

An update on iron chelation therapy

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Introduction

Iron overload is a common clinical problem, arising from disorders of increased iron absorption such as hereditary haemochromatosis or thalassaemia intermedia syndromes or as a consequence of chronic blood transfusions for various blood disorders.

Regular red blood cell (RBC) transfusions are the principal supportive therapy for many rare anaemias involving a decrease in RBC production, an increase in cell destruction, or chronic blood loss¹. Anaemias such as beta-thalassaemia and sickle cell disease are examples of chronic diseases that require long-term transfusion therapy to improve life expectancy.

Although transfusion requirements may vary according to the diagnosis, chronic blood transfusion therapy inevitably leads to secondary iron overload that can cause significant damage to many organs, such as the liver and heart, and to the endocrine system^{2,3}. Iron overload is associated with the production of free radicals that can damage tissues, resulting in cardiac toxicity, endocrine dysfunction, and liver toxicity. The effects of iron overload are visible after damage has been done, when patients already have liver dysfunction, cirrhosis, cardiomyopathy or diabetes^{1,4}.

Iron is an essential element within the body and its quantity is tightly regulated physiologically; however, the body has no mechanism to excrete excess iron and it deposits iron into end organs leading to severe dysfunction. Each unit of RBC transfused contains 180 to 200 mg of iron. Chronic packed RBC transfusion therapy increases liver iron by approximately 1 mg/mL (by dry weight) for every 15 mL/kg delivered⁵. Labile plasma iron (LPI) is a toxic and chelatable form of iron that is produced continually during conditions of iron overload, and has been linked to the development of co-morbidities⁶. It is very important to remove excess iron and suppress LPI to avoid the serious clinical sequelae associated with iron overload. In this specific context phlebotomy cannot be used because patients are usually anaemic and other means must be

used to mobilise the excess iron. The gold standard is iron chelation therapy.

Methods for evaluating iron overload

There are various different methods for evaluating the degree of iron overload, including serum ferritin levels, liver iron concentration determined from a biopsy, superconducting quantum interference device (SQUID) and magnetic resonance imaging (MRI). Each method has pros and cons, and often a combination of these tests is used to quantify and monitor iron burden.

The simplest way to quantify iron overload is to count the number of RBC units that a patient has been transfused over time⁷. Another simple method of evaluation is to test serum ferritin levels, which correlate with body iron stores. Although trends in serum ferritin remain an important monitoring tool, serum ferritin is a poor marker of iron balance because ferritin values can change in the presence of inflammation/infection, or ascorbate deficiency, and according to the intensity of blood transfusion therapy, making the reliability of ferritin levels questionable⁸.

The gold standard for assessing the degree of iron overload is a liver biopsy, but its invasiveness limits its use for routine screening at most institutions. Liver iron concentration >15 mg/g dry weight predicts a higher risk of cardiac disease and death⁹ and progression of hepatic fibrosis, which may be exacerbated by hepatitis C infection, a very common condition in patients transfused before the 1980s^{10,11}.

MRI is a non-invasive method which can quantify hepatic and cardiac iron, replacing liver biopsy for quantification of iron in the liver¹². The ability of MRI to quantify extra-hepatic iron has had a great impact on patients' care and on our understanding of the pathophysiology of iron overload. In particular, cardiac iron can be investigated in asymptomatic patients by cardiac T2*, and signal changes shown by MRI could be used as pre-clinical end-points for

evaluating response to chelation¹³. Therefore, after at least 10 transfusions (150 mL/kg), in the absence of significant losses, chronically transfused patients merit at least an initial MRI scan. In addition, patients with a high transfusion load, an unknown transfusion burden, or with Diamond-Blackfan syndrome (in which cardiac iron loading is exhibited early¹⁴) may warrant cardiac examination at their initial evaluation.

Recently, MRI estimates of cardiac and liver iron have become the primary outcome measures for clinical studies on iron chelation therapy¹⁵⁻¹⁷. Cardiac complications remain the most common cause of death in transfused thalassaemia patients⁸ and a central goal of iron chelation therapy is to prevent or remove cardiac iron loading. Cardiac T2* values of 10-20 ms indicate mild to moderate iron loading and values <10 ms indicate severe myocardial siderosis. In thalassaemia major, the risk of developing clinically relevant left ventricular dysfunction increases as the T2* falls below the lower limit found in healthy adults (approximately 20 ms). Patients with very low T2* values (<6 ms) have a 47% chance of developing congestive heart failure within the following year¹⁸. Low cardiac T2* values (<20 ms) should, therefore, trigger intensification of chelation regimes regardless of liver iron burden. The development of cardiac dysfunction or arrhythmia should also prompt intensification of chelation therapy, for example considering the combination of different iron chelators (as described below).

Iron is removed from different organs at different rates: hepatic iron burden usually improves more rapidly than cardiac iron burden with intensification of chelation. For this reason both hepatic and cardiac iron must be measured to optimise the chelation therapy. Changes in ferritin levels often parallel changes in liver iron concentration, even if a variety of factors, such as inflammation, infection and ascorbate deficiency, can decrease or increase ferritin levels. According to this evidence, serial ferritin levels may be used to assess trends in iron burden and to help to modify chelator dosing. In particular, ferritin levels above 2,500 ng/mL are associated with an increased risk of morbidity and mortality, and levels persistently above this value should trigger intensification of the chelation regimen.

Future frontiers in MRI monitoring include improved prevention of endocrine toxicities,

particularly hypogonadotropic hypogonadism and diabetes.

Iron chelation therapy

The overall aim of chelation therapy is to maintain a "safe" iron status at all times. Ideally, chelation therapy should be administered to prevent iron accumulation and iron-related complications including hepatic, endocrinological and cardiac dysfunction. There is evidence showing that the age at which iron chelation is started in patients with thalassaemia major is a key factor in their survival^{8,19,20}, although this aspect is often not considered in retrospective analyses of survival data.

In practice, chelation therapy is often used to remove excess stored iron and to reverse related complications. Generally, chelation therapy with deferoxamine (DFO; see below) has traditionally been started only after 2 to 3 years of transfusion or when ferritin exceeds 1,000 ng/mL. Iron chelation therapy provides a viable method of treating iron overload and minimising the adverse effects associated with iron burden. The direct capture of non-transferrin bound iron and LPI with effective chelation therapy may help to prevent the adverse consequences of iron overload⁶. Several iron chelators have been developed, designed to mobilise tissue iron by forming complexes that are excreted in the faeces and/or urine (Table I).

Before the routine availability of chelation therapy, chronically transfused patients died from cardiac iron overload in their teens and twenties²¹. Since the introduction of deferoxamine (Desferal®; DFO; Novartis Pharma AG, Basel, Switzerland) in the early 1970s, the life expectancy of such patients has improved dramatically⁸.

DFO was developed more than 40 years ago and the wealth of clinical experience in iron-overloaded patients has established a role for iron chelators in the improvement of patients' quality of life and overall survival^{22,23}. Data indicate that DFO is effective at lowering serum ferritin levels and hepatic iron^{24,25} and in preventing endocrine complications^{19,26}. Long-term therapy with DFO is also associated with a reduction in cardiac complications and improved survival⁸. In addition, doses of DFO higher than 60 mg/kg/day as a continuous intravenous infusion can reverse cardiac iron burden²⁷ as measured by cardiac T2*²⁸.

Table I - Overview of iron chelators.

Property	Deferoxamine	Deferiprone	Deferasirox
Stoichiometry (chelator:iron)	Hexadentate (1:1)	Bidentate (3:1)	Tridentate (2:1)
Route	Subcutaneous, intravenous	Oral tablet or solution	Tablets for oral suspension
Usual dose	20-40 mg/kg/day over 8-24 hours, 5 days/week	75-100 mg/kg/day in 3 divided doses daily	Recommended initial dose 20 mg/kg up to a maximum of 40 mg/kg/day
Excretion	Urinary, faecal	Mainly urinary	Faecal
Half-life	20-30 min	3-4 hours	8-16 hours
Adverse effects	Local skin reactions Ophthalmological Auditory Allergic reactions Growth retardation Bone abnormalities Pulmonary at high doses Neurological at high doses	Gastrointestinal Agranulocytosis/ neutropenia Arthralgia Elevated liver enzymes	Gastrointestinal Rash Rise in creatinine Proteinuria Ophthalmological Auditory Elevated liver enzymes
Challenges	Adherence due to parenteral administration; need for yearly ophthalmology and audiometric examination	Need for weekly blood count monitoring; not commercially available in all countries; limited data in children; variable efficacy in removal of hepatic iron	Cost, especially with higher doses; gastrointestinal side effects may limit optimal dosing Need for monthly monitoring of creatinine, transaminases, bilirubin, complete blood count for potential renal or hepatic failure and/or gastrointestinal haemorrhage (more frequently in patients with advanced age and existing comorbidities)
Status	Licensed	Licensed in USA and Europe	Licensed in USA and Europe
Indications	Treatment of chronic iron overload due to transfusion-dependent anaemias (and for treatment of acute iron intoxication)	Treatment of iron overload in thalassaemia major when DFO is contraindicated or inadequate.	In USA licensed for the treatment of chronic iron overload due to transfusion-dependent anaemias in individuals aged 2 years and older In Europe licensed for the treatment of transfusional iron overload in beta-thalassaemia major patients, 6 years and older, and approved for use when DFO is inadequate or contraindicated in patients with other anaemias, patients 2-5 years, and patients with non-transfusion-dependent thalassaemia
Age considerations	Not recommended for children <3 years with low transfusional burden	Limited or no data on children aged <6-10 years	Studied in children as young as 2 years old

DFO is a hexadentate chelator binding iron at a 1:1 molar ratio, thus preventing its participation in toxic reactions. In accordance with its relatively high molecular weight and highly hydrophilic properties, DFO does not readily enter most types of cells, with the exception of hepatocytes, which seem to have a facilitated uptake mechanism²⁹. The iron complex of DFO is highly stable, with good iron-scavenging properties at low concentrations of iron or chelator.

The most common adverse effects of DFO are listed in Table I. Redness and induration at the

infusion site are the most frequent. Ophthalmological, auditory and bone toxicity and growth retardation can be minimised by avoiding "over-chelation".

The greatest challenge with DFO is patients' adherence to therapy. Due to its poor oral bioavailability and short plasma half-life, DFO must be given by slow subcutaneous administration over 8-12 hours, 5-7 days/week, often resulting in poor compliance³⁰. DFO infusions frequently have a negative impact on patients' quality of life, as the infusions can be troublesome, time-consuming and

painful. A review of published data suggests that compliance with DFO is between approximately 60% and 80%³¹. Poor compliance leads to gaps in chelation coverage, during which LPI levels can increase and cause further tissue damage. Morbidity and mortality in thalassaemia are closely linked to the adequacy of chelation. Cardiac morbidity and mortality continue to occur in patients treated with DFO, probably related to difficulties with adherence³².

The burden of this demanding regimen and the poor compliance led to the search for more convenient oral chelators. There are currently two oral iron chelators licensed for the treatment of iron overload.

Deferiprone (Ferriprox[®]; DFP; Apotex Inc., Toronto, ON, Canada), first tested in clinical trials in the 1980s, is available in the European Union and Canada, and recently the U.S. Food and Drug Administration approved deferiprone for the treatment of iron overload due to blood transfusions in patients with thalassaemia, who had an inadequate response to prior chelation therapy (European Medicine Agency. <http://www.ferriprox.com>; U.S. Food and Drug Administration <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm275814.htm>).

DFP is a small lipophilic molecule, which binds to iron in a 3:1 ratio and can enter myocytes and capture LPI in specific organelles of cardiomyocytes and macrophages. DFP facilitates transfer of iron from extracellular media into nuclei and mitochondria, from endosomes to nuclei, and from intracellular compartments to extracellular apotransferrin. Furthermore, it mobilises iron from iron-loaded cells and donates it to pre-erythroid cells for haemoglobin synthesis, both in the presence and in the absence of transferrin. These unique properties of DFP mechanistically underlie its capacity to alleviate iron accumulation in several conditions, including neurodegeneration with brain iron accumulation, such as Friedreich's ataxia^{33,34}, and to donate tissue-chelated iron to plasma transferrin in patients with thalassaemia intermedia³⁵.

DFP has a short half-life (3-4 hours) and must, therefore, be given three times daily. DFP is often used in combination with DFO; in this case, treatment can be sequential (both chelators are given in any 24-hour period) or alternating (only one chelator is administered in any 24-hour period). Adherence is likely to depend

on the regimen used: a regimen that reduces the number of days of DFO therapy (e.g. alternating therapy) may improve adherence, while a regimen using the standard DFO treatment plus DFP (e.g. sequential therapy) may worsen adherence³⁶. A shuttling hypothesis, according to which DFP binds iron and then redistributes it to DFO, has been proposed^{37,38}, and co-administration of these two chelators with an additive effect, could be an optimal strategy.

Common adverse effects of DFP are presented in Table I. The most serious adverse effects associated with DFP are agranulocytosis and neutropenia, with an incidence of 0.2 and 2.8 per 100 patient-years, respectively³⁹. Weekly blood counts are strongly recommended in patients taking DFP. In particular, patients with bone marrow failure syndromes such as Diamond-Blackfan anaemia may be at higher risk of developing neutropenia with DFP⁴⁰.

Retrospective studies have demonstrated reduced cardiac morbidity and mortality^{32,41-43} and lower myocardial iron deposition¹³ among patients treated with DFP than among those treated with DFO. Furthermore, in a randomised clinical trial among patients with moderate cardiac siderosis and normal cardiac function, significantly greater improvements in cardiac T2* and left ventricular function were seen after treatment with DFP than after treatment with DFO⁴⁴. In a large clinical observational study, treatment with DFP resulted in an improvement in cardiac T2* among patients with all degrees of cardiac iron loading⁴⁵.

The combination of DFO and DFP is currently the most effective means of reducing cardiac iron loading and should be started in patients with significant cardiac siderosis. The chelators can be alternated to provide continuous exposure to chelation; for example, DFO given every night and DFP during the day can provide 14-hour removal of LPI⁶. The chelators can also be given at the same time, considering the possibility of a drug interaction through a so-called shuttle mechanism in which iron is chelated rapidly by DFP at sites relatively unavailable to DFO and then donated to the more stable DFO molecules. There is experimental evidence of this effect in animal models of iron overload³⁷, and this shuttling was recently shown to occur in the removal of non-transferrin bound iron from the plasma compartment of patients with thalassaemia major³⁸.

In practice, sequential use of DFO and DFP is more commonly adopted⁴⁶⁻⁵⁰.

The superiority of this combination compared with DFO alone was demonstrated in a randomised, placebo-controlled trial of 65 patients with mild to moderate cardiac iron loading⁵¹. Subjects who received combination therapy had significantly greater improvements in cardiac T2* and left ventricular ejection fraction than those receiving DFO with placebo. Furthermore, in a single-arm trial of patients with severe myocardial siderosis and myocardial dysfunction, combined treatment with DFO and DFP was effective in significantly improving cardiac T2* and left ventricular ejection fraction, as well as reducing serum ferritin and liver iron concentration after 12 months of therapy⁵².

More recently, a multicentre, randomised, open-label trial was designed to assess the effectiveness of long-term alternating sequential DFP-DFO versus DFP alone in patients with beta-thalassaemia⁵³. DFP 75 mg/kg for 4 days/week and DFO 50 mg/kg/day for 3 days/week was compared with DFP alone 75 mg/kg for 7 days/week during a 5-year follow-up. A total of 213 thalassaemic patients were randomised and intention-to-treat analysis was performed. The decrease of serum ferritin level was statistically significantly greater in patients treated with the alternating sequential DFP-DFO patients than in those treated with DFP alone ($P=0.005$). Kaplan-Meier survival analysis for the two chelation treatments did not show statistically significant differences (log-rank test, $P=0.3145$). Adverse events and costs were comparable between the groups. These findings were confirmed in a further 21-month follow-up. These data suggest that alternating sequential DFP-DFO treatment may be useful for some patients with beta-thalassaemia who may not be able to receive other forms of chelation treatment.

Formal safety data on combined treatments are limited. In general, alternating regimes are less likely to be an issue for toxicity compared with regimes in which chelation is simultaneous or overlapping. A meta-analysis of the incidence of agranulocytosis in patients treated with combined regimes suggested that the risk may be increased several-fold compared with that in patients treated with DFP monotherapy, although the number of evaluable patients was small⁵⁴. The increased

incidence seemed to occur mostly in regimes in which the drugs were administered simultaneously.

Deferasirox (DFX; Exjade[®]; Novartis Pharma AG, Basel, Switzerland) is the most recent oral iron chelator. It was developed as a once-daily oral iron chelator through a rational drug development programme and represents a new class of tridentate iron chelators⁵⁵. DFX is currently approved in many countries worldwide for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older (EXJADE[®] [deferasirox]. <http://www.pharma.us.novartis.com/product/pi/odf/exjade.pdf>).

The efficacy and the safety of DFX have been evaluated in patients with beta-thalassaemia²⁴ and in a wide range of patients with other underlying anaemias including myelodysplastic syndromes (MDS), sickle cell disease, aplastic anaemia, Diamond-Blackfan anaemia and various other rare anaemias^{30,47,55-61}.

Iron chelation with DFX may be beneficial because of its once-daily formulation, supported by its plasma half-life of 11 to 19 hours^{30,56}. There are now data on compliance with DFX which, in the Evaluation of Patients' Iron Chelation with Exjade (EPIC) study, was reported to be greater than 80%⁶⁰.

Two DFX studies in patients with beta-thalassaemia and sickle cell disease evaluated actual patients' feedback in the form of patient-reported outcomes. Most patients were more satisfied with DFX and found it more convenient than DFO therapy. A recent study by the Thalassemia Clinical Research Network examined adherence in 79 patients on DFO and 186 on DFX from 2007 to 2009. Adherence to both DFO and DFX was highest in children, followed by adolescents and older adults. Switching chelators resulted in increased adherence, regardless of the direction of the switch, although switching from DFO to DFX was more common.

The most common adverse effects of DFX are reported in Table I. DFX is typically well tolerated, with adverse events generally being mild. Transient gastrointestinal events, including abdominal pain, nausea and vomiting, diarrhoea and constipation occur in approximately 15% of patients with thalassaemia²⁴ and in higher numbers of patients with MDS. Gastrointestinal disturbances are, in fact, the most common side effects but can often be improved by changing the time of day of DFX administration.

Skin rashes occur early in approximately 10% of patients and are usually transient²⁴. There have been rare reports of fulminant hepatic failure, leading to the suggestion that liver function should be monitored every 2 weeks for 1 month after starting therapy with DFX and then monthly thereafter. The levels of serum creatinine increase in approximately one-third of patients within a few weeks of starting or increasing therapy, but rarely reach the abnormal range²⁴. Kidney function needs, therefore, to be monitored monthly. Audiometric effects and lens opacity did not differ significantly from those in patients treated with DFO²⁴, and no drug-related agranulocytosis was observed. Because of its poor solubility in water, DFX is administered as a suspension in fruit juice. Its metabolism is predominantly to iron-binding glucuronides in the liver; iron excretion is dose-dependent and almost entirely faecal^{30,56}.

The efficacy of DFX at a dose of 20-30 mg/kg/day was shown to be similar to that of DFO in reducing liver iron concentration and serum ferritin levels in a large randomised trial in patients with thalassaemia major²⁴. The drug's ability to remove hepatic iron has been demonstrated in several additional studies^{57,61}.

Deugnier *et al.* observed an improvement in liver pathology in iron-overloaded beta-thalassaemia patients treated with DFX for at least 3 years⁶². In this study, histological data from 219 patients who had biopsy samples taken at baseline and after at least 3 years of treatment with DFX. DFX reversed or stabilised liver fibrosis in 83% of the patients and this therapeutic effect was independent of a reduction in the concentration of liver iron or previous exposure to hepatitis C virus⁶².

In a trial of 101 patients with mild to severe cardiac iron loading treated with DFX, cardiac T2* improved significantly in both the groups with mild-to-moderate and severe iron loading over 2 years of treatment⁶³. No significant improvement in left ventricular ejection fraction was observed, although the ejection fraction was normal at baseline⁶³. In another study of 22 patients with cardiac T2* <20 ms treated with DFX for 18 months, cardiac T2* worsened in 14 patients and no change in left ventricular ejection fraction was seen over the 18 months of treatment.

The failure to respond was predicted by higher baseline liver iron concentration and ferritin levels¹⁷.

DFX can also prevent cardiac iron accumulation,

as shown by Pennell *et al.*¹⁶. In 78 patients with thalassaemia without evidence of cardiac iron loading, cardiac T2* did not worsen over 1 year of treatment and no subjects with normal cardiac T2* at baseline developed an abnormal value over the follow-up period. In contrast to the patients with low cardiac T2* values, a significant improvement in ejection fraction was observed in the group of patients with a normal cardiac T2* at baseline.

The combination of DFX and DFO has not been extensively studied. In a pilot study, patients with thalassaemia major and evidence of iron-related organ dysfunction were treated with DFX daily and DFO for 3-7 days/week⁶⁴. Liver iron concentration improved significantly and no toxicity was observed. Unfortunately, the combination of DFO and DFX did not show additive or synergetic effects on iron excretion in an iron-overloaded gerbil model, suggesting that the two chelators compete for a common iron pool⁶⁵. It is not clear whether the same happens in human beings, but sequential rather than combination therapy could be preferred if the two chelators compete for the same iron pool. Further research regarding the safety and efficacy of combined treatment with DFO and DFX is necessary before recommendations can be made for routine clinical practice. Likewise, the combination of DFX and DFP still needs to be studied.

The ability of DFX to reverse cardiac disease has not yet been investigated, because all the prior studies required normal heart function for inclusion. Reversal of heart failure with DFX was reported in one patient with beta-thalassaemia and transfusional iron overload⁶⁶. Further studies are needed to better delineate the effect of DFX on cardiac iron overload and iron-related cardiac dysfunction.

In the last year the level of "acceptable" iron burden in chronically transfused patients has been called into question⁶⁷ and more "aggressive" chelation regimens have been advocated. Comparing the efficacy of the three chelators in suppressing LPI, it can be seen that a limitation of both DFO and DFP monotherapy is their inability to control levels of LPI constantly as a result of their short plasma half-lives^{68,69}. In addition monotherapy may not be effective in all patients for a large variety of reasons. For example, adverse effects may prevent optimal dosing, while poor adherence to treatment may lead

to underdosing. Combination therapy may be more effective in these contexts.

DFO/DFP sequential therapy provides more consistent suppression of LPI than monotherapy with either chelator⁷⁰ and is accompanied by a subsequent reduction in the frequency and dose of DFO reducing the risk of chelator toxicity. Recently, the combination of high doses of DFO (20-60 mg/kg/day) and DFP (75-100 mg/kg/day) led to normalisation of total body iron load in thalassaemia patients⁷¹. Furthermore, cardiac and endocrine complications, including hypothyroidism, hypogonadism and non-insulin-dependent glucose intolerance, were reversed in some, but not all, patients treated with this regimen⁷¹.

As DFX is detectable in the blood within the therapeutic range over a 24-hour period, it offers complete chelation coverage with standard dosing and can provide a sustained reduction in LPI⁷². The first prospective study to report long-term monitoring of the efficacy and safety of iron chelation with DFX in both paediatric and adult patients with beta-thalassaemia suggests that treatment is generally well tolerated and effectively reduces iron burden⁷³. Many patients achieved maintenance serum ferritin levels of ~1,000 ng/mL, and treatment for ≤5 years was well tolerated. The study also provided the first data on the long-term effects on paediatric growth and adolescent sexual development for any oral iron chelation therapy. DFX did not show an adverse effect on paediatric growth or adolescent sexual development in paediatric patients who are prone to growth retardation as a result of iron overload⁷³. These data confirm the results obtained in the published shorter-term clinical trials of 1-year duration^{60,61}.

Iron chelation therapy in clinical practice

There are substantial data demonstrating the efficacy and safety of iron chelation therapy in the treatment of iron overload in regularly transfused patients with beta-thalassaemia^{8,57,60}. The blood transfusion rate influences the chelator dose and careful monitoring of transfusional iron intake is needed, especially in young children, in order to avoid exceeding the therapeutic index of the chelator and, as a consequence, increasing the risk of adverse effects.

Data supporting the use of iron chelation therapy in other transfusion-dependent anaemias such as MDS, aplastic anaemia and sickle cell disease are also

accumulating^{57,58,60,74,75} and suggest that the response in terms of iron balance is mainly dependent on chelator dose and transfusional iron loading rate^{57,58,60,74-76}.

Studies in patients affected by rare anaemias related to decreased RBC production, including Diamond-Blackfan anaemia and pure red cell aplasia, as well as those in patients with haemolytic anaemia have been limited⁵⁷, and response has not been analysed with respect to the underlying mechanism of anaemia. However, the 1-year EPIC study enrolled a large number of patients with different types of transfusion-dependent anaemia⁶⁰, thereby enabling the investigation of disease-specific factors that might affect iron chelation therapy with DFX. A subsequent study, including patients with rare transfusion-dependent anaemias from the EPIC study, examined how responses of these rare blood disorders to DFX chelation were affected by the underlying mechanism of the anaemia (decreased RBC production or haemolysis)⁷⁷. The efficacy and safety of DFX were evaluated over 1 year, with the change in serum ferritin concentration being the primary efficacy end-point. Transfusional iron-loading rates, mean DFX dosing and baseline median serum ferritin levels were comparable in patients with anaemia due to either decreased RBC production or haemolysis. In both cohorts the responses to DFX were similar at 1 year, irrespective of the underlying pathogenic mechanism necessitating the chronic blood transfusions⁷⁷. These data provide evidence that transfusional iron overload in patients with a variety of rare anaemias may be effectively managed using a tailored DFX dosing regimen, based on individual blood transfusion requirements, regular monitoring of serum ferritin trends and safety parameters⁷⁷.

The efficacy of iron chelation on survival in patients with MDS is still a matter of discussion because of the lack of randomised trials with a survival end-point, although evidence suggests that improvements in survival are likely⁷⁸⁻⁸¹. In the EPIC study, 341 patients with MDS were treated with DFX, obtaining a significant decrease in the overall median serum ferritin levels after 1 year of treatment⁸². Recently, data from patients with MDS showed that DFX can improve haematological parameters, including haemoglobin concentration, transfusion requirements and neutrophil and platelet counts⁸³⁻⁸⁶.

Survival data for patients with MDS treated with DFX are lacking; a randomised, double-blind, placebo-controlled phase III trial (TELESTO) comparing DFX to placebo is currently underway.

The benefits of reduced iron levels in bone marrow transplant patients, before and after transplantation, have been recognised and DFX could have a potential role in the treatment of iron load in this population of patients. Iron overload has been reported in adults after haematopoietic stem cell transplantation (HSCT)^{87,88} and could be a significant contributor to treatment-related mortality in patients with haematological malignancies undergoing HSCT. It is well known that iron overload is an important adverse prognostic factor for patients with thalassaemia undergoing HSCT^{89,90}. This may also hold true for patients who undergo transplantation for haematological malignancies⁹¹. Recent studies have suggested a link between iron overload and post-transplantation liver toxicity (including chronic liver disease and veno-occlusive disease)⁹², susceptibility to infections⁹³, and veno-occlusive disease⁹⁴.

Although iron overload both before and after transplantation and its effects on end organ toxicity are legitimate concerns in high-risk MDS, many questions remain unresolved with regards to the potential role of iron chelation therapy in this context. Prospective studies incorporating T2* MRI of the heart and iron as well as alternative biomarkers of iron stores are needed to improve our understanding of the extent as well as the temporal significance of iron overload in patients undergoing allogeneic HSCT. The studies should also address the relationship between pre-transplant transfusions and iron overload within each haematological disease group. Given the absolute difference in 5 year-overall survival for patients with MDS between those with the highest and lowest ferritin quartiles⁹⁵, judicious chelation therapy could lead to a significant improvement in transplantation outcomes for these patients.

Iron chelation therapy is currently focused on the treatment of patients with transfusional iron overload; however, a wider prospective is being taken with the use of DFX being investigated in a number of other conditions including hereditary haemochromatosis, characterised by progressive iron loading through increased intestinal iron absorption⁹⁶; porphyria cutanea tarda, a common type of porphyria which

can be associated with haemochromatosis⁹⁷; and mucormycosis⁹⁸.

Finally, studies have demonstrated that iron is a crucial element for the proliferation of tumour cells, and as a consequence, the potential role of iron chelation in the treatment of cancer must be considered in the near future⁹⁹.

Conclusion

Long-term RBC transfusion therapy is required for the treatment of several types of congenital and acquired anaemia, such as thalassaemia syndromes, sickle cell disease, MDS, Diamond-Blackfan anaemia and aplastic anaemia. Chronic blood transfusions inevitably lead to iron overload and serious clinical sequelae and patients receiving such transfusions, therefore, requires lifelong chelation therapy. Several factors, including the availability of a given chelator and its properties, drug tolerability, transfusional iron burden and the patient's compliance must be considered in the design of optimal, individualised chelation regimens, and all these factors must regularly be reviewed and the chelation modified accordingly. Adherence to DFO is generally poor and a patient's attitude to adherence can change over time. The availability of oral iron chelators, such as DFP and DFX, may contribute to improved compliance, especially among paediatric and adolescent patients in whom compliance is a particular issue. Adherence may also be improved by offering patients greater choice in chelation.

The challenging task for the future is to design a chelator that: (i) is orally active; (ii) can cross cell membranes; and (iii) is capable of scavenging iron from specific areas of the body, such as the heart, the liver, the endocrine glands and the brain, sparing the bulk of physiologically essential iron.

A number of oral iron chelators are currently under development, including an α -ketohydroxypyridine analogue of DFP, LINAI, and a novel oral once-daily iron chelator, FBS0701¹⁰⁰.

In a multicentre phase 2 study of the safety, tolerability and pharmacodynamics of FBS0701, 51 adult patients, stratified by transfusional iron intake, were randomised to FBS0701 at a dose of 14.5 or 29 mg/kg/day (16 and 32 mg/kg/day of the salt form)¹⁰¹. FBS0701 was generally well tolerated at both doses. Forty-nine patients (96%) completed the study. There

were no drug-related serious adverse events. No adverse events showed dose-dependency in frequency or severity. Treatment-related nausea, vomiting, abdominal pain, and diarrhea were each noted in <5% of patients. The most common treatment-related adverse event was increased transaminases (16%, N=8). Three of these eight patients acquired a hepatitis C virus infection on-study from a single blood bank; the five others had abnormal baseline alanine transaminase. Mean serum creatinine did not change significantly from baseline or differ between dose groups. The change in 24-week liver iron concentration (Δ LIC) differed according to the dose of FBS0701: the mean Δ LIC for patients treated with 14.5 mg/kg/day was +3.1 mg/g (dry weight); 29% achieved a decrease in LIC. The mean Δ LIC among the patients treated with 29 mg/kg/day was -0.3 mg/g (dry weight) and 44% achieved a decrease in LIC ($P < 0.03$ for Δ LIC between doses). The safety and tolerability profile at therapeutic doses compare favourably with those of other oral chelators¹⁰¹.

Finally, the development of more sensitive methods for quantifying iron could improve treatment and monitoring of therapeutic efficacy in iron overload disorders.

Keywords: iron overload, chelation therapy, transfusion-dependent disorders, thalassaemia, iron.

The Authors declare no conflicts of interest.

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