

Management of transfusional iron overload – differential properties and efficacy of iron chelating agents

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Abstract: Regular red cell transfusion therapy ameliorates disease-related morbidity and can be lifesaving in patients with various hematological disorders. Transfusion therapy, however, causes progressive iron loading, which, if untreated, results in endocrinopathies, cardiac arrhythmias and congestive heart failure, hepatic fibrosis, and premature death. Iron chelation therapy is used to prevent iron loading, remove excess accumulated iron, detoxify iron, and reverse some of the iron-related complications. Three chelators have undergone extensive testing to date: deferoxamine, deferasirox, and deferiprone (although the latter drug is not currently licensed for use in North America where it is available only through compassionate use programs and research protocols). These chelators differ in their modes of administration, pharmacokinetics, efficacy with regard to organ-specific iron removal, and adverse-effect profiles. These differential properties influence acceptability, tolerability and adherence to therapy, and, ultimately, the effectiveness of treatment. Chelation therapy, therefore, must be individualized, taking into account patient preferences, toxicities, ongoing transfusional iron intake, and the degree of cardiac and hepatic iron loading.

Keywords: transfusion, iron, chelation, magnetic resonance imaging

Iron overload Transfusional iron overload

Regular red cell transfusions are used in the management of numerous hematological disorders including beta-thalassemia major; sickle cell disease; other hemolytic anemias, such as pyruvate kinase deficiency; bone marrow failure syndromes; and myelodysplastic syndromes. Each milliliter of packed red blood cells contains 1.1 mg of iron. Because humans lack physiological mechanisms to excrete excess iron, chronic red cell transfusion therapy will lead to progressive iron accumulation in the absence of chelation therapy. A typical regular transfusion regimen leads to an average iron accumulation of approximately 0.3–0.5 mg/kg/day,^{1,2} although there is considerable interpatient variability in iron loading. In one study of 541 patients with beta thalassemia, 61% had transfusional iron intakes in the range 0.3–0.5 mg/kg/day, while 19% and 20% had average iron intakes below and above this range, respectively.¹ Chelation therapy is necessary to remove this iron accumulation to prevent or treat its associated toxicity.

Nontransfusional iron overload

Iron overload also can result from hereditary causes that lead to increased intestinal absorption of dietary iron. Dysregulation of hepcidin, a small peptide produced mainly

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in the liver that inhibits iron absorption, now appears to be central in many of the hereditary forms of hemochromatosis. The most common form of hereditary hemochromatosis is caused by mutations in the HFE gene, which prevent the appropriate upregulation of hepcidin expression in response to increased iron levels.³ Homozygosity for the cysteine to tyrosine substitution (C282Y) in the human hemochromatosis (HFE) protein is associated with the development of iron overload typically in the fifth to sixth decades of life, although clinical penetrance is variable.⁴ The standard treatment for hereditary hemochromatosis is phlebotomy to reduce iron stores, although iron chelation therapy may be used in patients who are unable to tolerate the procedure.⁵

Gastrointestinal iron absorption also is greatly increased in patients with ineffective erythropoiesis such as thalassemia intermedia and in some red cell enzyme deficiencies, particularly pyruvate kinase deficiency. The pathophysiology may be related to elevated levels of GDF15, a bone marrow–derived factor that suppresses hepcidin expression.^{6,7} The resulting increased absorption of dietary iron can cause iron overload, which may be further exacerbated by periodic transfusions. Serial phlebotomy is impractical for many patients with congenital anemias because of the level of anemia, and chelation therapy is effective in reducing iron burden in these patients.^{8–11}

The remainder of this review focuses on the management of transfusional iron overload including monitoring and treatment with chelation. The majority of data regarding chelation therapy has been derived from the thalassemia population and is the focus of this review; important differences relevant to other transfused populations are highlighted where possible.

Toxicity related to iron overload

Free iron is toxic to cells; normally, in the body iron is tightly complexed with proteins, protecting the cells from free iron. The main storage complex of iron is ferritin, which is found principally in the liver, reticuloendothelial cells, and red cell precursors; small amounts of ferritin are also found in the blood, allowing for easy measurement. In plasma, iron is bound to transferrin, which transports iron to the cells. In iron overload states, high levels of iron exceed the iron-carrying capacity of transferrin within the plasma, leading to the formation of nontransferrin-bound iron forms.¹² These nontransferrin-bound iron forms can be taken up into cells, including liver, heart, and endocrine cells, where the iron can participate in the generation of free radicals through Fenton's reaction:



These free radicals cause lipid peroxidation and organelle damage leading to organ toxicity. The organs most susceptible to iron-related injury include the heart, liver, and endocrine organs. Cardiac toxicity includes congestive heart failure and arrhythmias and is the leading cause of death related to iron overload in patients with thalassemia major.¹³ Excess iron deposition in the liver leads to inflammation, fibrosis, and cirrhosis,¹⁴ which may be further exacerbated by concomitant viral hepatitis, alcohol use, and other hepatotoxins. Iron is also toxic to the endocrine organs, leading to growth failure, delayed puberty,¹⁵ hypogonadotropic hypogonadism, diabetes mellitus, osteopenia, hypothyroidism, and hypoparathyroidism.¹⁶ Endocrinopathies are a significant cause of morbidity in chronically transfused patients: among 342 North American patients with transfusion-dependent thalassemia, 38% had at least one endocrinopathy, most commonly hypogonadism, and the prevalence of endocrine abnormalities increased with age.¹⁶ Similarly, in a French cohort of 215 chronically transfused patients with thalassemia, 47.8% had hypogonadism, 6% diabetes, and 9.9% hypothyroidism.¹⁷

Monitoring iron burden

Multiple methods of assessing the degree of iron overload exist, and each method has benefits and limitations. In clinical practice, combinations of the different techniques and serial measurements are utilized to assess iron burden and to adjust chelation therapy. Tables 1 and 2 provide a summary of the clinical implications of various iron measurements.

Serum ferritin level can be measured frequently via blood testing and is particularly useful to monitor trends in iron burden over time. The ferritin level correlates with total body iron burden in chronically transfused patients, although this correlation is not precise.¹⁸ Furthermore, changes in the serum ferritin level in response to chelation have been shown to parallel changes in liver iron concentration measured by both liver biopsy and noninvasive means.^{19,20} The ferritin level also has prognostic significance: sustained levels of over 2500 mg/mL are associated with an increased risk of cardiac toxicity and death in patients with thalassemia.^{21,22}

Unfortunately, a variety of disease states, including infection, inflammation, and ascorbate deficiency, can either raise or lower serum ferritin levels. This limitation of ferritin in predicting iron stores is particularly relevant for patients with sickle cell disease. For example, great variability in the rate of rise of serum ferritin level was evidenced among 50 children with sickle cell disease receiving similar transfusion programs

Table 1 Clinical implication of ferritin levels and liver iron concentration

Liver iron concentration (mg/g dw)	Ferritin level ^a (ng/mL)	Clinical implications
<2	<500	Low iron stores; consider decreasing or holding chelation temporarily ^b
2–7	500–1499	Ideal range; continue current chelation
>7–15	1500–2500	Increased iron stores; increase chelator dose ^c and/or change chelator if ferritin and/or liver iron trend is not improving
>15	>2500	Elevated iron stores associated with increased risk of complications and death; increase chelator dose ^c and/or change chelator; consider combination chelation therapy

Notes: ^aFerritin should be obtained when patient is clinically well and vitamin C replete; ^bchelation should not be held if cardiac iron loading is present (cardiac T2* <20 ms) ; ^cchelator dose should not exceed approved range (see Table 3).

for primary stroke prevention.²³ Despite this limitation, the serum ferritin level still may be useful in sickle cell disease: very high ferritin levels above 3000 ng/mL generally predict a liver iron concentration of 10 mg/g dry weight (dw) or higher, while ferritin levels below 1500 ng/mL usually correlate with a liver iron concentration below 10 mg/g dw.²⁴ Serum ferritin level also underestimates liver iron concentration in patients with thalassemia intermedia and nontransfusion-associated iron overload.²⁵

Given that the liver is the major target organ for iron accumulation following multiple transfusions, the liver iron concentration is a good indicator of total iron burden.²⁶ In untransfused individuals, the normal liver iron concentration

Table 2 Clinical implications of cardiac iron assessment by T2* magnetic resonance imaging

Cardiac T2* (ms)	Clinical implication
≥20	No significant cardiac iron loading; continue current chelation
10 to <20	Mild to moderate cardiac iron loading with increased risk of cardiac complications; consider intensification of chelation such as increased dose ^a and/or continuous infusion (for deferoxamine); combination therapy with deferiprone and deferoxamine if available
<10	Severe cardiac iron loading with high risk of cardiac complications; intensify chelation such as increased dose ^a and/or continuous infusion (for deferoxamine); combination therapy with deferiprone and deferoxamine if available

Note: ^aChelator dose should not exceed approved range (see Table 3).

ranges from 0.17 to 1.8 mg Fe/g dw. Traditionally, chelation therapy has been dosed to maintain slightly higher liver iron concentrations of 3 to <7 mg Fe/g dw of liver, a level of hepatic iron burden that is seen in asymptomatic heterozygotes for hereditary hemochromatosis.²⁷ More aggressive chelation regimens have been advocated recently, with a goal to achieve and maintain “normal” body iron stores,²⁸ although the risk of toxicity with “overchelation” must be considered. Liver iron concentration also has prognostic significance in patients with thalassemia. Levels in excess of 15 mg Fe/g dw of liver are associated with an increased risk of cardiac complications and death,^{21,22} although the inverse is not always true: high levels of cardiac iron and iron-related cardiac disease can be seen despite low liver iron concentrations, due to differential rates of iron loading and unloading in these organs.^{29,30}

Various methods are available to estimate liver iron concentration. Liver biopsy is generally considered to be the gold standard for accurate iron measurement and allows for direct assessment of liver inflammation and fibrosis. However, a number of limitations to liver biopsy exist: it is an invasive procedure, with risks including bleeding, bile leak, and pain; liver fibrosis and cirrhosis cause an uneven distribution of iron, which may lead to an underestimation of liver iron in patients with advanced liver disease;³¹ and sample size also affects the accuracy of iron measurement – samples that are at least 1 mg dw correlate better with iron burden than do smaller samples.²⁶

The superconducting quantum interference device (SQUID) technique uses magnetometers to measure very small magnetic fields and can be used as a noninvasive technique to measure ferritin and hemosiderin in the liver.³² Estimation of liver iron concentration by SQUID correlates linearly with concentrations measured by liver biopsy.³² Since this is a noninvasive technique, repetitive iron concentration measurements by SQUID have been utilized to monitor the efficacy of chelation in a number of studies.^{20,33–35} The biggest limitation to using SQUID is that it is a highly specialized and expensive approach and few sites worldwide offer the technology, limiting its accessibility to patients. In recent clinical trials, SQUID measurements also underestimated liver iron concentrations obtained by biopsy by approximately 50%,¹⁹ though the correlation is good when accurate conversion factors from wet to dry weight of liver are utilized.³⁶

Magnetic resonance imaging (MRI) is increasingly being used to monitor iron overload. This technique takes advantage of local inhomogeneities of the magnetic field caused by iron deposition in tissues.³⁷ Magnetic resonance

images darken at a rate proportional to the iron concentration. T2 and T2* refer to the half-life of darkening and these values are inversely proportional to the amount of iron accumulation in the organ. The reciprocals of T2 and T2*, known as R2 and R2*, respectively, refer to rates of signal decay and are directly proportional to iron concentration.³⁸ While MRI has been used to estimate iron levels in a variety of organs including the pituitary, pancreas, and bone marrow, it is most commonly used to measure hepatic³⁹ and cardiac iron.^{29,40} Studies using R2 to estimate liver iron have shown good correlation with iron levels determined by liver biopsy, as well as reproducibility across different scanners.³⁹ Other approaches using T2* or R2* are also promising for determining liver iron content.^{29,41}

Most important, cardiac iron levels also can be estimated using MRI, most commonly with T2* measurements. Determination of cardiac iron is particularly helpful because cardiac disease is the leading cause of death in patients with thalassemia and transfusional iron overload.¹³ Cardiac T2* values below 20 ms indicate mild to moderate cardiac iron overload, while levels below 10 ms are associated with an increased risk of cardiac disease including ventricular dysfunction and arrhythmias (Table 2).^{29,40} Patients with T2* values below 6 ms have a 47% chance of developing congestive heart failure within the next year.⁴² Thus, patients with low cardiac T2* values require intensification of chelation therapy.

Magnetic resonance scanners are more widely available than SQUID, and this technique is now available in many sites throughout the world. Limitations include the need for specialized programming and expertise in these MRI techniques. In addition, MRI is costly, making frequent monitoring prohibitive.

Most knowledge of the complications of iron overload comes from patients with thalassemia who require lifelong red blood cell transfusions, which are usually initiated within the first few years of life. Patients with different diseases requiring chronic transfusions, particularly sickle cell disease and Diamond–Blackfan anemia, appear to differ somewhat with respect to organ-specific transfusional iron loading.^{43–45} For example, iron-related cardiomyopathy and diabetes are less common in sickle cell disease than thalassemia despite comparable transfusion burdens,^{43,46} a finding that is paralleled by reduced iron loading in the heart and pancreas in sickle cell patients.^{44,47} In contrast, it was observed that liver iron concentration was higher in transfusion-dependent Diamond–Blackfan anemia patients than in thalassemia patients matched for age and iron intake.⁴⁵ Variability in

the duration of iron exposure, treatment with chelation, or processing of iron among underlying disease states may all contribute to the differences in organ-specific iron loading. Nonetheless, given the lack of substantial information about disease-specific responses to iron overload, data from the thalassemia population continue to guide monitoring and treatment for other transfused patient populations, although ongoing research studies may provide future insight into better disease-specific approaches.

Overview of chelation

The goal of chelation therapy is to maintain “safe” body iron levels to prevent the development of organ toxicities. Ideally, for patients who are regularly transfused, chelation should be administered in a manner to prevent excess iron accumulation by matching the ongoing transfusional iron intake. Chelators also bind nontransferrin-bound iron forms, protecting vulnerable organs such as the heart from damage by these toxic iron forms, and continuous chelator exposure is optimal in this regard. In practice, however, chelation therapy is often utilized to remove excess stored iron. Once iron-related organ toxicity has developed, chelation therapy can reverse some, but not all, of the complications.^{28,48}

Differential properties of chelators

A variety of factors differentiate the currently available iron chelators. First, pharmacological properties, including the stoichiometry of iron chelation, mode of administration, dosing schedule, plasma half-life, and route of excretion, vary among chelators. Second, drug efficacy is variable, particularly with regard to organ-specific (hepatic, cardiac) iron removal. Third, adverse-effect profiles differ among chelators. These various drug properties ultimately contribute to patient adherence, overall control of iron burden, and the complication profile. Differential properties of the iron chelators are summarized in Table 3 and the following sections provide detailed information for each of the currently available iron chelators. Chelation therapy needs to be individualized; the choice of chelator(s) and dosing should be made based on: drug availability and tolerability (including adverse effects), patient preference and ability to adhere to the regimen, ongoing transfusion burden, and trends in organ-specific iron loading.

Deferoxamine

Pharmacology

Deferoxamine, a naturally occurring iron chelator produced by *Streptomyces pilosus*, was the first approved iron chelator

Table 3 Properties of iron chelators

Property	Deferoxamine	Deferasirox	Deferiprone
Stoichiometry (chelator: iron)	Hexadentate (1:1)	Tridentate (2:1)	Bidentate (3:1)
Usual dose	25–60 mg/kg/day over 8–24 hours	20–40 mg/kg/day once daily	75–100 mg/kg/day in three divided doses
Route of administration	Subcutaneous, intravenous	Orally dispersible tablet	Oral tablet or suspension
Half-life	20–30 minutes	7–16 hours	1.5–2.5 hours
Excretion	Urinary, fecal	Fecal	Urinary
Ability to remove liver iron	+++	+++	++*
Ability to remove cardiac iron	++ [#]	++**	+++
Typical adverse events	Local reactions Sensorineural hearing loss Ophthalmic changes Allergic reactions Bone abnormalities Increased risk of <i>Yersinia</i> and <i>Klebsiella</i> infections Pulmonary at high doses Neurological at high doses	Gastrointestinal Rash Rise in creatinine Proteinuria Elevated hepatic enzymes Gastrointestinal bleeding (rare) Fulminant hepatic failure (rare) Renal insufficiency (rare)	Gastrointestinal Neutropenia/Agranulocytosis Arthralgia Elevated hepatic enzymes
Availability	Licensed	Licensed	Licensed in Europe and Asia as second-line agent; not licensed in North America

Notes: *Reports of insufficient liver iron removal in some patients at doses of 75 mg/kg/day, but higher dosing, especially for subjects with high transfusional iron burden may be more effective; [#]with continuous infusion; **data are limited regarding efficacy with very low cardiac T2* and in heart failure; cardiac iron removal also may be less effective in patients with high liver iron concentration.

and has been used in routine clinical practice for more than 40 years.⁴⁹ It is a hexadentate iron chelator that binds iron stably in a 1:1 ratio (Table 3). Deferoxamine is not well absorbed from the gastrointestinal tract so it must be administered parenterally.⁵⁰ Furthermore, the drug's plasma half-life is very short at approximately 20 minutes.⁵⁰ Thus, deferoxamine is usually administered as a continuous infusion of 25 to 50 mg/kg given over 8 to 12 hours, 5 to 7 days per week either subcutaneously or intravenously. Because the drug's half-life is short, the chelator is rapidly cleared after the infusion is completed and the drug is no longer available to bind and detoxify iron. Thus, intravenous administration of longer durations of up to 24 hours daily is often employed for patients with high iron burden and/or evidence of cardiac iron loading or iron-related cardiac toxicity. Very high dosing of deferoxamine (such as 10 mg/kg/hour) has been utilized in the past.⁵¹ However, acute pulmonary and neurotoxicity may develop with higher doses,^{52,53} so, in general, doses >60 mg/kg/day should be avoided. Excretion of iron bound to deferoxamine occurs through both the urine and feces.

The parenteral mode of administration is painful and time consuming, which can adversely affect treatment adherence. To overcome this limitation, alternative modes of administration have been investigated. Twice-daily bolus injections of 1000 mg of deferoxamine diluted in 10 mL of distilled water have been

administered. Iron excretion with bolus injection was similar to that seen with subcutaneous infusion.⁵⁴ Unfortunately, painful swelling that lasted for several hours following injection led many patients to discontinue this treatment⁵⁵ and, thus, this mode of administration is infrequently utilized.

Efficacy

The efficacy of deferoxamine is well established. The drug induces substantial iron excretion and can induce a net negative iron balance⁵⁶ in chronically transfused patients. Iron excretion is hindered in the presence of vitamin C deficiency, a common consequence of iron overload. Oral supplementation with vitamin C increases urinary iron excretion with deferoxamine, but excessive vitamin C can also increase the toxicity of iron.⁵⁷ Thus, patients with documented vitamin C deficiency are usually treated with 100 mg of vitamin C orally, given only at the time of deferoxamine infusion. Multiple studies dating back over three decades have shown that regular administration of deferoxamine effectively lowers serum ferritin levels.^{19,58,59} Chelation therapy with deferoxamine can also prevent other organ toxicities such as diabetes and other endocrinopathies.^{49,60}

Hepatic iron removal

In the 1970s, regular intramuscular administration of deferoxamine therapy was shown to reduce hepatic iron

accumulation and slow the progression of hepatic fibrosis.⁶¹ Subsequently, in the early 1980s, daily subcutaneous continuous infusion of deferoxamine was shown to reduce hepatic iron content to normal or near-normal levels in chronically transfused patients with thalassemia.⁶² Recent clinical trials have continued to show the efficacy of deferoxamine in hepatic iron removal in patients with transfusion-dependent anemias.^{19,20} Nonetheless, the improvement in liver iron concentration correlates with the rate of transfusional iron intake.¹ Patients with higher transfusional iron intake generally require more chelator, which may be achieved by administering deferoxamine for a greater number of days per week and/or at the higher end of the therapeutic dose range.

Cardiac iron removal

Most important, the regular use of deferoxamine is associated with a reduced incidence of cardiac complications and death.^{21,49,59} In addition, deferoxamine, usually given in higher doses up to 60 mg/kg/day as a continuous intravenous infusion, can reverse cardiac complications.⁶³ Cardiac iron burden as measured by T2* MRI also improves with continuous infusion of deferoxamine.⁴⁸

Adverse effects

Local infusion site reactions, including induration and erythema, are commonly seen with administration of deferoxamine. Allergic reactions can also develop. Other adverse effects – including high-frequency hearing loss; ophthalmologic toxicity;⁶⁴ growth retardation; and skeletal changes, including rickets-like lesions and genu valgum in growing children⁶⁵ – are more common when patients receive high doses of deferoxamine relative to their total body iron burden. Ocular and audiological toxicity can be minimized by maintaining a ratio of deferoxamine dose (mg per kg of body weight) to the serum ferritin level below 0.025.⁶⁶ Increased risk of infection with *Yersinia* and *Klebsiella* species in patients with iron overload may be exacerbated by use of this chelator.^{67,68} Low zinc levels can also develop with deferoxamine use, and levels of this trace element should be measured periodically. Acute pulmonary toxicity with respiratory distress, hypoxemia, and a diffuse interstitial pattern on chest roentgenogram, and acute neurotoxicity have both been reported with the administration of very high doses of deferoxamine (10–20 mg/kg/hr).^{52,53}

Adherence

The greatest challenge with deferoxamine is patient adherence, because the need for parenteral administration

is cumbersome, uncomfortable, inconvenient, and time consuming. A recent review of published studies showed compliance rates with deferoxamine to range from 59% to 78%.⁶⁹ Older age⁷⁰ and concomitant psychiatric disorders⁷¹ have been found to predict poor adherence. Patient-reported reasons for missing deferoxamine doses included patients' feelings and beliefs, adverse effects, and lack of support from others.⁷⁰ Considerable morbidity and preventable, premature iron-related deaths continue to occur in patients treated with deferoxamine, which are probably related to difficulties with adherence.^{72,73}

Deferiprone

Pharmacology

Deferiprone (1,2-dimethyl-3-hydroxypyrid-4-one), introduced into clinical trials in the 1980s, was the first oral chelator to undergo extensive testing. This chelator was designed by modifying siderophore chemistry.⁷⁴ Most studies of the drug have involved open-label, noncomparative studies, often including patients with a history of inadequate iron chelation, but a few randomized trials comparing deferiprone with deferoxamine have been reported. A substantial amount of data on the safety and efficacy of the drug has been acquired but considerable controversy surrounds the drug. Deferiprone is approved for use in the European Union and other countries for patients in whom deferoxamine therapy is inadequate or not tolerated, but the drug has not been approved for use in North America and is currently only available to a limited number of patients through compassionate use programs or research trials.

Deferiprone is a bidentate chelator, meaning that three molecules of the drug are required to bind iron fully. Given its relatively short plasma half-life of 1.5 to 2.5 hours,^{75,76} the drug usually is dosed three times daily. The typical daily dose is 75 mg/kg, but doses of up to 100 mg/kg/day are approved in Europe. The drug is available as 500 mg tablets or as an oral solution (100 mg/mL), which has been shown to have a similar safety and efficacy profile to the tablet form.⁷⁷ Deferiprone induces iron excretion almost exclusively in the urine, with minimal contribution from fecal elimination.^{78,79}

Efficacy

Urinary iron excretion with deferiprone at doses of 75 mg/kg is comparable to that induced by deferoxamine at a dose of 50 mg/kg.^{78,79} The mean urinary iron excretion with deferiprone at 75 mg/kg was 0.48 mg/kg/day in one study,⁷⁸ a level that would be predicted to maintain or

decrease iron stores in most patients; however, significant interpatient variability exists. Higher doses of deferiprone, 90–119 mg/kg, induced greater urinary iron excretion and may be beneficial for patients with inadequate responses at lower doses.^{80–82} Current European product labeling, however, cautions against using doses above 100 mg/kg/day due to the potential for increased toxicity.

Short- and long-term studies of treatment with deferiprone for transfusional iron overload have generally shown a reduction^{35,80,83–86} or stabilization^{87–89} in mean serum ferritin levels. Similar responses have been shown across different disease states including sickle cell disease and thalassemia. However, a small proportion of patients demonstrated a significant increase in serum ferritin levels while receiving long-term deferiprone.^{35,86,88,89} In a group of 151 Italian patients who received deferiprone for 3 years or more, 20% had clinically significant rises in ferritin levels.⁸⁶

Hepatic iron removal

Studies on the effect of chelation with deferiprone on liver iron concentration have also shown mixed results.^{35,84,88,90,91} In a report of 21 patients who received deferiprone at 75 mg/kg/day, mean liver iron concentration assessed by biopsy or SQUID, decreased from 15 to 8.7 mg/g dw liver, after a mean treatment duration of 3.1 years.³⁵ With longer follow-up of a mean of 4.6 years in 18 patients, there was an overall reduction in liver iron concentration from baseline (16.5–12.1 mg/g dw, $P = 0.07$), but the liver iron concentration still remained at a concerning level above 15 mg/g dw in seven patients.⁹¹ In another report of 20 patients who received deferiprone (70 mg/kg/day) for 1 year or more, the mean liver iron concentration increased from 16 to 21 mg/g dw, although this change did not reach statistical significance.⁹⁰ Liver iron content decreased in seven patients, rose in 12 patients, and remained the same in one patient. Thus, chelation with deferiprone at a dose of 70–75 mg/kg/day may not reduce liver iron concentration effectively in some patients.

Although there are few randomized trials comparing deferiprone with deferoxamine, these studies have generally shown the two drugs have comparable efficacy with regard to hepatic iron removal. In one study of 144 subjects, the reduction in serum ferritin levels was similar between treatment groups (deferiprone 75 mg/kg/day compared with deferoxamine 50 mg/kg/day) and mean reduction in liver iron concentration was also similar among a subset of 36 subjects who underwent liver biopsy.⁸⁴ Similarly, in a more recent study of 61 patients randomized to receive either deferoxamine at 50 mg/kg/day for 5 days per week or deferiprone

(75 mg/kg/day initially, then increasing to 100 mg/kg/day) changes in liver iron concentration over the 1-year period did not significantly differ between the two groups.⁹²

The lack of reduction in serum ferritin levels or liver iron concentration in some patients receiving deferiprone may be explained by a variety of reasons including individual differences in pharmacokinetics, inadequate adherence with therapy, or higher transfusional iron intake. Increasing the dosage of deferiprone might help overcome some of these issues. In one study, increasing the daily dose of deferiprone from 75 mg/kg to 83–100 mg/kg resulted in a reduction in serum ferritin level in nine patients who had received inadequate chelation at the lower dose.⁸² Similarly, in a study of twelve transfused thalassemia patients, the mean serum ferritin level significantly improved from 3901 ng/mL to 2205 ng/mL after 2 years of treatment with deferiprone at 100 mg/kg/day and no increased toxicity was observed.⁹³

Cardiac iron removal

Deferiprone is a small molecule that is lipophilic, enabling entry into myocytes, and this chelator appears to be particularly efficacious in cardiac iron removal. Retrospective studies have demonstrated reduced cardiac morbidity and mortality^{94,95} and lower myocardial iron deposition⁹⁶ among patients treated with deferiprone compared with deferoxamine. Furthermore, in a randomized controlled trial of 61 beta-thalassemia patients with moderate cardiac siderosis ($T2^*$ 8 to <20 ms) and normal cardiac function, a significantly greater improvement in cardiac $T2^*$ and left ventricular function was seen with treatment with deferiprone compared with deferoxamine.⁹² In a large clinical observational study, treatment with deferiprone resulted in improvement in cardiac $T2^*$ among patients with all degrees of cardiac iron loading (including severe iron loading with $T2^* < 8$ ms) and treatment with deferiprone resulted in a significantly greater overall reduction in cardiac iron compared with deferasirox.⁹⁷

Adverse effects

The most serious adverse event associated with deferiprone is agranulocytosis. In a multicenter study of 187 patients with thalassemia major treated with deferiprone in which weekly blood counts were monitored, the incidence of agranulocytosis (absolute neutrophil count $< 500 \times 10^9/L$) was 0.6 per 100 patient-years and the incidence of milder neutropenia (absolute neutrophil count 500 to $1500 \times 10^9/L$) was 2.8 per 100 patient-years.⁸⁷ In the largest study reported to date, similar rates of

0.2 per 100 patient-years for agranulocytosis and 2.1 per 100 for neutropenia were reported.⁸⁶ Neutropenia is usually reversible with discontinuation of the drug but often recurs with reinstatement of therapy.^{86,98} In clinical practice, weekly blood counts are recommended, which can be inconvenient for patients, to monitor for this side effect. Treatment with deferiprone may not be appropriate for patients with underlying bone-marrow failure syndromes, such as Diamond–Blackfan anemia or myelodysplastic syndromes, who may be more likely to develop agranulocytosis or neutropenia.^{99,100} Similarly, caution should be exercised when using this drug in combination with hydroxyurea, interferon, or other drugs that can cause neutropenia.

Gastrointestinal symptoms including nausea, vomiting, diarrhea, and abdominal pain are common side effects reported with deferiprone, occurring in 33% of subjects in one large study.⁸⁹ These symptoms usually improve after the first few weeks of treatment and rarely require discontinuation of therapy.^{86,87} Arthropathy with pain and/or swelling of the knees and other large joints is another common complication, and can occur early or late in treatment.^{85,86,89} In a large study of 532 patients, the prevalence of this complication was only 4%,⁸⁶ but other studies have reported higher rates of up to 38.5%.⁸⁰ The arthropathy is usually reversible with discontinuation of the drug.^{80,87} Low plasma zinc levels have also developed in a minority of patients receiving deferiprone, thus periodic monitoring of zinc levels is warranted.^{80,87}

Elevations in serum alanine aminotransferase (ALT) can occur with drug administration but are often transient and resolve even with continued drug administration at the same or reduced dose.^{85,86} Patients with hepatitis C infection^{86,87} or higher hepatic iron concentrations⁸⁶ may be more likely to develop ALT elevations. Concerns have been raised about the possible progression of hepatic fibrosis with deferiprone therapy.⁹¹ In a retrospective study, progression of hepatic fibrosis was seen among five of 14 patients after a mean duration of 2.3 years of treatment with deferiprone; four of the subjects with progression of fibrosis also had concomitant hepatitis C infection.⁹¹ In contrast, no fibrosis was seen in 12 subjects treated with deferoxamine, five of whom were hepatitis C seropositive.⁹¹ The contribution of deferiprone to the development of fibrosis in these patients is difficult to decipher given that the majority of subjects who developed fibrosis had concomitant hepatitis C infection, which can cause hepatic fibrosis itself. Furthermore, the effect of deferiprone on hepatic fibrosis has not been confirmed in follow-up studies.^{101,102} In the largest study to date, no significant progression of fibrosis was observed in 56 patients

(11 seropositive for hepatitis C) with liver biopsy specimens obtained before and after treatment with deferiprone at a mean interval of 3.1 years.¹⁰²

Adherence

In a review of studies assessing adherence with treatment with deferiprone, overall compliance ranged from 79% to 96%.⁶⁹ In these studies, adherence was monitored by pill counts, patient report, physician assessment, and/or medication event monitoring system. Similarly, comparative studies of adherence with deferoxamine versus deferiprone suggest overall better compliance with the oral chelator.⁶⁹

Deferasirox

Pharmacology

Deferasirox is the first oral iron chelator approved for use in the USA, and it has also been approved in a number of other countries (Table 3). Deferasirox, a triazole compound, was designed using computer-aided molecular modeling.¹⁰³ Deferasirox binds iron in a 2:1 ratio (tridentate chelator). The drug has a high specificity for iron, with minimal binding to copper and zinc. Deferasirox is supplied as orally dispersible tablets that are dissolved in water or juice and should be administered on an empty stomach at least 1/2 hour before a meal.¹⁰⁴ Deferasirox is rapidly absorbed, achieving peak plasma levels within 1–3 hours after administration. Its half-life ranges from 7 to 16 hours,³⁴ and is longer with higher doses,¹⁰³ supporting a once-daily dosing regimen. The deferasirox-iron complex is excreted almost exclusively in the feces, with minimal urinary excretion.¹⁰³ Mean iron excretion was 0.3 mg/kg/day with a deferasirox dose of 20 mg/kg and rose to 0.5 mg/kg/day with a 40 mg/kg dose.¹⁰⁵

Efficacy

Hepatic iron and ferritin levels

Deferasirox in doses of 20–30 mg/kg/day was shown to have similar efficacy to deferoxamine with regard to reduction in liver iron concentration and serum ferritin levels in a randomized trial of 586 patients with thalassemia major.¹⁹ In that trial, four different dose levels of deferasirox were tested (5, 10, 20, and 30 mg/kg), with initial dosing determined according to baseline liver iron concentration (lower doses for lower liver iron concentrations). A similar dosing algorithm was utilized for deferoxamine in that study, but subjects were allowed to remain on their prestudy deferoxamine dose, which resulted in proportionately higher deferoxamine than deferasirox

doses in the lowest two liver iron concentration groups. The primary objective of noninferiority of deferasirox to deferoxamine across all treatment groups was not attained, which was probably related to this relative underdosing of deferasirox in the lowest two dose groups. However, noninferiority of deferasirox was demonstrated at the 20 and 30 mg/kg dose groups. The average reduction in liver iron concentration over the 1-year treatment period with deferasirox at 20 or 30 mg/kg was 5.3 ± 8.0 mg/g dw, compared with a reduction of 4.3 ± 5.8 mg/g dw with deferoxamine, $P = 0.367$.¹⁹ Trends in serum ferritin levels over the course of the study paralleled the changes in liver iron concentration.

Phase II studies in patients with other transfusion-dependent anemias have demonstrated similar results. In a multicenter study, 195 patients with sickle cell disease were randomized to receive deferasirox (10–30 mg/kg/day) or deferoxamine (20 to ≥ 50 mg/kg, 5 days per week) with dosing based on the pretreatment liver iron content.²⁰ A mean reduction in liver iron concentration of 3 mg/g dw, was seen after 1 year of treatment with deferasirox, comparable to the decrease in liver iron concentration seen with deferoxamine (2.8 mg/g dw). Similarly, an overall significant reduction in liver iron concentration was seen in a Phase II study of 184 patients with myelodysplasia, thalassemia, Diamond–Blackfan anemia, and other rare transfusion-dependent anemias, in patients who received deferasirox at 20–30 mg/kg for a period of 1 year.²

Subsequent analyses have shown that the response to deferasirox is dependent on ongoing transfusional requirements. For most patients with transfusional iron intake averaging <0.3 mg/kg/day, a dose of 20 mg/kg of deferasirox was effective in reducing liver iron concentration, while in over 50% of patients with the highest iron intake of >0.5 mg/kg/day, the dose of 20 mg/kg/day did not reduce liver iron concentration effectively.¹ In addition to ongoing transfusional iron intake, individual variability in drug pharmacokinetics may impact response to deferasirox.¹⁰⁶ Both of these factors might be addressed by using higher doses of the drug. A subanalysis of 264 subjects treated with deferasirox at doses >30 mg/kg/day for a median duration of 36 months demonstrated a reduction in serum ferritin levels without increased toxicity.¹⁰⁷ Currently, doses of deferasirox of up to 40 mg/kg/day are approved for use. Dosing of deferasirox should be guided by the goal of maintenance or reduction of body iron stores, ongoing transfusional requirements, and trends in ferritin and liver iron content during treatment.

Cardiac iron removal

Early clinical data suggest that deferasirox is able to remove cardiac iron. In a prospective study of 114 patients with thalassemia and evidence of cardiac iron loading (cardiac T2* values of 5 to <20 ms) but normal left ventricular function, cardiac T2* significantly improved from a mean of 11.2 to 12.9 ms after 12 months of treatment with deferasirox at a mean dose of 32.6 mg/kg/day.¹⁰⁸ A further improvement in cardiac T2* to 14.8 ms was seen with an additional year of treatment at a mean dose of 36.1 mg/kg/day.¹⁰⁹ A concomitant significant reduction in serum ferritin levels and liver iron concentration was demonstrated. Interestingly, there was no significant improvement in left ventricular ejection fraction (LVEF) over the 2 years of study, although the ejection fraction was normal at baseline.¹⁰⁹ Nonetheless, significant improvement in LVEF has been demonstrated with deferiprone in a group of patients with a similar degree of cardiac iron loading and normal baseline LVEF,⁹² suggesting that deferiprone may cause a more rapid improvement in cardiac function than deferasirox. In a second study of 27 patients with thalassemia and cardiac T2* <20 ms with LVEF of 56% or higher, cardiac iron measurements improved by 16% ($P = 0.06$) following 18 months of treatment with deferasirox (mean ending dose of 33.3 mg/kg/day).¹¹⁰ However, cardiac T2* worsened in about 50% of these patients and this failure to respond was predicted by higher baseline liver iron concentration and ferritin levels.¹¹⁰ Similar to the previous study, no change in LVEF was seen over the 18 months of treatment. A third study of 19 patients with beta thalassemia and iron overload also demonstrated improvement in cardiac T2* over 18 months of treatment (17.2 to 21.5 ms).¹¹¹ Administration of deferasirox (mean dose 27.6 mg/kg/day) also can prevent cardiac iron accumulation; in 78 patients with thalassemia without evidence of cardiac iron loading (cardiac T2* ≥ 20 ms), cardiac T2* did not worsen over a year of treatment (32 to 32.5 ms).¹⁰⁸ Moreover, in that study, no subjects with normal cardiac T2* at baseline developed an abnormal study (T2* <20 ms) over the follow-up period.

The ability of deferasirox to reverse cardiac disease has not yet been investigated, as the prior studies all required normal left ventricular function for inclusion. A case report of a 15-year-old boy with beta thalassemia and congestive heart failure showed improvement in LVEF from 33% to 58% with 15 months of treatment with deferasirox at 30 mg/kg/day¹¹² and a second report showed normalization of LVEF following 3 years of treatment with deferasirox in a 22-year-old woman with severe aplastic anemia and

iron-related cardiac dysfunction (initial LVEF of 26.5%).¹¹³ Before a recommendation can be made regarding the use of deferasirox to treat patients with iron-related cardiac disease, prospective studies are needed that assess the rapidity and degree of cardiac iron removal, improvement in left ventricular function, and ability to reverse iron-related cardiac complications with deferasirox compared with other chelators.

Adverse effects

The toxicity profile of deferasirox generally is similar across disease states.^{2,19,20} Gastrointestinal disturbances, including nausea, vomiting, and abdominal pain are common.¹⁹ Although usually transient and dose related, these symptoms have led to discontinuation of the drug in some patients. The gastrointestinal side effects may be related to lactose intolerance in some patients because lactose is present in the drug preparation.²⁰ Diffuse, maculopapular skin rashes that usually resolve even if the drug is continued, have been reported in approximately 10% of subjects receiving deferasirox.^{19,20,33} Nephrotoxicity also can be seen with use of the drug. Approximately 33% of patients experience mild elevations in serum creatinine levels, although few patients have experienced elevations beyond the normal range.^{19,20} Rare reports of renal impairment and renal failure with deferasirox use have led to a black box warning about this side effect. Intermittent proteinuria has also been seen with the administration of the drug.¹⁹ Fanconi syndrome, a proximal renal tubular dysfunction leading to electrolyte abnormalities, has been reported in a several patients taking deferasirox, sometimes in the setting of acute illness; this toxicity resolved after discontinuation of the drug and recurred in some patients with reinstatement of the drug.^{114–116} Elevations in hepatic transaminases to more than five times baseline values also have been reported.^{19,20} Fulminant hepatic failure has also been reported in rare cases, often in patients with comorbidities. Gastrointestinal bleeding also has been reported rarely with deferasirox use. Although more common in older patients with significant comorbidities, this toxicity has been reported in children as well.¹¹⁷ Cataracts or lenticular opacities and audiototoxicity were reported at low rates, similar to deferoxamine.^{19,20} Importantly, agranulocytosis has not been seen with deferasirox administration and the rare reports of neutropenia with deferasirox were thought unlikely to be drug related but rather related to the underlying hematological disorder.

Adherence

Adherence with deferasirox therapy has been reported to be better than with deferoxamine.¹¹⁸ Similarly, patients reported

greater satisfaction and convenience with deferasirox in comparison with deferoxamine.¹¹⁹ In a preliminary report of patients participating in the Thalassemia Clinical Research Network comprised of subjects living in North America and London, UK, deferasirox was the most commonly used chelator at the time of enrollment (2007–2009), being taken by 57% of patients on chelation.¹¹⁸

Combination chelation therapy Deferiprone and deferoxamine

The most extensively studied combination chelation therapy is that of deferiprone and deferoxamine. A variety of dosing regimens have been utilized^{82,120,121} and iron balance studies have shown an additive effect when the two drugs are administered together. A significant reduction in serum ferritin levels was shown with combination therapy.^{120,121} Most important, the combination of deferoxamine and deferiprone appears to be particularly efficacious for cardiac iron removal and treatment of iron-related cardiac disease. A shuttling hypothesis, whereby deferiprone, a smaller molecule, enters cardiac cells, binds iron, and then transfers it to deferoxamine for excretion has been proposed.^{122,123} Significant reduction in cardiac iron stores measured by MRI,¹²¹ and significant improvement in left ventricular shortening fraction^{120,121} have been reported using combination therapy, without unexpected toxicities.

The largest randomized placebo-controlled clinical trial compared the use of deferoxamine alone or in combination with deferiprone in the treatment of 65 patients with mild to moderate cardiac iron loading (cardiac T2* 8–20 ms).¹²⁴ The beneficial effect of combined therapy on cardiac iron removal and improvement in cardiac function was confirmed. After a 12-month treatment period, those receiving combination therapy had significantly greater improvement in cardiac T2* (from 11.7 to 17.7 ms compared with 12.4 to 15.7 ms) and in LVEF (2.6% compared with 0.6%) than those receiving deferoxamine alone. Furthermore, in a single arm trial of 15 patients with severe myocardial siderosis (T2* <8 ms) and myocardial dysfunction, treatment with deferoxamine (mean dose 38 ± 10.2 mg/kg for 5.3 days/week) combined with deferiprone (73.9 ± 4 mg/kg/day) resulted in significant improvement in cardiac T2* (5.7 to 7.9 ms) and LVEF (51.2% to 65.6%) as well as a reduction in serum ferritin and liver iron concentration.¹²⁵ A second, smaller, prospective study of combination therapy with deferoxamine and deferiprone compared with deferoxamine monotherapy for patients with established cardiac disease showed a significantly lower rate of cardiac events in heavily iron-loaded patients treated

with combined therapy (no events among nine subjects) compared with monotherapy (four cardiac events with three deaths among five subjects).¹²⁶ Similarly, prospective and retrospective analyses have supported that the combination of deferoxamine and deferiprone is superior to other chelators in reducing cardiac iron in clinical practice.^{97,127}

Deferasirox and deferoxamine

Limited data, consisting mostly of animal studies, small case series, and pilot studies, exist regarding treatment with deferasirox combined with deferoxamine. In an iron-overloaded gerbil model, the addition of deferoxamine to deferasirox did not cause any detectable increase in organ toxicity above treatment with deferasirox alone.¹²⁸ However, in that study, combination treatment with deferasirox and deferoxamine did not show additive iron excretion, suggesting that the chelators may simply compete for a common iron pool.¹²⁸ It is unclear if this will hold true in humans but sequential (administered on different days) rather than combination (administered on the same day) therapy would be expected to be a better strategy if the two chelators simply compete for a common iron pool. Such an approach could limit toxicity associated with each chelator and improve adherence.

Limited information is available regarding the use of sequential or combined therapy with deferoxamine and deferasirox in humans. In a retrospective study, seven patients with thalassemia and iron overload were treated with deferasirox (20–30 mg/kg/day) for 4 consecutive days followed by deferoxamine (20–40 mg/kg/day, subcutaneously over 8–12 hours) for 3 days with median treatment duration of 25 months (range 8–32 months).¹²⁹ A significant reduction in serum ferritin levels was evidenced and no patients experienced significant toxicity. In addition, overall costs were reduced because deferasirox was significantly more expensive than deferoxamine, even including the supplies needed for administration.

In a second preliminary report, 14 subjects with transfusion-dependent thalassemia with severe iron overload and/or evidence of organ dysfunction were treated prospectively with deferoxamine (35–50 mg/kg/day for 3–7 days/week) and deferasirox (20–30 mg/kg daily, 7 days/week).¹³⁰ In contrast to the previous report, the two drugs were given on the same days, rather than sequentially. After 26 weeks of combined therapy, a significant reduction in liver iron concentration from 12 to 10.6 mg/g dw was seen, but there was no significant change in myocardial T2*, ejection fraction, or serum ferritin. It remains to be seen whether these parameters

will improve with longer follow-up. One subject died from sepsis and one interrupted drug treatment secondary to abdominal pain, but no elevations in serum creatinine or ALT were seen. Additional safety and efficacy data are needed before clinical recommendations for the combination of deferasirox/deferoxamine can be made.

Deferasirox and deferiprone

Combination therapy with deferasirox and deferiprone would be particularly desirable, as it would avoid the use of parenteral therapy; however, data regarding such therapy are lacking. In one report, two subjects who experienced significant toxicity during monotherapy with each chelator (deferoxamine, deferiprone, and deferasirox) individually were treated with deferasirox (30 mg/kg/day) alternating with deferiprone (75–85 mg/kg/day).¹³¹ The toxicities experienced with monotherapy were not evidenced and iron burden improved or remained well controlled. In a second report, three subjects with severe cardiac iron loading (T2* <6 ms) were treated with deferasirox (20–40 mg/kg/day) and deferiprone (75–100 mg/kg/day) for 7 days/week.¹³² After a treatment duration of 7–28 months, a significant improvement in cardiac T2* was evidenced, but with worsening of liver iron concentration in one, and minimal to no improvement in the other two subjects. Adverse events included gastrointestinal upset and fluctuating transaminase levels, but renal dysfunction and neutropenia were not seen. Prospective studies are needed to determine the optimal dosing regimen, efficacy, and safety of this treatment approach.

Other oral chelators in development

FBS0701 is a new oral chelator that has undergone Phase I testing in patients with transfusion-dependent anemias.¹³³ The drug is a desferrithiocin derivative that has been modified to minimize nephrotoxicity. It binds iron in a ratio of two molecules of drug to one molecule of iron (tridentate). In a Phase Ib dose escalation study, FBS0701 was administered for a total of 7 days to patients with transfusion-dependent anemias; four different dose levels were tested (3, 8, 16, and 32 mg/kg).¹³³ The mean half-life was 16.2–21.3 hours, supportive of daily dosing. Adverse effects were rare and included urinary discoloration, headache, and gastrointestinal symptoms. One patient with sickle cell disease experienced a mild prolongation of the QTc on electrocardiogram, which was not clearly drug-related. One serious adverse event, hospitalization for vaso-occlusive pain, occurred in a patient with sickle cell disease, also thought to be unrelated to the

drug. Further studies are needed to determine the effect of FBS0701 on iron removal and a Phase II trial is ongoing.

Conclusion

Three iron chelators, deferoxamine, deferiprone, and deferasirox, have undergone extensive study and are in clinical use worldwide, although deferiprone is not currently approved for use in North America. Individual properties of the chelators, including efficacy at both cardiac and liver iron removal, adverse-effect profile, tolerability, and patient preference should be considered in tailoring an individual's chelation regimen. Trends in liver and cardiac iron burden and ongoing transfusional iron intake should be utilized to adjust the dosing of the chelator. Combination therapy with deferiprone and deferoxamine has been shown to be the most efficacious with regard to improvement in cardiac function and cardiac iron removal. Other chelator combinations require further study before routine clinical use can be recommended.

Disclosure

The author reports no conflicts of interest in this work.

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