



Iron chelation: an update

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Purpose of review

This review provides an update on advances in the area of iron chelation therapy, including new indications and uses of currently available agents, and preliminary data on potential new agents in development.

Recent findings

Two new oral agents, deferasirox and deferiprone, have become available in the last 8 years. These have been used at higher doses, in combination with the older agent desferrioxamine, and recent trials' data have shown efficacy in preventing or treating the toxicity associated with iron overload. Advances in measuring tissue iron noninvasively by magnetic resonance techniques have enhanced diagnostic capabilities and allowed for more precise measurement and monitoring of iron burden. The primary use of chelation has been transfusional iron overload. There is now an increasing body of evidence for the benefits of iron chelation in myelodysplasia, pre-stem cell transplantation, and potentially in the treatment of malignancies. Two new iron chelators are in development, one in phase 3 clinical trials and the other in preliminary animal studies.

Summary

The last decade has ushered in a new era in iron chelation therapy. Coupled with advances in tissue iron quantitation, there is tremendous promise of an individually tailored approach to chelation, and subsequent reduction in morbidity and mortality.

Keywords

combination therapy, deferasirox, deferiprone, new uses

INTRODUCTION

Over the last decade, iron chelation has undergone dramatic changes, with the approval by the US Food and Drug Administration of two novel, orally effective chelators, deferasirox (DFX) and deferiprone (DFP). Prior to this, parenteral desferrioxamine (DFO) was the only option available to individuals with transfusional hemosiderosis, and compliance was not optimal, resulting in increased morbidity and mortality. We have learned much about the efficacy, toxicity and long-term outcomes related to the use of these new chelators. Tremendous advances in our ability to quantify tissue iron by magnetic resonance techniques have facilitated a more rational and targeted approach, which has enabled individual tailoring of chelation. Improved protocols have been developed based on these data, including combination use, and are being implemented with success. Whereas the use of iron chelation was almost exclusively in transfusion-dependent patients with red cell disorders (mostly sickle cell anemia and thalassemia), newer indications have recently been better defined, such as non-transfusion-dependent thalassemia (NTDT)

and myelodysplastic syndromes (MDS). There are data to suggest that chelation may inhibit tumorigenesis. Finally, there is also anticipation of two additional novel agents, one under study in animal models and the other already in phase 3 clinical trials. It must be kept in mind that though more data continue to be published related to iron overload in other transfusion-dependent conditions, most studies to date have been in transfusion-dependent thalassemia, and most recommendations for chelation are made based on these data.

IRON BURDEN AND RELATED TOXICITY

Inherited hemochromatosis syndromes cause iron loading from increased intestinal absorption and are

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KEY POINTS

- New and improved MRI techniques allow more precise quantitation of body iron burden and differential tissue deposition.
- Therapy can be tailored based on regular assessments of tissue iron levels.
- New orally effective chelators have improved compliance with therapy.
- Combination therapy allows for intensification of chelation in those with higher iron burdens, as well as allowing for adequate chelation in those who have dose-limiting toxicity with a single agent.

usually managed by serial phlebotomy. At present, iron chelation is used primarily for transfusional iron overload, which results in a variety of conditions, including hemoglobinopathies (thalassemia and sickle cell anemia), hemolytic anemias (pyruvate kinase deficiency, spherocytosis), inherited and acquired marrow failure syndromes (Diamond–Blackfan anemia (DBA), congenital dyserythropoietic anemias (CDA), and aplastic anemia), and premalignant and malignant conditions (MDS, following myelosuppressive chemotherapy or stem cell transplantation). With each milliliter of packed red cells (PRBCs) containing approximately 1 mg of iron, transfusional siderosis usually results following about 20 transfusions (appropriately dosed based on size, one or two units of PRBC at a time). With the body unable to excrete excess iron, tissue deposition results, with ensuing organ dysfunction and manifestations including cardiac arrhythmias, congestive heart failure, diabetes, other endocrinopathies and hepatic fibrosis. Cardiac failure is the most frequent cause of death. Toxicity of free iron is mediated by the free radicals generated through the Fenton reaction.

ASSESSMENT OF BURDEN

In the last decade, our ability to quantify tissue iron using magnetic techniques has enabled markedly improved monitoring of iron burden and the ability to tailor chelation therapy based on serial measurements of iron in tissues, primarily the liver and the heart. Two magnetic resonance (MR) methods exist for assessing the liver iron concentration (LIC), measurement of R2 (Ferriscan) and R2*. R2 appears to be more sensitive at higher iron concentrations than R2*. Traditionally, the ideal range for LIC has been thought to be 3–7 mg/g dry weight (based on the range in which heterozygotes for hereditary

hemochromatosis have some excess iron but are asymptomatic) [1], but more recently there has been some advocacy for chelating down to near-normal LIC levels (<1.6 mg/g dry weight) [2]. MRI of the heart provides valuable functional information as well as assessment of myocardial iron by cardiac T2* (cT2*), with the desired range being above 20 milliseconds (ms). Cardiac T2* values under 10 ms are associated with high risk of both rhythm disturbances as well as contractile dysfunction [3]. More recent data has emphasized the lack of good correlation between the LIC and cT2* values. Differential deposition and chelation of iron is thought to be the reason, with the liver being first to load into and also easier to unload from [4]. The patient's underlying hematologic condition also seems to impact cardiac iron loading, with individuals with DBA seemingly more susceptible and those with sickle cell disease less so than patients with thalassemia major [5–7]. Finally, iron deposition in the pancreas [8] and pituitary [9] is being studied, with some prognostic implication, but these scans are not routinely done yet. There is very little debate on the lack of utility of the serum ferritin level in predicting the actual body iron burden, this marker showing poor correlation with liver and cardiac iron. Especially in inflammatory conditions such as sickle cell anemia, MDS and malignancy, elevation of this marker as an acute-phase reactant makes it even less reliable. MRI is now the recommended method of assessing iron in the tissues and this data should be used to make decisions regarding initiation and tailoring of chelation therapy.

IRON CHELATORS

At present, three iron chelators are approved for clinical use. This section will focus on the most recent trials which have used these agents, either singly or in combination. While information related to long-term efficacy and safety is available for DFO, such data are not available yet for the newer agents, DFX and DRP (see Table 1).

Desferrioxamine

This hexadentate molecule, which binds iron stably in a 1:1 ratio, has been in use for over 40 years and remains a valuable agent despite the cumbersome nature of its parenteral use. It has a mild toxicity profile, with local skin reactions and infections being the most common side effects. Ototoxicity, nephrotoxicity and visual impairment are also rare. While still used exclusively by some individuals, the availability of the oral agents has resulted in relegation of this agent to patients who have a high iron

Table 1. Chelators in clinical use

	Desferrioxamine	Deferasirox	Deferiprone
Structure, iron binding (chelator: iron)	Hexadentate, 1:1	Tridentate, 2:1	Bidentate, 3:1
Half-life	20–30 min	10–16 h	1.5–2.5 h
Route of administration, frequency	Parenteral i.v. or SQ, over 8–12 h, 5–7 nights a week SQ	Oral, once daily	Oral, in 3 divided doses
Iron excretion	Urinary and fecal	Fecal	Urinary
Dose range	30–60 mg/kg	10–40 mg/kg	75–100 mg/kg
Usual chelation application	Second or first choice as single agent, or in combination	Usually first choice, and in combination	Usually second choice, and in combination
Reported efficacy	Efficient hepatic and cardiac iron removal	More efficient clearance of hepatic iron, also effective in cardiac iron removal	More effective in removing cardiac iron, less efficient in hepatic iron clearance
Adverse events	Local and allergic reactions, optic neuritis, sensorineural hearing loss	Gastrointestinal upset, rash, hepatic and renal toxicity, proteinuria	Neutropenia/agranulocytosis, gastrointestinal upset, arthralgia/arthropathy, hepatotoxicity
Dose adjustment required if	Impaired renal function	Hepatic or renal toxicity	Hepatotoxicity

i.v., intravenous; SQ, subcutaneous.

burden, in whom it is used in combination with one of the other agents, and in individuals who need but are not able to tolerate higher doses of these agents.

Deferasirox

This tridentate molecule, which binds iron highly specifically in a 2:1 ratio, has been in clinical use for the last 8 years. Its advantages are oral administration, a longer half-life allowing for once-daily dosing and a relatively good toxicity profile. Common mild side-effects include transient skin rashes and gastrointestinal upset. Hepatic and renal toxicity may be seen at higher doses, and other rare toxicities include a Fanconi-like syndrome of hypophosphatemia, and cataracts. Initially used at doses of 20–30 mg/kg/day, studies have shown that it is safe at doses up to 40 mg/kg/day in individuals with high iron burden [10]. In longer-term studies over 5 years, DFX is able to reduce LIC in most patients with transfusion-dependent beta-thalassemia, when administered at a dose of 20 mg/kg/day or above, and is well tolerated without major toxicity [11]. It has been demonstrated to effectively reduce myocardial iron by T2* in the short and long term [12,13], though this seems to be dependent on the total body iron burden. In fact, some individuals with a very high LIC had some worsening of myocardial T2*. Interestingly, these studies did not show an improvement in cardiac function in the short term. The use of DFX for individuals with poor cardiac function is still being investigated.

Deferiprone

A bidentate chelator which binds iron in a 3:1 ratio, DFP was approved for use in the USA just 2 years ago, though it had been in use in other parts of the world for several years. It has a shorter half-life, requiring administration three times a day in doses of 75–100 mg/kg/day. Safety remains a concern with this agent, with significant toxicities including neutropenia, rare instances of agranulocytosis and arthropathy, all requiring interruption of therapy. Gastrointestinal and hepatic toxicity do not appear to be major limiting factors, with initial reports of hepatic fibrosis [14] not being confirmed in subsequent studies [15]. The efficacy of DFP in reducing LIC is variable, but is thought to be comparable to that of DFO [16]. The primary advantage of this agent appears to be its ability to enter cardiac myocytes and remove iron from these cells, resulting in improvement of cardiac T2*, myocardial function and a reduction in morbidity and mortality [17,18].

COMBINATION THERAPY

In situations when intensification of chelation is required for individuals with a very high burden, or with the occurrence of dose-limiting toxicity with single agents, combination therapy is used to increase iron excretion and reduce adverse effects. Moreover, with the improved means of quantifying tissue iron, tailoring chelation to individual needs based on the differential distribution of iron, as well as the proposed synergy between agents, has led to combinations of the chelators described above (see Table 2).

Table 2. Combination chelation therapy

Combination	DFX and add DFO	DFO and add DFP or DFP and add DFO	DFX and add DFP
Documented efficacy	Improvement in LIC as well as cardiac T2*	Improvement in cardiac T2* and cardiac function (LVEF), as well as decrease in LIC	??
Synergy	??	Yes	??
Indication	Rising LIC despite maximal DFX dosing, DFX dose limited by toxicity	Worsening cardiac T2* despite maximal DFO/DFP dosing, or to spare number of nightly DFO infusions per week	Possibly for worsening cardiac T2* despite maximal DFX dosing, DFX dose limited by toxicity
Regimens described	DFX 20–30 mg/kg with DFO 30–40 mg/kg, simultaneously or sequentially	DFO 30–40 mg/kg with DFP 75–100 mg/kg, various combinations used	DFX 20–40 mg/kg with DFP 75–100 mg/kg, concomitantly or alternating

DFO, desferrioxamine; DFP, deferiprone; DFX, deferasirox; LIC, liver iron concentration.

Desferrioxamine and deferiprone

DFO and DFP is the most extensively studied combination. Several different dosing schedules have been used, all of which seem to show a significant decline in serum ferritin [19,20], and more importantly, the combination demonstrated great efficacy at purging cardiac iron [21]. This is likely based on a hypothesis that DFP is able to enter cardiac myocytes and shuttle iron out into the plasma for DFO to bind and excrete [22]. A more recent study comparing this combination with DFO alone in thalassemia patients with heart failure did not demonstrate benefit to using the combination [23].

Desferrioxamine and deferasirox

Data on this combination are limited. In the animal model, it is safe and effective [24], and case reports and series in humans have confirmed these findings [25,26]. It does not seem that there is synergy, as with the previous combination, but the longer half-life of DFX would provide more continuous chelation and, therefore, possibly increased iron excretion overall. Dosing regimens have varied from sequential to concomitant, with no data-based consensus on an optimal regimen. More recently, a prospective study in 22 patients treated concomitantly with both agents demonstrated a significant improvement in systemic (as measured by LIC) and myocardial iron, also reducing the toxic labile plasma iron species [27].

Deferasirox and deferiprone

DFX and DFP would be the ideal combination as both agents are orally administered. However, once again, there are limited case report data on this combination [28,29]. Data from animal models in

which the combination has been used to chelate other metals such as mercury, cadmium, aluminum and chromium have shown few toxic effects.

NEW CHELATORS IN DEVELOPMENT

Two new agents are currently under study, but at very different levels of development. These are discussed briefly below:

SSP-004184

Previously termed FBS0701, this is a desferrithiocin derivative, a tridentate chelator, currently in phase 2/3 trials in several centers around the world. In the phase 1b study, it was found to be safe at four escalating doses, with a mean half-life of 16.2–21.3 h. It was administered once-daily for 7 days, with toxicity including headache, gastrointestinal symptoms and a mild prolongation of the QTc in one individual with sickle cell disease [30]. Current phase 2/3 studies in individuals with thalassemia and sickle cell anemia with transfusional siderosis are underway, but results of these trials are still some time away.

Deferitritin

Development of this tridentate chelator stalled initially when the animal models (rodent and primate) developed severe nephrotoxicity. Several modifications in the chemical structure of the molecule with numerically designated derivatives 2, 3, 6, 7, 8, 9 and 10 have been studied in animals [31,32]. Specifically, each ligand's iron-clearing efficacy (ICE), tissue distribution, biliary ferrokinetics and tissue iron reduction profile are being analyzed in both models. Once the appropriate molecule has

been synthesized, there is hope that it will move into human clinical trials.

INDICATIONS FOR IRON CHELATION

Traditionally, chelation has been used almost entirely for secondary hemosiderosis related to regular transfusions in individuals with inherited red cell abnormalities, predominantly transfusion-dependent thalassemia (major), sickle cell disease for treatment or prevention of stroke, and other conditions such as DBA and CDA. More recently, the scope of chelation has broadened considerably, to include a variety of other disorders, some with iron overload and others in which it appears that iron may play an important role in the pathophysiology of that condition.

Non-transfusion-dependent thalassemia

Individuals with the phenotype of thalassemia intermedia, including those with the various globin gene mutations, are not dependent on regular transfusions, but are at risk for developing iron overload as well. In addition to sporadic transfusions, these individuals load iron through increased intestinal absorption, mediated by the relative deficiency of hepcidin as a result of ineffective erythropoiesis [33]. The degree of iron loading depends on the number of transfusions and the degree of ineffective erythropoiesis, and is not predictable in these patients. A recent report confirms that the serum ferritin level, which was previously used exclusively to monitor these individuals, underestimates the degree of iron loading, and recommends MRI for a more accurate picture [34]. DFX at lower dose has been used effectively to reduce the iron burden in these patients in the short term, though a longer-term regimen has not been devised yet [35[¶]].

Myelodysplastic syndromes

There has been much attention focused on iron chelation in patients with MDS in the last few years. Although the major cause of siderosis is transfusional, ineffective erythropoiesis does contribute as well. No prospective studies of the effect of iron overload exist to date in this population, but there is some evidence of the benefit of chelation. In contrast to most patients with the transfusion-dependent anemias, those with MDS are older and have other preexisting morbidities, which may be exacerbated by the iron overload. A review of the epidemiology of MDS, the risk stratification, transfusion dependence rates and iron overload complications was published recently [36]. Several studies have

demonstrated the improved survival of individuals with a lower body iron burden [37], whereas others have found no correlation [38]. However, the majority of these studies relied on the serum ferritin level as the marker for iron overload. Those patients who received regular transfusions had higher rates of cardiac events than those who did not. Interestingly, several reports found no significant increase in iron deposition in the heart of these patients. The mechanism by which iron reduction may improve survival is not clear, possibly being related to improvement in organ function. In addition, there are data suggesting that chelation therapy and reduction in iron overload may actually improve tri-lineage hematopoiesis in these patients as well, with a reduction in transfusion requirements in many patients, some even achieving transfusion independence [39–43], believed to be related to a reduction in oxidative stress, increase in erythropoietin levels or inhibition of NF- κ B [44].

In the past, a minority of patients with MDS and transfusional siderosis received infusions of DFO. Systematic data are not available for the efficacy of chelation in those patients. More recently, systematic, prospective trials have used DFX in these patients with some success [45,46, 47[¶]]. Most studies reported a decrease in serum ferritin levels, but the major studies also reported that approximately 50% of patients discontinued chelation, some as a result of side-effects (similar to those described in the section on chelators) and others because of progression of MDS to leukemia. Future studies will focus on better evaluation of both tissue iron parameters as well as organ function in an effort to further define the role of chelation in MDS.

Pre-stem cell transplantation

The role of chelation before stem cell transplantation in patients with transfusional iron overload has also been further clarified. Previous studies, using serum ferritin values to define iron overload, showed improved outcomes in individuals with lower levels [48–50]. However, a recent prospective study in patients with MDS or acute leukemia undergoing stem cell transplantation found no correlation between iron burden, as measured by MRI methods, and mortality, relapse, or graft-versus-host disease [51]. Hyperferritinemia still correlated with poorer outcomes, raising the question of the true implication of this marker – inflammation or iron overload. It appears that the role of chelation in the pretransplant setting is now less certain than previously thought.

CONCLUSION

Significant advances in tissue iron quantitation by MRI techniques have changed our approach to transfusional iron overload in the last decade. Moreover, our understanding of the differential tissue deposition of iron and our ability to study the effects of non-transferrin bound iron, the labile plasma iron pool and reactive oxygen species in greater depth have allowed for a more rational approach to chelation. The introduction of two new oral iron chelators has improved outcomes, likely in most part because of improved compliance with therapy compared with the original parenteral chelator. Phase 3 and 4 trials of these chelators, and longitudinal studies of cohorts of patients have provided better protocols for dose modification, combination therapy and switching of chelators, all resulting in improved care of patients with transfusional iron overload and a reduction in morbidity and mortality. The promise of new chelators in development can be viewed with additional optimism for a new age in iron chelation therapy.

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Conflicts of interest

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The author is currently participating in the Phase 3 trial of the new chelator discussed (SSP-004184). No information from that participation is part of this article, and only already published data are presented related to this chelator.

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MDS is also a potential new indication for chelation. This study discusses the rationale and results of this trial.

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