding factors, including acute phase reactions such as infections, inflammation or malignancy, or by hepatic damage. It has a poor correlation with hepatic iron.[4] Nevertheless, the close relationship between serum ferritin and survival and its relative ease of measurement makes it the most practical parameter for sequential monitoring.

In most Australian haemoglobinopathy units, serum ferritin is measured monthly, providing regular feedback to both the physician and patient. However

due to the possible confounding factors above, the values should not be interpreted in isolation, as the trend over a longer period such as 3 months is more informative and should form the basis of the assessment. Serum ferritin has therefore been a very important parameter for monitoring iron chelation, using the available iron chelators of desferrioxamine, deferiprone and deferasirox (see Section B). On the basis that very few patients with a serum ferritin level consistently within the range of 1000-1500 μg/L develop cardiac iron loading, this has been considered to be a reasonable target, although the optimal target may still be reduced with future studies. The incidence of side effects of desferrioxamine and deferasirox may be increased at serum ferritin levels less than 500 μg/L, and this is the basis for a recommendation not to reduce the serum ferritin below this level using these chelating agents. There is no similar recommendation for patients taking deferiprone. Recent studies have indicated that low ferritin levels and hepatic iron may be associated with a significant reduction in morbidities without an increase in adverse events.[12, 13]

II. Liver biopsy

Liver biopsy was previously considered to be the gold standard of liver iron assessment, but is an invasive procedure associated with risk of complications and is subject to sampling error. Liver biopsy is still performed to evaluate liver fibrosis, cirrhosis or hepatocellular carcinoma which are possible complications in all patients with liver iron overload, particularly in those with coexisting hepatitis C.

III. MRI assessment of liver iron

The quantitation of liver iron by MRI is one of the most significant recent advances in iron monitoring.[14] The most widely adopted method is based on the measurement of tissue proton transverse relaxation rates (R2), showing excellent correlation with liver iron concentration (LIC) measured by biopsy.[14] Algorithms predicting risk of complications from liver biopsy LICs have been applied to LICs obtained by MRI (see Table I), and hepatic iron remains the best measure of total body iron loading.[15]

Although this procedure is not yet widely available in Australia, the expert panel considers it to be a very useful method of monitoring liver iron load and in directing iron chelation therapy. An appropriate monitoring strategy would comprise annual R2 MRI for the majority, while this can be extended to every 2 years for patients with normal LIC or at the lower end of the ideal range (e.g. 3 – 5 mg/g dry weight) when there has been no change to chelator regimen, and perhaps increased to every 6 months in at-risk patients, such as those with LIC above 15 mg/g dry weight. LIC results should also be correlated with standard liver function tests.

IV. MRI assessment of cardiac iron

The most important cause of premature death in thalassaemia major is iron-overload cardiomyopathy.[1, 2] MRI has been successfully applied to quantify iron

content in the heart. The most widely adopted measure is T2*, a relaxation parameter intrinsic to protons placed under the magnetic field.[16] Due to accessibility and cost, availability of this procedure is still restricted in Australia. The correlation between cardiac T2*, cardiac iron loading and its utility in predicting cardiac events has been validated.[16, 17] The panel considers cardiac MRI to be a very important means of monitoring cardiac iron load. Ideally cardiac MRI should be monitored at least annually. In at-risk patients, such as those with T2* indicative of severe iron load (<10 ms) or in those patients who already have impaired cardiac function, cardiac MRI should be performed every 6 months. For stable patients with normal cardiac iron (T2* >20 ms), monitoring every 2 years is likely to be adequate. The measurements of T2* and their implications on cardiac risk are summarised in Table II. Cardiac MRI can also provide measurements of ejection fraction and ventricular mass, but an annual assessment of cardiac function (ejection fraction) by either echocardiography or gated heart pool scan remains very important. An abnormal ejection fraction is indicative of very severe iron load associated with a high risk of mortality, thus the aim should be to detect increased iron load by MRI *before* the development of overt cardiomyopathy.

V. Additional comments on MRI assessment of total body iron

While the measurement of liver and cardiac iron by MRI are important developments in facilitating the tailoring of iron chelation therapy, it is important to note that discrepancies between liver and cardiac iron load can be observed.

This is likely to be due to differences in kinetics of iron loading and clearance between the liver and heart, with a time-lag in cardiac iron loading and clearance.[18] Hence while LIC has been used to indicate the risk of complications of increased total body iron load including the heart (Table I), it is emphasised that a low level of liver iron can still be associated with abnormal cardiac iron accumulation. Thus the panel considers it an important goal for *both* liver and cardiac MRI assessments to be made available to all patients.

MRI assessment of iron load in endocrine glands, including the pancreas and pituitary gland, is currently under development.[19, 20] These are presently research methods and have not yet been incorporated into routine clinical practice.

VI. Labile plasma iron (LPI)/ Non-transferrin bound iron (NTBI)

LPI and NTBI are toxic iron species in the circulation, not bound to transferrin, which mediate cellular iron damage through an increase in the labile cellular iron pool.[21] The three available iron chelators (desferrioxamine, deferiprone and deferasirox) have been evaluated with respect to their effect on LPI. Although desferrioxamine suppresses LPI during the infusion, once it is stopped a significant rebound in LPI may occur which may lead to increased toxicities.[21] Deferiprone administered at the recommended schedule of three times a day suppresses LPI, but the levels show significant fluctuation and are more persistently reduced by the addition of desferrioxamine.[21] Deferasirox has a

longer half-life of approximately 16 hours, and 24-hour suppression of LPI has been shown to be achieved by once daily treatment.[21] At present, LPI and NTBI are mainly applied in research, but may be useful in determining the risk of organ toxicity and the effectiveness of iron chelation as the assays become more widely available.

B. Modes of chelation

I. Available chelators

The properties of the three iron chelators approved for clinical use – desferrioxamine, deferiprone and deferasirox - are summarised in Table III. An accurate estimation of transfusion iron intake is important in the choice and dosing of iron chelation.[22] Most Australian units transfuse at four-weekly intervals, aiming for a pre-transfusion haemoglobin level of 90-100 g/L. All three available iron chelators exhibit dose-dependent iron chelation. As desferrioxamine has poor oral bioavailaibility and a short half-life (20-30 min), it is infused subcutaneously or intravenously, whereas deferiprone and deferasirox are oral agents. Deferiprone has a half-life of 3-4 hours and is therefore administered three times a day. In contrast, deferasirox has a half-life of 8-16 hours and can be administered daily. Toxicities are also different as noted in Table III.

II. When and how to start chelation

Previous guidelines have generally recommended starting chelation after 10-20 units packed red cells transfused and when ferritin exceeds 1000 μg/L or lies between the range of 1000-2500 μg/L.[5-10] Australian practice is largely consistent with these recommendations. Paediatric haematologists often commence chelation after 12-18 months of transfusions, when the serum ferritin usually (but not necessarily) lies between 1500 and 2000 μg/L. Chelation by

desferrioxamine is usually not started until the patient is aged 4-5 years, due to concern regarding the adverse effect of desferrioxamine on bone development and growth. The treatment dose is 30-60 mg/kg/day infused subcutaneously over 8-10 hours by infusion pump for 5-7 days per week.

Thus while it is rare to start chelation between 2 and 4 years, deferasirox should be the preferred option in this age group, as clinical trials of this agent have included a significant number (up to ~600) of patients between 2 and 6 years,[13, 23] with no increase in the incidence of side-effects. The starting dose should be 20-30 mg/kg/day. In Australia, deferasirox can be used from the age of 6 years as a first line agent, and if other chelation (i.e. desferrioxamine) is ineffective or contraindicated at 2 – 6 years; as noted above desferrioxamine is contraindicated before the age of 4 years.

There are limited data on the use of deferiprone in children. In Australia deferiprone is approved as second line therapy if desferioxamine is ineffective. One study of 44 patients under the age of 6 years noted a significant increase in reversible thrombocytopenia (45.5%) occurring 3 months to 1 year after commencing treatment, but no other increased side-effects specific to this age group.[24] A liquid formulation of deferiprone is available and there is early experience reporting efficacy in reducing serum ferritin in a paediatric population, but a 2% incidence of agranulocytosis and 6% risk of neutropenia were also observed.[25]

Summary of main points – When and how to start chelation

a. Chelation is started after 10-20 transfusions, and when serum ferritin is in the range of 1000-2500 μg/L; this usually occurs after 12-18 months of transfusion and after 2 years of age.

b. In general chelation can be delayed until 4 years without any significant known detrimental effect.

c. Children aged 4-6 years are started on desferrioxamine, and if this is not effective, can be changed to deferasirox.

d. Children over 6 years can be started on desferrioxamine or deferasirox, with an increasing trend towards using deferasirox in first line; currently deferiprone is licensed in Australia in second line.

III. Choice of agent in continuing iron chelation

For many years, desferrioxamine has been the only available iron chelator. While clearly efficacious,[4] parenteral administration can be a significant impediment to adherence.[3] Several studies have found significant numbers of patients on desferioxamine with abnormal cardiac iron, but this is most likely due to poor adherence,[26] and under-dosing in some cases. Not surprisingly many patients changed from desferrioxamine to one of the two oral agents when they became available. However some patients who have been well-

chelated on desferrioxamine have chosen to remain on this drug, which remains an appropriate option if compliance is maintained and there is no excessive iron load.

The choice between deferiprone and deferasirox has not only been influenced by clinical data, but also by the “history” of individual units. The development of deferiprone pre-dated deferasirox. Some units which used deferiprone from early in its development continued to do so, converting to deferasirox or desferrioxamine only when patients demonstrated intolerance or failure. Other units did not use deferiprone due to initial concerns of liver fibrosis (which have been refuted)[27] and other toxicities such as neutropenia and arthritis, and subsequently adopted deferasirox as the major oral chelator. The main clinical data of the 2 oral chelators which have guided clinical practice are summarised below:

a. Deferiprone:

The efficacy of deferiprone as a single agent has been evaluated using serum ferritin alone for assessment; there are trials demonstrating both the presence[28] and absence[29, 30] of efficacy. With respect to LIC, a recent Cochrane review found no definitive evidence showing efficacy due to the data being “handicapped” by pronounced differences in baseline LIC, variable presence of Hepatitis C, and wide variation in treatment duration among studies.[31] For cardiac iron, significant benefit of deferiprone in reversing cardiac iron loading

has been demonstrated[30] and further results from randomised studies are awaited.

Combination therapy with deferiprone and deferoxamine has been shown to be effective, particularly in improving cardiac iron load (as assessed by T2* assessment) .[12, 32] The two agents should be administered simultaneously on the same day - an accepted protocol is to administer deferiprone at 75-100 mg/kg/day in 3 divided doses during the day, together with desferrioxamine overnight for at least 3 nights per week.

b. Deferasirox:

The efficacy of deferasirox was evaluated in a large phase III study which randomised patients to receive deferasirox or desferrioxamine, concluding that deferasirox at a dose of 20 mg/kg/day maintained and 30 mg/kg/day reduced body iron, and that dosing was highly dependent on the mean iron intake.[23] A subsequent phase IV prospective one-year study demonstrated a significant reduction in serum ferritin from baseline.[33] The efficacy of deferasirox in reducing liver iron has also been shown, with at least equal efficacy compared with desferrioxamine.[23, 33, 34] With respect to cardiac iron, current available data indicate efficacy in reducing iron load as measured by cardiac T2* (see Section B V below).[34-36] The daily schedule of administering deferasirox is considered an advantage in improving adherence. Unlike desferrioxamine, deferasirox was also found not to affect growth in children.[37]

Hence, the issues influencing the choice of chelation agent as continuation therapy are summarised as follows:

1. In the majority of patients, due to the effects on adherence, an oral iron chelator is preferred. This may be deferasirox or deferiprone, depending on physician experience and patient preference.

2. In patients susceptible to side effects of one oral chelator, the other is trialled, if also not tolerated then the only alternative would be desferrioxamine.

3. Reasons for administering deferiprone include the synergy with desferrioxamine as combination therapy in chelating excess cardiac iron.

4. Reasons for ceasing deferiprone include agranulocytosis/ neutropenia, significant abnormalities in liver function tests and severe arthralgia or gastrointestinal side-effects, and inadequate control of iron load (see Section B IV below).

5. Reasons for administering deferasirox include the daily regimen which may improve adherence, and the lower incidence of neutropenia and agranulocytosis.

6. Reasons for ceasing deferasirox include significant rises in serum creatinine and liver function abnormalities, severe gastrointestinal

disturbances and allergic reactions, and inadequate control of iron load (see Section B IV below).

IV. Adjusting iron chelation according to efficacy and toxicity

The main determinants for modification of chelator regimen or dosage are

(1) Changes in iron load as measured by the parameters detailed in section A

(2) Intolerance of first-line agent

(3) Patient preference

(4) Risk of cardiac compromise which is associated with a high risk of mortality

Where iron overload is not adequately controlled, adherence should be assessed, and if suboptimal, the cause should be identified (discussed Section C III below). Strategies to deal with reduced tolerability or effectiveness of each agent are discussed. Modifications required due to an increased risk or the occurrence of cardiomyopathy are summarised.

1. Desferrioxamine

For patients on desferrioxamine, the target serum ferritin is considered to be 1000 μg/L, with a range of 1000-1500 μg/L. Patients with repeated serum ferritin levels of 2000-2500 μg/L have significantly increased cardiomyopathy

and mortality,[4] while ferritin levels below 500 ug/L are generally considered to be associated with an increased incidence of side-effects though this is not universally accepted. Doses used are 40-60 mg/kg/day 5-7 days per week. An apparent lack of efficacy is most commonly due to non-adherence (although under-dosing may also be present in some cases), when a change to an oral iron chelator should be considered. Many physicians on the panel would change to deferasirox first due to the daily scheduling and the absence of requirement for weekly full blood count monitoring, as specified for deferiprone. A change to deferiprone in combination with desferrioxamine may be preferred in units with greater experience in using deferiprone, particularly in patients with significantly increased cardiac iron loading. Reduction in desferrioxamine dose or cessation is considered in severe skin reactions or allergy; it is rare for ophthalmologic and auditory side effects to be the cause of dose reduction.

2. Deferiprone

The registered dose of deferiprone is 75 mg/kg/day in 3 divided doses, but up to 100 mg/kg/day is commonly used, as multiple studies have shown no additional concerns with safety.[38, 39] Deferiprone is generally prescribed in combination with desferrioxamine, which may be ceased once chelation has been optimised. In the presence of increasing iron load, which can be due to non-adherence, substitution by deferasirox may be considered.

Agranulocytosis is an important side effect. When this occurs deferiprone should be ceased, while the occurrence of neutropenia also necessitates treatment interruption or cessation. It is recommended for full blood counts to be tested weekly, although the risk of agranulocytosis is much lower after twelve months of treatment. Other adverse events such as gastrointestinal effects, abnormal liver function tests and arthralgia, if moderate to severe, may lead to dose reduction or a change to deferasirox or desferrioxamine.

3. Deferasirox

The recommended starting dose of deferasirox is 20-30 mg/kg/day. The appropriate dose to achieve a negative iron balance is highly dependent on the mean iron intake. Where there is evidence of increasing iron load, the deferasirox dose should be increased by 5-10 mg/kg/day to a maximum of 40 mg/kg/day. A reversible and non-progressive increase in the serum creatinine is observed in approximately one-third of patients taking deferasirox but is not believed to be clinically significant. It is currently recommended for deferasirox to be stopped when serum ferritin falls below 500 μg/L as adverse events are considered to be more common below this level. However a comparison of patients whose serum ferritin levels were >1000 μg/L with <1000 μg/L showed no difference in the incidence of increased serum creatinine; whether lower levels can be achieved without increased toxicity requires further study.[13]

When chelation appears to be ineffective at the maximal deferasirox dose, most likely due to non-adherence, or when there are severe side-effects, a change to desferrioxamine or combination desferrioxamine/deferiprone should be considered

V. Treatment of patients with iron-overload cardiomyopathy with abnormal ejection fraction and cardiac T2* <10 ms

1. Established cardiomyopathy

In patients with impaired cardiac function, intravenous (IV) desferrioxamine is the drug of choice given its efficacy in reversing iron overload and improving cardiac function.[40] This is administered through a central venous access device over 24 hours with an infusion pump. The rationale is to achieve 24-hour chelation, minimising toxic labile plasma iron and maximising iron chelation in cardiac tissue. The intravenous device can be associated with thrombosis and infection. If cardiac function improves or becomes normal, IV desferrioxamine should not be stopped immediately or reduced as this can precipitate a relapse or deterioration.[40] A dose of 50 mg/kg/day infused seven days per week has been found to be effective and is recommended. Although the panel considers IV desferrioxamine the drug of choice, some members or patients who do not favour the insertion of an IV device would, as an initial step, intensify subcutaneous desferrioxamine (e.g. to a maximum dose of 60 mg/kg/day seven

days per week, which can be administered by subcutaneous infusion with a pump over 20-24 hours each day) or change to combination deferiprone and desferrioxamine which has been shown to be effective in decreasing cardiac iron and improving left ventricular dysfunction in patients with impaired cardiac function.[12, 32, 41, 42] Although deferasirox has been shown to improve cardiac iron (see below),[35] there are no definitive data on its effectiveness in patients with impaired ejection fraction, and studies are being performed.

2. For patients at risk of cardiomyopathy (T2*<10 ms, or LIC > 15 mg/g dw)

In patients with a normal ejection fraction but is at high risk of cardiomyopathy indicated by a T2* <10 ms, there are three possible options – IV desferrioxamine,[40] combination deferrioxamine/deferiprone[12, 32] or deferasirox.[35, 36] As noted earlier studies have clearly shown the efficacy of IV desferrioxamine[40] and combination desferrioxamine/deferiprone in reducing cardiac iron.[12, 32] There is also evidence that patients with severe cardiac iron load (T2* 5-10 ms) but normal ejection fraction respond well to deferasirox 30-40 mg/kg/day,[34-36] with the finding in one study that some patients with severe liver iron load may respond less well with respect to cardiac iron clearance.[36] Hence until more confirmation is obtained, it may be prudent to use deferasirox at the higher dose of 40 mg/kg/day only when T2* has reached 10 ms or above.

C. Special clinical scenarios and considerations

I. Iron chelation in Thalassaemia Intermedia

Thalassaemia intermedia (TI) is defined clinically by being not as severe as transfusion-dependent thalassaemia major, nor asymptomatic as in thalassaemia trait.[43] There is a large spectrum of severity, with more severe patients requiring intermittent transfusions. Iron overload may result from the cumulative transfusion burden, as well as increased iron absorption and release from the reticulo-endothelial system due to factors such as the suppression of hepcidin. Importantly, serum ferritin often underestimates the level of iron load in TI.[44]

There is a relative paucity of data on the optimal mode of chelation and monitoring in TI.[44] Most of the previous reported experience has been small studies in the use of desferrioxamine. For deferiprone, data are also limited; one small study indicated efficacy with significant reductions in ferritin, hepatic iron and NTBI.[45] A one-year study of >150 patients with TI treated with deferasirox is being conducted and results are awaited.[44] It has been recommended to commence chelation when LIC > 7mg/g dry weight and serum ferritin > 400-500 μg/L.[44] The Australian panel would consider this to be appropriate advice until more evidence is available.

II. Iron chelation in pregnancy and lactation

Iron chelation should be ceased as soon as pregnancy is confirmed. Neither deferasirox nor deferiprone should be used in pregnancy. In the first half of pregnancy, desferrioxamine should not be used due to concerns with foetal development, but in Australian practice it is generally recommenced between 16 to 20 weeks' pregnancy to prevent exacerbation of iron overload, especially since rapid iron loading during pregnancy has been reported.[46] Others have recommended iron chelation at the end of the second trimester only for patients with high levels of liver or cardiac iron load.[47] As cardiac dysfunction is the most important cause of maternal mortality, it is extremely important that patients are well chelated prior to conception.

There are few data on the use of desferrioxamine in lactation. The molecular weight is small enough for excretion into breast milk but the effects, if any, in a nursing infant are unknown. In many practices, unless the mother has severe iron overload at risk of cardiomyopathy, breast feeding is encouraged for 6 weeks after delivery without iron chelation. There are no data on deferasirox or deferiprone in lactation and neither is recommended.

III. Compliance/ Adherence

Clinical studies have shown the most important cause of suboptimal chelation to be non-adherence.[2] The causes are varied, and need to be approached individually, ranging from difficulty of administering subcutaneous injections,

other psychological issues to dosing frequency.[3] Strategies used to improve compliance range from a change to oral medication, aide-memoires and psychological counselling. Interventions for non-adherence are challenging and are examined by Cochrane reviews in which many specialised publications are included.[48]

Conclusions

Iron chelation is a crucial concern in the management of patients with transfusion-dependent congenital anaemias, especially thalassaemia major. Failure to achieve iron control results in morbidity and mortality. While a patient's adherence to iron chelation regimens remains one of the most important factors in prognosis, the advent of new oral agents for iron chelation has provided additional options. New methods of iron monitoring such as MRI have also provided the means to monitor iron load more accurately, although access to these investigations is still limited. This should be improved in the future so as to increase the efficacy and safety of iron chelation**.**

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Authors contributions:

PJH and DKB chaired the workshops and subsequent discussion at which the guidelines were formulated. PJH wrote and revised the manuscript; DKB, LT, RL and LC reviewed the manuscript and contributed to revisions.

Table I. Measurements of hepatic iron and clinical implications in transfusion-dependent patients with beta-thalassaemia (Adapted from Olivieri & Brittenham, 1997)

Hepatic iron (mg/g dry weight)	Severity	Implications*
<1.2	Normal	Nil
3 -7	Mild	"Optimal" level
7 -15	Moderate	Increased risk of complications
>15	Severe	Increased risk of cardiac disease and early death**

*As noted in Section A V, discrepancies can occur in individual patients between liver and cardiac iron load, most likely due to differential iron loading and clearance in the heart and liver. Thus while the thresholds in this table are useful in indicating the risk of hepatic complications and an overall risk, some patients with "optimal" levels of liver iron according to the table may still experience high cardiac iron loading. The latter is more accurately assessed by specific measurement of cardiac iron (see section A IV on cardiac MRI and Table II).

** The measurement of T2* by cardiac MRI provides a more accurate assessment of cardiac risk (see Section A IV and Table II). However the category of greater than 15 mg/g/dw liver iron would still constitute "severe" risk with respect to the sequelae of liver iron load and overall risk assessment, including the risk for cardiac iron loading.

Table II. Assessment of iron load and cardiac risk by cardiac MRI [16]

Cardiac T2* (ms)	Cardiac iron load and risk
> 20	Normal
10 – 20	Moderate to severe
< 10	Severe

Table III. Summary of available iron chelators, characteristics of administration, excretion and side-effects.

	Desferrioxamine	**Deferiprone**	**Deferasirox**
Usual dose	20 – 60 mg/kg/day	75 – 100 mg/kg/day	20 – 40 mg/kg/day
Route	s.c., i.v. s.c. over 8 – 12 hrs 5 – 7 nights per week	p.o. 3 times a day	p.o. once a day
Half-life	20-30 min	3 – 4 h	8 – 16 h
Excretion	Urinary, faecal	Urinary, some faecal	Faecal
Main side-effects	• Injection site – lumps, infections • Bone changes • Ototoxicity • Ophthalmic changes • Increased risk of yersinia & klebsiella infections	• Arthralgia/ arthritis • Abnormal liver function tests • Neutropenia, agranulocytosis	• Rash • Diarrhoea, nausea • Abnormal renal function (reversible, non-progressive) • Abnormal liver function tests

REFERENCES

1 Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini MD, Del Vecchio GC*, et al.* Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematologica*. 2004; **89**: 1187-93.

2 Modell B, Khan M, Darlison M. Survival in beta-thalassaemia major in the UK: data from the UK Thalassaemia Register. *Lancet*. 2000; **355**: 2051-52.

3 Evangeli M, Mughal K, Porter JB. Which psychosocial factors are related to chelation adherence in thalassemia? A systematic review. *Hemoglobin*. 2010; **34**: 305-21.

4 Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. *Blood*. 1997; **89**: 739-61.

5 National Institutes of Health National Heart Lung and Blood Institute. The Management of Sickle Cell Disease. 2002.

6 United Kingdom Thalassaemia Society. Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK. 2008.

7 Anemia Institute for Research & Education and the Thalassemia Foundation of Canada. Guidelines for the Clinical Care of Patients with Thalassemia in Canada. 2009.

8 Angelucci E, Barosi G, Camaschella C, Cappellini MD, Cazzola M, Galanello R*, et al.* Italian Society of Hematology practice guidelines for the management of iron overload in thalassemia major and related disorders. *Haematologica*. 2008; **93**: 741-52.

9 Cappellini M-D, Cohen A, Eleftheriou A, Piga A, Porter J, Taher A. The Thalassemia International Federation Guidelines for the Clinical Management of Thalassemia 2nd Revised Edition. 2008.

10 Children's Hospital and Research Center Oakland. Standards of Care Guidelines for Thalassemia. 2009.

11 Leighton DM, de Campo JF, Matthews R, Sephton RG. Dual energy CT estimation of liver iron content in thalassaemic children. *Australas Radiol*. 1988; **32**: 214-9.

12 Farmaki K, Tzoumari I, Pappa C, Chouliaras G, Berdoukas V. Normalisation of total body iron load with very intensive combined chelation reverses cardiac and endocrine complications of thalassaemia major. *Br J Haematol*. 2010; **148**: 466-75.

13 Porter J. Optimizing iron chelation strategies in beta-thalassaemia major. *Blood Rev*. 2009; **23 Suppl 1**: S3-7.

14 St Pierre TG, Clark PR, Chua-anusorn W, Fleming AJ, Jeffrey GP, Olynyk JK*, et al.* Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. *Blood*. 2005; **105**: 855-61.

15 Angelucci E, Brittenham GM, McLaren CE, Ripalti M, Baronciani D, Giardini C*, et al.* Hepatic iron concentration and total body iron stores in thalassemia major. *N Engl J Med*. 2000; **343**: 327-31.

16 Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH*, et al.* Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. *Eur Heart J*. 2001; **22**: 2171-9.

17 Kirk P, Roughton M, Porter JB, Walker JM, Tanner MA, Patel J*, et al.* Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. *Circulation*. 2009; **120**: 1961-68.

18 Noetzli LJ, Carson SM, Nord AS, Coates TD, Wood JC. Longitudinal analysis of heart and liver iron in thalassemia major. *Blood*. 2008; **112**: 2973-8.

19 Lam WW, Au WY, Chu WC, Tam S, Ha SY, Pennell DJ. One-stop measurement of iron deposition in the anterior pituitary, liver, and heart in thalassemia patients. *J Magn Reson Imaging*. 2008; **28**: 29-33.

20 Noetzli LJ, Papudesi J, Coates TD, Wood JC. Pancreatic iron loading predicts cardiac iron loading in thalassemia major. *Blood*. 2009; **114**: 4021-6.

21 Zanninelli G, Breuer W, Cabantchik ZI. Daily labile plasma iron as an indicator of chelator activity in Thalassaemia major patients. *Br J Haematol*. 2009; **147**: 744-51.

22 Cohen AR, Glimm E, Porter JB. Effect of transfusional iron intake on response to chelation therapy in beta-thalassemia major. *Blood*. 2008; **111**: 583-87.

23 Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, Agaoglu L*, et al.* A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. *Blood*. 2006; **107**: 3455-62.

24 Naithani R, Chandra J, Sharma S. Safety of oral iron chelator deferiprone in young thalassaemics. *Eur J Haematol*. 2005; **74**: 217-20.

25 El Alfy M, Sari TT, Lee CL, Tricta F, El-Beshlawy A. The safety, tolerability, and efficacy of a liquid formulation of deferiprone in young children with transfusional iron overload. *J Pediatr Hematol Oncol*. 2010; **32**: 601-5.

26 Aessopos A, Fragodimitri C, Karabatsos F, Hatziliami A, Yousef J, Giakoumis A*, et al.* Cardiac magnetic resonance imaging R2* assessments and analysis of historical parameters in patients with transfusion-dependent thalassemia. *Haematologica*. 2007; **92**: 131-2.

27 Wanless IR SG, Dhillon AP, Guido M, Piga A, Galanello R, Gamberini MR, Schwartz E, Cohen AR. Lack of progressive hepatic fibrosis during long-term therapy with deferiprone in subjects with transfusion-dependent beta-thalassemia. *Blood*. 2002: 10:1566-9.

28 Taher A, Sheikh-Taha M, Koussa S, Inati A, Neeman R, Mourad F. Comparison between deferoxamine and deferiprone (L1) in iron-loaded thalassemia patients. *Eur J Haematol*. 2001; **67**: 30-34.

29 Maggio A, D'Amico G, Morabito A, Capra M, Ciaccio C, Cianciulli P*, et al.* Deferiprone versus deferoxamine in patients with thalassemia major: a randomized clinical trial. *Blood Cells Mol Dis*. 2002; **28**: 196-208.

30 Pennell DJ, Berdoukas V, Karagiorga M, Ladis V, Piga A, Aessopos A*, et al.* Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. *Blood*. 2006; **107**: 3738-44.

31 Roberts D, Brunskill S, Doree C, Williams S, Howard J, Hyde C. Oral deferiprone for iron chelation in people with thalassaemia (Review)- The Cochrane Library. John Wiley & Sons, Ltd 2009.

32 Tanner MA, Galanello R, Dessi C, Smith GC, Westwood MA, Agus A*, et al.* A randomized, placebo-controlled, double-blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. *Circulation*. 2007; **115**: 1876-84.

33 Cappellini MD, Porter J, El-Beshlawy A, Li CK, Seymour JF, Elalfy M*, et al.* Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias. *Haematologica*. 2010; **95**: 557-66.

34 Pathare A, Taher A, Daar S. Deferasirox (Exjade) significantly improves cardiac T2* in heavily iron-overloaded patients with beta-thalassemia major. *Ann Hematol*. 2010; **89**: 405-09.

35 Pennell DJ, Porter JB, Cappellini MD, El-Beshlawy A, Chan LL, Aydinok Y*, et al.* Efficacy of deferasirox in reducing and preventing cardiac iron overload in beta-thalassemia. *Blood*. 2010; **115**: 2364-71.

36 Wood JC, Kang BP, Thompson A, Giardina P, Harmatz P, Glynos T*, et al.* The effect of deferasirox on cardiac iron in thalassemia major: impact of total body iron stores. *Blood*. 2010; **116**: 537-43.

37 Piga A, Forni GL, Kattamis A, Kattamis C, Aydinok Y, Rodriguez M*, et al.* Deferasirox (Exjade(R)) in Pediatric Patients with {beta}-Thalassemia: Update of 4.7-Year Efficacy and Safety from Extension Studies. *ASH Annual Meeting Abstracts*. 2008; **112**: 3883-.

38 Kattamis A, Ladis V, Berdousi H, Kelekis NL, Alexopoulou E, Papasotiriou I*, et al.* Iron chelation treatment with combined therapy with

deferiprone and deferioxamine: a 12-month trial. *Blood Cells Mol Dis*. 2006; **36**: 21-25.

39 Cappellini MD, Musallam KM, Taher AT. Overview of iron chelation therapy with desferrioxamine and deferiprone. *Hemoglobin*. 2009; **33 Suppl 1**: S58-69.

40 Anderson LJ, Westwood MA, Holden S, Davis B, Prescott E, Wonke B*, et al.* Myocardial iron clearance during reversal of siderotic cardiomyopathy with intravenous desferrioxamine: a prospective study using T2* cardiovascular magnetic resonance. *Br J Haematol*. 2004; **127**: 348-55.

41 Tsironi M, Deftereos S, Andriopoulos P, Farmakis D, Meletis J, Aessopos A. Reversal of heart failure in thalassemia major by combined chelation therapy: a case report. *Eur J Haematol*. 2005; **74**: 84-5.

42 Wu KH, Chang JS, Tsai CH, Peng CT. Combined therapy with deferiprone and desferrioxamine successfully regresses severe heart failure in patients with beta-thalassemia major. *Ann Hematol*. 2004; **83**: 471-3.

43 Ho PJ, Hall GW, Luo LY, Weatherall DJ, Thein SL. Beta-thalassaemia intermedia: is it possible consistently to predict phenotype from genotype? *Br J Haematol*. 1998; **100**: 70-8.

44 Taher A, Hershko C, Cappellini MD. Iron overload in thalassaemia intermedia: reassessment of iron chelation strategies. *Br J Haematol*. 2009; **147**: 634-34.

45 Pootrakul P, Sirankapracha P, Sankote J, Kachintorn U, Maungsub W, Sriphen K*, et al.* Br J Haematol. *Clinical trial of deferiprone iron chelation therapy in beta-thalassaemia/haemoglobin E patients in Thailand*. 2003; **122**: 305-10.

46 Farmaki K GE, Tzoumari I, Berdoukas V. Rapid iron loading in a pregnant woman with transfusion-dependent thalassemia after brief cessation of iron chelation therapy. *Eur J Haematol* 2008; **81**: 157-9.

47 Origa R PA, Quarta G, Forni GL, Longo F, Melpignano A, Galanello R. Pregnancy and beta-thalassemia: an Italian multicenter experience. *Haematologica*. 2010; **95**: 376-81.

48 Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev*. 2008: CD000011.