Overview of Current Treatment Regimens in Iron Chelation Therapy

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Abstract

As humans have no physiological mechanism for the elimination of excess body iron, chronic red blood cell transfusion therapy, which is necessary for the treatment of a number of transfusion-dependent anemias, inevitably results in iron overload. Cumulative iron overload can lead to iron toxicity with organ dysfunction and damage, particularly affecting the liver and heart. Once iron overload has been identified in patients with transfusion-dependent anemias, it should be treated with chelation therapy to prevent and limit iron toxicity. Iron chelation with deferoxamine, deferiprone, and deferasirox has been demonstrated to reduce iron burden and the associated risk for morbidity and mortality from iron toxicity; however, there are important differences among these iron chelators.

Keywords

Transfusion, cardiac iron overload, deferasirox, sickle cell disease, myelodysplastic syndrome, transfusional iron overload, iron-chelating agents, iron toxicity, deferoxamine, deferiprone

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As a unique electron donor and acceptor, iron is an essential element in most biological systems. However, its chemical reactivity can result in iron potentially becoming a toxin when present in excessive quantities; accordingly, total body iron must be tightly regulated. As humans have no physiological mechanism for the elimination of excess iron, body iron is controlled mainly by the degree of absorption of dietary iron from the gastrointestinal tract. The regulation of body iron, including its absorption, transport in plasma by transferrin, and storage in a number of organs as ferritin, has been reviewed elsewhere.[1–4] Excessive accumulation of body iron can occur with prolonged intake of iron-containing supplements, with chronic liver disease, from some hereditary disorders of iron metabolism, from chronic ineffective erythropoiesis, and from multiple blood transfusions. This article will focus on the clinical significance of iron overload from chronic transfusion therapy and the role of iron chelation therapy to reduce excessive levels of body iron.

Clinical Significance of Iron Overload

Iron overload occurs when the binding capacity of transferrin for iron is surpassed, resulting in non-transferrin-bound iron (NTBI) circulating in the blood and the subsequent deposition and storage of free iron in tissues (see *Figure 1*). Excessive accumulation and storage of free iron in tissues over time can occur with chronic transfusion therapy in patients with transfusion-dependent anemias (e.g. aplastic or hypoplastic anemias, myelodysplastic syndromes, hemolytic anemias, hereditary hemoglobinopathies, hereditary red blood cell defects, and chronic blood loss) and following myeloablative allogeneic hematopoietic stem-cell transplantation. Iron overload is generally defined as serum ferritin levels consistently >1,000ng/ml,[5] a concentration that is likely to be detected after cumulative transfusions of about 100ml packed red blood cells/kg bodyweight.[6] As one unit of packed red blood cells has a volume of ~220ml (and corresponds to an excess of about 200mg of iron[7]), this translates to approximately 20 transfusions for a 40kg child or 10 transfusions for an 80kg adult. Iron toxicity can be defined as organ dysfunction and damage resulting from untreated iron overload.[1,8] The critical level of serum ferritin at which iron toxicity and organ dysfunction occur, the 'tipping point,' has not been definitively established and probably differs among patients as well as in different organs.[9] Iron overload, particularly affecting the liver or heart, is associated with poorer outcomes, is responsible for substantial morbidity, and is accompanied by increased mortality.[10,11] For example, in patients with sickle cell disease, iron overload is associated with cirrhosis and the development of cardiac dysfunction.[12] In transfusion-dependent patients with myelodysplastic syndromes, the probability of survival decreases significantly over time compared with that of patients who do not require transfusions.[13] In addition, survival decreases with increasing

red blood cell transfusion requirements,[14] and serum ferritin >1,000ng/ml is an adverse factor for survival even in lower-risk patients.[15] In patients undergoing myeloablative allogeneic hematopoietic stem-cell transplantation, an elevated pre-transplant serum ferritin level is an adverse prognostic marker for survival[16,17] and has been accompanied by an increase of acute graft-versus-host disease (GvHD), bloodstream infection, and mortality.[17] Iron overload after stem-cell transplantation also can mimic hepatic GvHD (resulting in unnecessary continuation or intensification of immunosuppressive therapy),[18] and is a predictive factor for poor stem-cell mobilization.[19]

In the liver, which is the major site of iron storage, iron overload is associated with oxidative damage to the DNA[20] and causes mitochondrial swelling and rupture of mitochondrial membranes of hepatocytes, leading to cell death.[21] Elevated serum ferritin and liver iron content are predictors of moderate to severe iron overload in the liver.[22] The main sequelae of excess iron deposition in the liver are fibrosis/cirrhosis and hepatocellular carcinoma,[23] and hepatic failure is a common cause of death.[10] In patients requiring chronic transfusion therapy, portal fibrosis can occur within two years of the first transfusion and cirrhosis within the first decade of life if excess iron is not removed.[23]

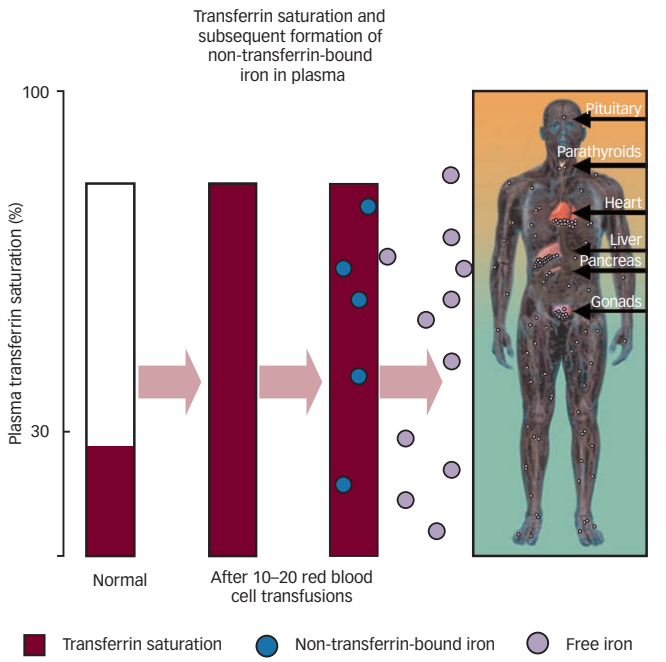
In the heart, free iron is toxic to cardiomyocytes even at extremely low concentrations. The potential mechanism is cardiomyocyte damage and loss of myofibers, with extensive iron deposition in lysosomes.[24] The most common form of cardiac injury due to iron overload is congestive cardiomyopathy,[25] and cardiac iron storage is also associated with an increased relative risk for impaired ventricular function. In patients with thalassemia major, the main cause of death is iron-mediated cardiomyopathy,[26] particularly congestive heart failure and fatal tachyarrhythmias[27] accompanied by elevated levels of NTBI.[28] However, cardiac iron burden often increases asymptomatically until a critical level is reached, after which systolic function can deteriorate rapidly.[29] In young patients with chronic transfusional requirements, serious consequences such as arrhythmias and/or refractory heart failure can occur as early as the second or third decade of life,[30] and survival without cardiac disease in thalassemia patients is related to a lower iron burden.[31] Older patients requiring chronic transfusion therapy also experience a high rate of cardiac events.[32] It should be noted that one recent literature review found a lack of consistency in terms of an association between body iron stores and cardiovascular disease in adults.[33]

To summarize, overwhelming evidence supports the observation that excessive storage of iron in body tissues over time among transfusion-dependent patients results in poorer outcomes, increased morbidity, and greater mortality, especially due to cardiac dysfunction.

Iron Chelation Therapy

Currently, the only way to prevent iron overload in patients requiring regular red blood cell transfusions is by long-term iron chelation therapy.[34] Management of iron overload and treatment of iron toxicity by chelation in patients with transfusion-dependent anemias has been shown to reduce iron burden and thereby improve outcomes and survival,[35] particularly by preventing cardiac mortality.[36] Oxygen and nitrogen atoms within iron-chelator molecules allow these agents to bind tightly with iron,[35] which is then excreted with the chelating agent. The three major factors to be considered when selecting an iron chelator are the route of administration, iron chelation efficiency, and the toxicity profile.[35] Ideally, an iron-chelating agent should be orally active, highly specific, safe, and economical. Three iron-chelating agents are currently available: deferoxamine mesylate (desferrioxamine, DFO, Desferal®), deferiprone (DFP, Ferriprox®), and deferasirox (ICL670, Exjade®); only deferoxamine and deferasirox are approved in the US (see *Table 1*).[34,37–39]

Figure 1: Progression of Iron Overload from Chronic Red Blood Cell Transfusion Therapy



Deferoxamine

As deferoxamine is poorly absorbed from the gastrointestinal tract, it must be parenterally administered, and because of its extremely short serum half-life of five to 10 minutes, most of the drug may be rapidly cleared after a single intramuscular injection without binding any iron. One treatment regimen for chronic iron overload calls for 500–1,000mg to be administered intramuscularly each day plus an additional 2,000mg to be infused intravenously with each unit of blood transfused, given separately from the blood.[40] Another regimen calls for continuous intravenous infusion through an implantable venous catheter.[41] An alternative regimen requires a daily dose of 1,000–2,000mg to be administered into the subcutaneous tissue of the abdomen over eight to 24 hours with a portable mini-infusion pump[40] or a balloon infuser.[34] When administered in this manner, deferoxamine effectively maintains normal or near normal iron stores.[42] However, low compliance with the prolonged subcutaneous administration of deferoxamine can result in ineffective treatment,[41] which is associated with substantial morbidity and mortality as well as increased costs.[43] In addition, the potential auditory, ocular, and neurological toxicity of deferoxamine[41] has led to guidelines for monitoring therapy including annual audiometric and eye examinations.[42] Growth and skeletal abnormalities may also occur.[40] Over 30 years of experience with deferoxamine have shown iron chelation to be an effective therapeutic modality in the management of transfusional iron overload.[44]

Table 1: Currently Available Iron-chelating Agents[34,37–39]

	Deferoxamine Mesylate (Desferrioxamine, DFO, Desferal®)	Deferiprone (DFP, Ferriprox®)	Deferasirox (ICL670, Exjade®)
US FDA-approved	Yes	No	Yes
MW of the active substance	656.8	139.2	373.4
Molar ratio of chelator:iron-binding	1:1	3:1	2:1
Route of administration	Parenteral	Oral	Oral
Plasma half-life	5–10 minutes	47–134 minutes	8–16 hours
Route of excretion	Urinary, fecal	Urinary	Fecal
Major side effects	Auditory, ocular, and neurological toxicity, growth and skeletal abnormalities	Neutropenia and agranulocytosis, musculoskeletal and joint pain, gastric intolerance, hepatic dysfunction, zinc deficiency	Gastrointestinal disturbances, rash, possibly renal toxicity
Advantages	Widely available, inexpensive, extensive clinical experience	Good chelation of cardiac and hepatic iron in general, inexpensive, extensive clinical experience	Good chelation of cardiac and heparin iron, no growth abnormality, no agranulocytosis, QD oral administration, indicated in children ≥2 years of age
Disadvantages	Inadequate chelation of cardiac iron, compliance problems	Variable chelation of cardiac or hepatic iron in some cases, weekly CBC testing necessary, TID dosing	Slurry solution volume may be distasteful for younger patients, monthly serum creatinine and ALT testing

FDA = Food and Drug Administration; MW = molecular weight; QD = every day; CBC = complete blood count; TID = three times daily; ALT = alanine aminotransferase.

Deferiprone

Deferiprone can be orally administered, but because it has a relatively short plasma half-life of 47–134 minutes, it must be taken three times daily.[41] The dose range is 75–100mg/kg/day, and the most frequently used dose is 25mg/kg three times daily. Although total iron excretion with deferiprone is somewhat less than with deferoxamine, deferiprone may remove cardiac iron more efficiently due to its ability to penetrate cell membranes, and it has been used in combination with deferoxamine.[36] Combining a weaker chelator such as deferiprone that has a better ability to penetrate cell membranes with a more efficient chelator such as deferoxamine that penetrates cells poorly may result in a better therapeutic effect by shuttling iron between the two agents and enhancing renal iron excretion.[36] Major side effects of deferiprone include neutropenia and agranulocytosis, musculoskeletal and joint pain, gastric intolerance, hepatic dysfunction, and zinc deficiency.[39,41] The risk for agranulocytosis requires a weekly complete blood count with differential,[42] and serum alanine aminotransferase (ALT) should be measured monthly for three to six months and then every six months. Due to its toxicity profile, deferiprone is currently licensed in Europe only for the treatment of thalassemia major when deferoxamine therapy is contraindicated or inadequate, with regional variations in indications elsewhere.[45]

Several retrospective clinical trials and one prospective clinical trial show an apparent benefit when combining deferiprone with deferoxamine in terms of the treatment of myocardial iron deposition.[46] Two recently reported studies are summarized below. First, Maggio et al. studied the long-term sequential administration of deferiprone and deferoxamine compared with deferiprone alone for iron overload in 213 patients with thalassemia major.[47] Deferiprone at 75mg/kg divided into three oral daily doses for four days per week and deferoxamine by subcutaneous infusion over eight to 12 hours at 50mg/kg per day for the remaining three days per week was compared with deferiprone alone at 75mg/kg per day divided into three daily oral doses administered seven days per week over a five-year period. The reduction in serum ferritin levels was significantly greater in patients treated with sequential deferiprone/deferoxamine compared with deferiprone-alone patients (p=0.005), with similar adverse events and cost. Second, Maggio et al. also studied the effect of different chelation regimens on survival among 265 patients with thalassemia major.[48] No deaths occurred among patients treated with deferiprone alone or with combined deferiprone–deferoxamine, and only one death occurred with sequential deferiprone–deferoxamine. In contrast, 10 deaths occurred among patients treated with deferoxamine only. In addition to treatment with deferoxamine, other risk factors for death were increasing patient age, female gender, and complications of iron deposition, including cirrhosis, arrhythmia, diabetes, hypogonadism, hypothyroidism, and a previous episode of heart failure.

Deferasirox

Deferasirox is administered orally once daily, as it has a long plasma half-life of eight to 16 hours, which provides 24-hour chelation with a single dose.[39,41] The recommended initial daily dose is 20mg/kg, taken on an empty stomach at least 30 minutes before food. Regular assessment of the iron burden is necessary to achieve the optimal dose. Efficacy has been good in various clinical trials.[39] Deferasirox is generally well-tolerated, with an acceptable safety profile in pediatric and adult patients; the most common adverse effects are gastrointestinal disturbances and rash. Pre-clinical studies in animals suggested that the kidney is a potential organ of toxicity when deferasirox is administered in high doses.[49] A one-year study comparing deferasirox with deferiprone in 195 pediatric and adult patients with sickle cell disease and normal baseline serum creatinine levels (sickle cell disease is often accompanied by abnormal renal function) identified mild, stable increases in serum creatinine accompanying treatment with each compound in about one-third of subjects.[50] Reversible mild increases in serum ALT were also noted in a small percentage of patients. Although these changes were not clinically relevant, there is a need to assess renal function, and serum creatinine (and ALT) should be monitored monthly.[42] Cost analyses comparing deferasirox with deferoxamine in the UK[51] and the US[52] concluded that deferasirox is cost-effective compared with standard parenteral iron chelation therapy with deferoxamine, primarily due to the quality of life benefits derived from the simpler and more convenient mode of oral administration.

Several phase II trials and a pivotal phase III trial have established that the efficacy of deferasirox is similar to that of deferoxamine in transfusion-dependent patients.[53] One-year results from the large, prospective, open-label, single-arm, multicenter Efficacy and Safety of Deferasirox in Patients with Transfusion-Dependent Anemias (EPIC) study support this conclusion.[54] In this study, patients receiving two to four units of packed red blood cells per month were treated with an initial dose of deferasirox of 20mg/kg/day. Patients receiving more frequent transfusions were considered for 30mg/kg/day, and those receiving less frequent transfusions were considered for 10mg/kg/day. Dose adjustments were made in 5–10mg/kg/day increments based on three-month serum ferritin trends. In EPIC patients with myelodysplastic syndromes, deferasirox for one year resulted in a significant reduction in serum ferritin. In a substudy of EPIC, deferasirox also removed iron from the heart in patients with β-thalassemia, based on a statistically significant improvement in T2(*) magnetic resonance imaging (MRI) without a decrease in left ventricular ejection fraction.[55] A number of recently reported studies are summarized below. Metzgeroth et al. reported a study of 12 patients treated with deferasirox 20–30mg/kg once daily for 12 months for transfusion-associated iron overload in myelodysplastic syndromes.[56] The results showed a significant reduction in liver iron concentration at one year, as well as a reduction in serum ferritin levels. In another study of deferasirox for iron overload in myelodysplastic syndromes, Wimazal et al. treated 14 patients with 500–1,500mg daily for up to 24 months.[57] Serum ferritin levels declined in all but one patient during therapy. Side effects were mild and tolerable, although treatment was discontinued in one patient because of impaired kidney function. In a retrospective study of 59 pediatric patients, most of whom were being treated with deferasirox for iron overload associated with sickle cell disease, Raphael et al. found the mean serum ferritin level to be 2,117ng/ml at baseline.[58] After treatment for 12 months, serum ferritin levels decreased in 44% of compliant patients and 11% of poorly compliant patients. Changes in serum creatinine and liver function tests were mild and did not result in long-term discontinuation of deferasirox. Taher et al. studied deferasirox in 252 heavily iron-overloaded patients with β-thalassemia in the ESCALATOR trial.[59] Most patients began treatment with 20mg/kg/day, and doses were then adjusted in response to markers of over- or under-chelation. After one year, 56.3% of patients (p=0.022) experienced a reduction of liver iron concentration ≥3mg iron/g dry weight of liver (the primary end-point). About 80% of patients underwent dose increases above 20mg/kg/day, primarily to 30mg/kg/day. Changes in serum ferritin appeared to parallel dose increases at around 24 weeks. Drug-related adverse events were mostly mild to moderate and resolved without discontinuing treatment. One recently published case report described a 15-year-old patient with β-thalassemia major and dilated cardiomyopathy due to iron overload who failed to respond to deferoxamine (presumably due to non-compliance).[60] After 15 months of treatment with deferasirox, the patient's left ventricular function normalized and his ejection fraction improved to 58%.

Conclusions

Iron chelation therapy plays a major role in reducing the morbidity and mortality associated with iron overload in patients receiving chronic transfusion therapy. Newer orally administered iron chelators with convenient dosing schedules and acceptable safety profiles appear to improve outcomes in these patients. ■

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