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Optimal Management Strategies for Chronic Iron Overload

James C. Barton

Southern Iron Disorders Center, Birmingham, Alabama, USA

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Abstract

Iron overload is characterised by excessive iron deposition and consequent injury and dysfunction of target organs, especially the heart, liver, anterior pituitary, pancreas and joints. Iron overload disorders are common worldwide and occur in most major race/ethnicity groups. Physiological mechanisms to excrete iron are very limited. Thus, all patients with iron overload need safe and effective treatment that is compatible with their co-existing medical conditions. Treatments for iron overload include phlebotomy and erythrocytapheresis that remove iron predominantly as haemoglobin, and chelation therapy with drugs that bind excess iron selectively and increase its excretion. The most important potential benefits of therapy are preventing deaths due to cardiac siderosis and hepatic cirrhosis. Preventing iron-related injury to endocrine organs is critical in children. Successful treatment or prevention of iron overload increases quality of life and survival in many patients. This article characterises the major categories of iron overload

disorders, tabulates methods to evaluate and treat iron overload, and describes treatment options for iron overload disorders. Research needed to advance knowledge about treatment of iron overload is proposed.

Iron overload is characterised by excessive iron deposition and consequent injury and dysfunction of target organs, especially the heart, liver, anterior pituitary, pancreas and joints.[1-3] Iron overload disorders are common worldwide and occur in most major race/ethnicity groups. Haemochromatosis typically occurs in Caucasians of western European descent; increased absorption of dietary iron is usually caused by mutations in genes encoding proteins that mediate or control iron absorption or storage.[4,5] In natives of sub-Saharan Africa, a hereditary factor and consumption of traditional beer containing iron cause iron overload;[6] a related group of disorders occurs in African Americans.[7,8] Most patients with β-thalassaemia, haemoglobin (Hb) E and sickle cell disease have Mediterranean, African, Asian or Arab ancestry; iron from transfused erythrocytes is the predominant cause of iron overload.[5] Some patients with hyporegenerative anaemia due to myelodysplastic syndromes (MDS) or rare inherited types of anaemia develop iron overload primarily secondary to transfusion.[3,9-14] Ingestion of iron supplements for many years can cause iron overload; some patients have haemochromatosis-associated mutations or heritable forms of anaemia.[14]

Physiological mechanisms to excrete iron are very limited. Thus, all patients with iron overload need safe and effective treatment that is compatible with their co-existing medical conditions. Prevention of death due to cardiac siderosis is the most important potential benefit of therapy. The incidence and prevalence of cardiac complications are greatest in β-thalassaemia major and other common heritable anaemias treated with multiple transfusions.[3,15-17] The liver is the primary target organ of iron overload in haemochromatosis and African iron overload,[6,18] although maintaining normal hepatic function is important in all patients. Preventing iron-related injury to endocrine organs is critical in children, especially those with β-thalassaemia major or early age-of-onset forms of haemochromatosis.[17-20] Successful treatment or prevention of iron overload increases quality of life and survival in many patients.

In this article, major categories of iron overload disorders are characterised, methods to evaluate and treat iron overload are tabulated, and treatment options for iron overload disorders are described. Research needed to advance knowledge about treatment of iron overload is proposed.

1. Evaluation of Iron Overload

Iron overload phenotypes are variable, even across individuals with similar underlying disorders.[1-3,5,18] There may be discordance in the apparent severity of iron overload in major target organs such as the heart and liver in the same individual; this disparity may change after treatment of iron overload therapy has commenced. Complications of iron overload are related to organ and tissue sensitivity to iron deposition and toxicity, and the rate and duration of iron accumulation.[1-3,5,18]

Clinicians must evaluate all patients regularly using appropriate history, physical examination and iron overload measures. It is important to inquire about symptoms related to heart, liver and joint disease; growth and development; diabetes mellitus and other endocrine abnormalities; and sexual function. A dietary history should focus on general dietary habits and food choices, use of dietary supplements and ingestion of alcohol (ethanol). Any history of blood donation, receipt of blood transfusion and illness associated with blood loss should be documented. The physical examination must include assessment of the heart, liver, spleen, musculoskeletal system, endocrine status and sexual development, and height and weight measures.[2,18,21]

There is no optimal test for the evaluation of iron overload (table I). Monitoring of units of transfusion or therapeutic phlebotomy, measurement of serum

Table I. Methods to evaluate iron overload[a]

Method	Iron measurement	Advantages	Disadvantages
Count erythrocyte transfusions	One unit = 200–250mg Fe; 1mL erythrocytes ≈ 1mg Fe	Reflects total iron burden; non-invasive, universal availability; prospective; inexpensive	Not organ-specific
Count phlebotomy units	One unit = 200–250mg Fe; 1mL erythrocytes ≈ 1mg Fe	Reflects total iron burden; non-invasive, universal availability; inexpensive	Not organ-specific; retrospective
Serum ferritin concentration	Grossly proportional to total iron load, liver iron measures; trends reflect changes in iron burden	Widely available; non-invasive; inexpensive	Not organ-specific; altered by inflammation, liver disease, recent chelation, alcohol consumption, ascorbate nutriture
Bone marrow evaluation	Semi-quantification of iron in macrophages, erythroblasts with Perls stain	Detects abnormal erythroblast iron ('ringed sideroblasts'); permits estimate of macrophage iron	Invasive; usually not helpful in haemochromatosis or in absence of undiagnosed anaemia
Liver biopsy	Quantification by AAS; semi-quantification, cell localisation with Perls stain	Major target organ; 'gold standard'; liver histology	Invasive; sampling errors; expensive
Endomyocardial biopsy	Semi-quantification with Perls stain	Major target organ; organ-specific; heart histology	Invasive; correlation with functional studies fair
CT scanning	Organ iron content	Non-invasive; widely available	Involves radiation exposure; insensitive to early iron overload; common liver disorders may yield false positive readings; expensive; inferior to MRI techniques
MRI scanning	Organ iron content	Adaptable to multiple target organs; non-invasive; can detect small primary liver cancers; widely available	Sensitivity, specificity must be evaluated for each machine; various scanning, interpretation routines; expensive
MRI (T2-weighted) scanning	Organ iron content	Adaptable to multiple target organs but best for liver iron assessment after calibration	Limited value for assessing cardiac iron content
MRI (T2*-weighted) scanning	Organ iron content	Adaptable to multiple target organs but best for cardiac iron assessment; calibration to heart tissue not available but in progress	Investigational but availability and acceptance increasing
Biomagnetic susceptometry (SQUID)	Liver iron content	Non-invasive; radiation not involved	Investigational; few SQUID devices exist

a This table of methods is not all-inclusive. Many methods have been devised to estimate hepatic iron content and, to some extent, they yield discordant results.[18,22-24] Clinicians should choose methods based on the underlying iron overload disorder and complications, patient acceptance, cost, safety and availability.[1,25-27] Measurements of haemoglobin concentration, mean corpuscular volume, serum iron concentration, and transferrin saturation are helpful adjuncts to treatment of iron overload in some patients.

AAS = atomic absorption spectrometry; **MRI** = magnetic resonance imaging; **SQUID** = superconducting quantum interference device.

ferritin, quantification of liver iron content using a specimen obtained by biopsy, and assessing organ-specific iron burdens using various magnetic resonance imaging (MRI) techniques are widely available, generally acceptable to patients and physicians, and provide sufficient information to make routine decisions about the need for and progress of therapy (table I). Additional tests of target organ function are often indicated to assess management needs.

2. Treatments for Iron Overload

Phlebotomy and erythrocytapheresis remove iron predominantly as Hb (table II). Phlebotomy is suitable treatment for individuals who have no or mild anaemia, and whose rate of effective erythropoiesis is sufficient to replace phlebotomy losses efficiently.[21] Isovolaemic, large-volume erythrocytapheresis removes more blood erythrocytes per session than phlebotomy, while sparing plasma proteins, coagulation factors and platelets.[28]

Chelation therapy employs drugs that selectively bind excess iron and increase its excretion. At present, three iron chelators are available for routine clinical use, although each drug is not available in all locations, and indications for use of the same drug according to various regulatory agencies are not identical (table II).

2.1 Deferoxamine

Deferoxamine, a hexadentate siderophore derived from *Streptomyces pilosus* (deferoxamine mesylate; Desferal®, Novartis Pharma Stein AG, Stein, Switzerland),[1] was introduced as parenteral therapy for iron overload associated with β-thalassaemia major in 1976 (table II). Deferoxamine therapy has been reviewed extensively. The half-life of deferoxamine is short (~20 minutes). Therefore, standard treatment involves the subcutaneous infusion of deferoxamine 40 mg/kg for 8–12 hours nightly for 5–7 nights weekly using a battery-operated infusion pump. Much of the chelated iron is excreted in the urine as a reddish complex, the quantity of which is proportional to peak plasma concentrations; some iron is excreted in the stool via the bile, and this quantity remains fairly constant, regardless of deferoxamine doses or peak plasma concentrations.[31-33] Oral ascorbic acid (vitamin C) 200mg enhances urine iron excretion, but should be administered only during days of deferoxamine infusion.[1] A stringent infusion routine is necessary for optimal iron chelation and excretion.[34] Alternative routes of administration have been reported.[35-37] Although deferoxamine mobilises iron deposited in parenchymal cells and macrophages, iron mobilisation from the heart occurs less rapidly than that from the liver and other sites.[38] Urinary iron excretion often wanes after several consecutive days of infusion, but usually returns to higher rates after several days off-therapy. Lack of compliance, cost and physician dissatisfaction are major impediments to successful deferoxamine therapy. Painful local reactions at the infusion site are the major reason for non-compliance, but severe allergic reactions are uncommon. High-frequency hearing loss, deafness and retinal damage can occur when large doses of the drug are given to patients with mild or moderate iron overload. In children, growth retardation and skeletal damage have also been reported. Zinc deficiency can occur. Susceptibility to infection with *Yersinia* spp. and perhaps other Gram-negative bacilli is increased.[5]

2.2 Deferiprone

Deferiprone, an orally administered bidentate iron chelator (L1, CP20; Kelfer®, Cipla Ltd, Mumbai, India; Ferriprox®, Apotex Inc., Montreal, Canada) [table II],[39] is indicated for the treatment of iron overload in β-thalassaemia major that cannot be treated with deferoxamine. First licensed in 1987, deferiprone is available in >30 countries. Deferiprone therapy has been reviewed extensively. Absorption is rapid and peak plasma concentrations are achieved within 45–60 minutes. Deferiprone traverses cell membranes more readily than deferoxamine. This possibly accounts for the greater capacity of deferiprone to reduce myocardial siderosis and

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table II. Treatments for iron overload[ab]

Treatment	Iron overload disorders	Usual route of treatment	Advantages	Compliance with treatment	Disadvantages	Adverse Effects
Phlebotomy	Haemochromatosis, porphyria cutanea tarda, post-transplant, post-chemotherapy, overload due to supplements	Venipuncture	Much clinical experience; effective, widely available, safe, inexpensive	Excellent for iron depletion; good for maintenance	Requires repeated visits to healthcare facility	Transient hypovolaemia; fatigue; increases iron absorption; iron deficiency if monitoring inadequate
Erythrocytapheresis	Haemochromatosis, sickle cell disease	Venipuncture	Rapid, safe	Excellent	Limited clinical experience; requires special apparatus, careful patient selection; limited availability; expensive	Transient hypovolaemia; fatigue; increases iron absorption
Deferoxamine chelation	β-Thalassaemia major, intermedia; sickle cell disease; MDS; rare anaemias	Subcutaneous infusion	Much clinical experience; widely available	Fair	Inadequate chelation of cardiac iron; expensive	Reactions at infusion sites; hearing, vision, growth, skeletal abnormalities; zinc deficiency; *Yersinia* infection
Deferiprone chelation	β-Thalassemia major, intermedia; sickle cell disease; MDS; rare anaemias	Oral	Much clinical experience; drug of choice for chelation of cardiac iron when given in adequate doses; good chelation hepatic iron; widely available	Excellent	Moderate expense	Agranulocytosis; transient neutropenia; arthralgias; zinc deficiency; mild gastrointestinal symptoms
Deferasirox chelation	β-Thalassaemia major, intermedia; sickle cell disease; MDS; rare anaemias	Oral	Good chelation of hepatic iron; no growth abnormalities in children; no agranulocytosis	Excellent	Paucity of clinical experience because of recent introduction; no substantial reports about chelation of cardiac iron; expensive; limited availability	Skin rash; non-progressive elevation of serum creatinine; mild gastrointestinal symptoms; mild transaminase elevations; rare hearing, vision abnormalities

a Deferoxamine is widely available. Deferiprone is routinely available in Europe and many other locations. In Europe, deferiprone is indicated as second-line treatment for iron overload associated with β-thalassaemia major (in patients in whom deferoxamine therapy is contraindicated or inadequate). Deferiprone is not presently available in the US. Deferasirox is available in the US for the treatment of chronic iron overload due to blood transfusions (transfusional haemosiderosis) in patients aged ≥2 years. In Europe, deferasirox is indicated for the treatment of chronic iron overload due to frequent blood transfusions (>7 mL/kg/month of packed red blood cells) in patients with β-thalassaemia major aged ≥6 years. Deferasirox is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups: patients with other anaemias; patients aged 2–5 years; and patients with β-thalassaemia major with iron overload due to infrequent blood transfusions (<7 mL/kg/month of packed red blood cells). Other countries or regulatory agencies may provide other specifications or limitations for the use of deferoxamine, deferiprone or deferasirox. Consult authoritative sources before recommending chelation therapy to patients.

b Many patients benefit from measures to reduce iron intake and absorption. All patients should avoid ingesting supplemental iron or eating excessive quantities of red meat.[21] Tea consumption can decrease iron absorption in patients with β-thalassaemia major or haemochromatosis.[29,30] Some patients treated with chelation may need zinc supplements.

MDS = myelodysplastic syndromes.

to remove erythrocyte iron.[40,41] Deferiprone also removes iron from non-cardiac parenchyma, macrophages, transferrin, ferritin and haemosiderin. Chelated iron is excreted predominantly via the urine in proportion to the dose of deferiprone,[42,43] although only ~4% of oral deferiprone doses are excreted with bound iron. Daily urinary iron excretion remains constant over long periods. A 'standard' dose of deferiprone 75 mg/kg/day taken in three divided doses is approximately equivalent to a 'standard' dose of deferoxamine, measured by urinary iron excretion.[31,44] This drug is licensed for prescription up to 100 mg/kg/day. Deferiprone is inactivated by glucuronidation, partly explaining individual variation in response to the drug.[45]

The incidence of adverse effects of deferiprone have been determined in prospective trials.[46-48] Agranulocytosis (<500 neutrophils + eosinophils + basophils/μL) occurs as an idiosyncratic reaction in ~1% of patients;[5] such patients should be permanently withdrawn from deferiprone therapy. In contrast, patients who developed neutropenia (<1500 neutrophils/μL) have been re-treated without recurrence. Mean alanine aminotransferase (ALT) levels did not increase significantly among 151 patients treated for 3 years,[47] although some patients have been withdrawn from DFP therapy trials as a result of elevated ALT levels.[46] Some patients with β-thalassaemia major develop elevation of serum concentrations of hepatic transaminases, especially those with chronic hepatitis C. The incidence of hepatic cirrhosis was not increased in β-thalassaemia major patients who underwent repeat liver biopsy for >3 years, on average, after the outset of deferiprone therapy.[49] The occurrence of arthralgias may cause some patients to discontinue use of deferiprone. Some patients develop gastrointestinal symptoms, which are usually transient. Zinc deficiency sometimes occurs, and some clinics routinely prescribe oral zinc supplements to patients undergoing deferiprone therapy. Overall, the compliance with deferiprone therapy is much greater than that typical with deferoxamine therapy.[5]

2.3 Deferasirox

Deferasirox (ICL670; Exjade®, Novartis Pharma Stein AG, Stein, Switzerland) is an orally administered tridentate iron chelator first licensed in 2005 (table II). Pre-clinical data and phase I and II data for deferasirox are summarised elsewhere.[50-56] In an iron-overloaded marmoset model, the avidity of deferasirox was much greater for iron than for copper or zinc. Oral bioavailability is approximately 70% and increases significantly when the drug is administered with food. Peak plasma concentrations are achieved 2 hours after a single oral dose; the drug is 99% protein-bound. The pharmacokinetics of deferasirox are characterised by a half-life of 8–16 hours, and by glucuronidation and enterohepatic recirculation.[52] Deferasirox enters a variety of cells, especially cardiac myocytes, and chelates intracellular iron readily.[57,58] More than 80% of deferasirox, with or without bound iron, is eliminated in the faeces.[50] Net iron excretion after 6 days of exposure was linearly related to the drug dose. Currently recommended starting doses are 20 mg/kg/day,[59] although this dosage is only sufficient to prevent net iron accumulation in most patients. Because the relationship of iron excretion to deferasirox dose is a linear one, many patients must be treated with 30 mg/kg/day, if tolerated, to achieve net iron excretion.[60]

The most prevalent adverse effect of deferasirox therapy is mild to moderate skin rash (10–15% of patients). Mild, non-progressive elevations in serum creatinine levels occur in ~35% of patients across diagnoses; no renal failure has been reported. Drug-induced increases of transaminase levels or mild nausea, diarrhoea or abdominal pain sometimes occur. Auditory (high-frequency hearing loss) and ocular (lens opacities, cataracts, elevated intraocular pressure, retinal disorder) abnormalities are rare. No growth abnormalities have been documented in paediatric patients,[61] and deferasirox therapy has not been implicated as a cause of neutropenia or agranulocytosis.[61] Auditory and ophthalmological testing are recommended before treatment is started and yearly thereafter. Altogether, deferasirox is at least as effective as deferoxamine and appears to

have a tolerability and safety profile suitable for long-term, once-daily administration in children aged >6 years and in adults.[51] In Europe, deferasirox has been approved as first-line therapy for patients with β-thalassaemia major aged >6 years, and as second-line therapy in other chronic iron overload conditions in patients aged 2–5 years. However, the overall length of clinical experience with deferasirox is much shorter than that with deferoxamine.

3. Major Iron Overload Disorders and Their Treatment

3.1 Haemochromatosis

The most common form of haemochromatosis is associated with homozygosity for the C282Y mutation of the *HFE* gene. Approximately 1% of C282Y homozygotes develop severe iron overload;[5] some other homozygotes and heterozygotes develop iron overload of lesser degrees. Less prevalent haemochromatosis-like disorders are caused by mutations of genes encoding ferroportin (*FPN1*, *SLC40A1*), alternate transferrin receptor (*TFR2*), haemojuvelin (*HJV*, *HFE2*), hepcidin (*HAMP*), ceruloplasmin (*CP*), H-ferritin (*FTH1*) and divalent metal transporter-1 (*DMT1*, *SLC11A2*).

In early case series, patients treated with phlebotomy had significantly longer survival than those who were not treated.[62] Thus, phlebotomy has become the preferred treatment for patients with iron overload associated with *HFE* haemochromatosis.[21] Patients with other types of haemochromatosis, iron overload or porphyria cutanea tarda who do not have severe anaemia can also be treated with phlebotomy.[21] Phlebotomy should be initiated when serum ferritin levels exceed 300 μg/L in men and 200 μg/L in women;[21,63] progress in most individuals can be evaluated adequately with serum ferritin or mean corpuscular volume.[21,64] Treatment prevents all known complications of iron overload in haemochromatosis when applied appropriately in patients diagnosed before target organ injury has occurred. More than 90% of patients comply with 'induction' phlebotomy to achieve iron depletion, although the proportion of individuals who present for 'maintenance' phlebotomy declines linearly over time.[65] In small case series, erythrocytapheresis reduced iron measures in haemochromatosis patients with severe iron overload, intolerance of phlebotomy or co-inheritance of β-thalassaemia;[28,66-70] erythropoietin therapy may enhance such treatment.[68,69]

Early age-of-onset forms of haemochromatosis are typically associated with *FPN1*, *TFR2*, *HJV* or *HAMP* mutations. Myocardial siderosis with consequent cardiomyopathy or arrhythmia can cause death only days after iron overload is diagnosed. Some patients appear to benefit from a combination of aggressive phlebotomy therapy and deferoxamine infusions, or with combined deferoxamine and deferiprone therapy.[21,71] Trials of chelation therapy in adults with haemochromatosis were reported soon after the introduction of deferoxamine.[72]

3.2 African Iron Overload

African iron overload is a common disorder which is characterised by multiorgan iron deposition that occurs predominantly in macrophages. Contributing factors include a putative genetic factor and consumption of traditional beer that contains much iron (and sometimes other adulterants).[6] Associated disorders include hepatic cirrhosis, cardiomyopathy, osteoporosis, scurvy, primary liver cancer and carcinoma of the oesophagus. The relative importance of iron, alcohol, nutritional deficiencies, hepatitis B and other factors implicated in the causation of these disorders is incompletely understood. Iron overload in African and in African American patients with primary iron overload can be treated with phlebotomy.[7,73]

3.3 β-Thalassaemia Major

β-Thalassaemia major is a common group of disorders that is typically caused by the inheritance of two abnormal β-globin genes. Severe anaemia, ineffective erythropoiesis and increased iron absorption appear in early infancy. Periodic erythrocyte transfusion is necessary to sustain life, and decreases cardiomegaly, hepatomegaly, splenomega-

ly, and bone and orthodontic abnormalities, promotes growth until adolescence, and improves well-being.[5] All patients develop iron overload as a result of transfusion, although iron absorption is also increased by ineffective erythropoiesis and decreased hepcidin levels.[74] Cardiac iron overload is a major cause of morbidity and mortality.[3,75-77] Hepatic cirrhosis and primary liver cancer are also common, especially in patients with hepatitis C.[78] The rate of iron accumulation due to transfusion is 20–40 mg/day (0.3–0.7 mg/kg/day).[1] Therefore, regular monitoring for iron overload is necessary in all patients.

Deferoxamine therapy is usually begun after 10–20 units of erythrocyte transfusion, or when serum ferritin reaches 1000 μg/L.[1] Deferoxamine removes liver iron more readily than cardiac iron.[79,80] Iron-induced cardiomyopathy is not reversible with deferoxamine in all patients,[37,81] and continuous intravenous deferoxamine improves ventricular function more rapidly than it removes cardiac iron.[79] Despite rigid adherence to a deferoxamine treatment protocol that is associated with low hepatic iron levels, cardiomyopathy due to iron overload can occur in patients with β-thalassaemia.[80] Although deferoxamine therapy significantly improves life expectancy,[34,82,83] the predominant cause of death after therapy is initiated is cardiac failure, often associated with lack of compliance with deferoxamine therapy.[15,34,83]

A crucial issue in the management of patients with β-thalassaemia major is the use of chelation treatment that offers the greatest reduction in incidence rates for cardiac disease and death. Deferiprone treatment was associated with lower cardiac iron levels, less cardiac dysfunction and fewer deaths due to cardiac disease than was deferoxamine therapy in two retrospective studies.[38,84] A brief prospective randomised study revealed no significant differences in measures of iron overload-related cardiac disease between patients treated with deferoxamine and those treated with deferiprone.[85] However, in a randomised controlled trial of patients with β-thalassaemia major previously maintained on subcutaneous deferoxamine, those switched to oral deferiprone monotherapy (92 mg/kg/day) had significantly greater improvement in myocardial T2* and left ventricular ejection fraction (LVEF) over 1 year than patients who continued to take deferoxamine (43 mg/kg for 5–7 days/week). Changes in liver iron level and serum ferritin level did not differ significantly between the two groups.[86] Altogether, this demonstrates that deferiprone monotherapy is significantly more effective than deferoxamine over an interval of 1 year in improving asymptomatic myocardial siderosis in patients with β-thalassaemia major. In a large study of patients with β-thalassaemia major who had not experienced a previous cardiac event, the incidence of cardiac events, including cardiac-related deaths, were significantly higher in patients treated with deferoxamine than in those switched to deferiprone therapy. No cardiac events occurred during deferiprone therapy or within at least 18 months after its discontinuation.[77] Taken together, these reports indicate that deferiprone therapy provides significantly greater cardiac protection than deferoxamine in patients with β-thalassaemia major who have not developed symptoms or other abnormalities attributable to cardiac siderosis.[38,84,85]

In six studies in which serial liver iron determinations were made in deferiprone-treated patients, a significant decline in mean hepatic iron concentrations was reported in only one study.[87] In one study of 54 children and young adults, median liver iron concentration measured by biomagnetic liver susceptometry increased over >3 years as a result of increasing transfusion, despite deferiprone treatment.[88] In another retrospective study, significantly greater liver iron concentrations were observed in patients treated with deferiprone than in those treated with deferoxamine.[38] Serum ferritin concentrations often fall with deferiprone therapy, especially in patients with severe pre-treatment hyperferritinaemia.[87] In a short-term study, increasing the dose of deferiprone to 100 mg/kg/day led to reduction of serum ferritin levels in patients inadequately chelated at 75 mg/kg/day.[89] A retrospective, multicentre study of patients with β-thalassaemia major confirms that cardiomyopathy, poor compliance with

deferoxamine chelation therapy and high ferritin levels are significant risk factors for death, and the results suggest that including deferiprone in the therapeutic plan may protect against mortality.[16]

Deferasirox therapy was non-inferior to deferoxamine therapy after 1 year in a phase III trial.[61] Patients with liver iron concentrations ≥7 mg/g dry weight treated with either deferoxamine or deferasirox (40 mg/kg/day) had significant and similar dose-dependent reductions in serum ferritin, liver iron concentration and net body iron balance.[61] However, at present there are no reports describing the effect of deferasirox on cardiac function or iron levels in patients with β-thalassaemia major.

Combination chelation therapy of patients with deferiprone and deferoxamine has been conceived as a means to increase chelation efficacy, sometimes allow drug doses and toxicity to be reduced, and the number of days of deferoxamine infusion to be decreased, improving compliance and quality of life.[90] In β-thalassaemia major patients with severe iron overload and low compliance with subcutaneous deferoxamine therapy, mean urinary iron excretion during combined therapy was double that with deferoxamine or deferiprone monotherapy. Serum ferritin levels declined significantly in patients who received combination therapy. In a subset of patients receiving heart therapy at the outset of the study, LVEF increased significantly without modifying the cardiac treatment.[90] Other studies with fewer patients or shorter follow-up intervals report corresponding results.[91,92] In a prospective randomised controlled trial of deferoxamine and deferiprone combination therapy (alternating deferoxamine and deferiprone vs deferiprone monotherapy), both arms resulted in equivalent decreases of serum ferritin and liver iron concentration. There was no significant difference in the proportion of patients with adverse events in the two therapy groups, although the nature of the adverse events differed according to the chelation regimen.[93] Long-term outcomes have not been reported from this trial.[93] Acute heart failure due to iron overload in β-thalassaemia major patients may respond to combination deferoxamine and deferiprone treatment.[94,95] In a retrospective analysis of survival in β-thalassaemia major patients, one report suggests that combination therapy using deferoxamine and deferiprone may account for improvements in survival documented since 2000.[96]

3.4 β-Thalassaemia Intermedia

β-Thalassaemia intermedia is caused by numerous genotypes, all of which include at least a single β-thalassaemia allele. Clinical phenotypes vary widely, but are usually less severe than that of β-thalassaemia major. Deferiprone therapy reduced serum ferritin and liver iron measures in patients with β-thalassaemia intermedia (including those with Hb E/β-thalassaemia) who were intolerant of phlebotomy.[41,97]

3.5 Sickle Cell Disease

The sickle cell disease group of disorders is usually associated with Hb SS, or with co-inheritance of Hb S and either Hb C or β-thalassaemia alleles. Clinical syndromes are characterised by chronic anaemia of variable severity, diverse complications caused mainly by intravascular sickling of erythrocytes, and increased susceptibility to infection. Iron overload is caused primarily by transfusion, although hepcidin levels are also down-regulated;[98] unusual patients have mutations in iron regulatory genes.[99] Stroke, a major complication, affects approximately 11% of patients by age 20 years;[100] at-risk patients can be identified by transcranial Doppler examinations. Regular transfusions significantly reduce the incidence of stroke in at-risk children, but risk increases after transfusions are discontinued.[101-103] Some patients receive transfusions to alleviate other complications. Because iron overload is an important cause of morbidity and mortality,[104,105] all patients who have received multiple transfusions should be evaluated regularly for iron overload. Treatment should be initiated as described for β-thalassaemia major in section 3.3.

Erythrocytapheresis can be used as an automated method of erythrocyte exchange, especially in patients with sickle cell disease at risk for stroke. Treatment reduces Hb S levels, prevents further iron

accumulation, decreases body iron burdens and eliminates the need for deferoxamine therapy in some patients, including children.[104-110] However, long-term erythrocytapheresis therapy was associated with significantly greater cardiac dysfunction than was detected in non-transfused patients, possibly as a result of greater pre-treatment iron overload in patients managed with erythrocytapheresis.[111]

Iron chelation with deferoxamine has been used for many years,[112,113] but compliance with therapy is suboptimal.[114,115] Deferiprone can remove pathological iron deposits from sickle cells *in vitro* and *in vivo*.[40,116] In a short-term study, deferiprone maintained negative iron balance in patients who also required transfusion.[31] At dosages of 75 mg/kg/day, deferiprone significantly reduced serum ferritin levels and measures of hepatic iron content. However, there was no significant correlation of serum ferritin levels, liver and heart iron measures, and LVEF. Compliance with therapy was good and there were no significant adverse effects.[117] It has been proposed that deferasirox could eventually replace deferoxamine as the 'standard' therapy for iron overload associated with sickle cell anaemia, although few treatment data have been reported.[118]

3.6 Myelodysplastic Syndromes (MDS)

Myelodysplastic syndromes (MDS) are a common, heterogeneous group of disorders characterised by haemocytopenias, dysmorphic and genetically abnormal marrow and blood cells of myeloid lineage, and increased risk to develop acute leukaemia. The majority of patients are 60–80 years old.[119] Approximately 80% of patients have anaemia at presentation, >50% become transfusion dependent[120,121] and some develop iron overload.[3,9,10] Patients at greatest risk of developing iron overload include (i) those with refractory anaemia (with or without ringed sideroblasts); (ii) those with 5q− syndrome; (iii) those with a good prognosis (low or lower intermediate International Prognostic Scoring System score); (iv) those who have received >100 units of transfusion; and (v) those aged <70 years.[122] There is a significant inverse correlation of transfusion and survival.[123] The relationship of increased iron absorption observed in some patients with MDS to inheritance of common *HFE* polymorphisms is unclear.[124-126] Overall survival is limited as a result of age at diagnosis and common complications of MDS (infections, bleeding, acute leukaemia). It has been recommended that chelation therapy be initiated after 20–30 transfusions or when serum ferritin exceeds 2500 μg/L.[127]

Deferoxamine therapy induced negative iron balance in some MDS patients.[128-130] Improvement of haemocytopenias sometimes observed after deferoxamine therapy may be related to effects of deferoxamine on haematopoietic stem cells.[130-134] Reports of deferiprone treatment include relatively few patients, and rates of iron excretion may be less than those typical of β-thalassaemia major.[135-138] Deferiprone may act in synergy with defective granulopoiesis inherent to MDS to increase risks for neutropenia or agranulocytosis in some patients.[135-138] However, data from a phase II study of 47 MDS patients indicate that deferasirox was convenient, effective and well tolerated.[55,139]

3.7 Other Types of Anaemia Associated with Iron Overload

Iron overload may persist after successful stem cell transplantation or chemotherapy of heritable types of anaemia, haematological malignancies or other conditions.[124,135,140] Some patients with aplastic anaemia and inherited bone marrow failure syndromes such as Blackfan-Diamond syndrome and Fanconi anaemia are transfusion dependent. In congenital dyserythropoietic anaemia, pyruvate kinase deficiency and X-linked sideroblastic anaemia due to *ALAS2* mutations, iron absorption is increased as a result of ineffective erythropoiesis, although some patients also require transfusion. Serious complications of iron overload have been reported in these categories of patients.[11-13,141,142]

Normal erythropoiesis is re-established after successful stem cell transplantation for β-thalassaemia major or hereditary sideroblastic anaemia, permitting residual iron overload to be alleviated with therapeutic phlebotomy.[135,140] After remission induction of acute leukaemia, transfusion iron over-

load can be treated safely with phlebotomy.[143] Iron overload in patients with MDS, non-Hodgkin's lymphoma, and autoimmune haemolytic anaemia in remission or post-transplant can be treated similarly. Patients with Blackfan-Diamond syndrome and other rare anaemias have been treated with deferasirox,[144-146] although many have been removed from clinical trial participation as a result of disease-related complications.[55]

3.8 Iron Overload Due to Iron Supplements

Patients who chronically ingest iron supplements and develop iron overload are rare. Therapeutic phlebotomy is feasible and effective, and would prevent complications of iron overload.[14]

4. Research Needs and Future Directions

4.1 *HFE* Haemochromatosis

Phase II trials are needed to determine whether patients with *HFE* haemochromatosis who are non-compliant with phlebotomy, especially those needing 'maintenance' therapy, can be treated satisfactorily with deferiprone or deferasirox. Phase III trials comparing 'induction' phlebotomy with oral chelation therapy (or erythrocytapheresis) should await a means to ascertain which *C282Y* homozygotes will develop progressive, injurious iron overload and, therefore, benefit from treatment.

4.2 African Iron Overload

Prospective clinical trials are needed to assess the acceptability of and compliance with phlebotomy, and to determine more precisely the role of iron overload in the development of hepatic cirrhosis, primary liver cancer and carcinoma of the oesophagus in patients with African iron overload.

4.3 β-Thalassaemia and Sickle Cell Disease

Prospective trials are needed to assess if deferiprone 100 mg/kg/day can be given long term with safety in patients with β-thalassaemia or sickle cell disease, and if it will result in more effective iron chelation in patients inadequately treated with 75 mg/kg/day. The superiority of deferiprone to deferoxamine monotherapy in asymptomatic β-thalassaemia patients in reducing the incidence of cardiac events and deaths indicates that results of trials with deferasirox monotherapy, and combination therapy with deferoxamine and either deferiprone or deferasirox, are needed in β-thalassaemia and in sickle cell disease to determine if cardiac iron deposits are more susceptible to chelation with these oral drugs than with deferiprone monotherapy alone, and if cardiac mortality rates can be reduced further. There is a need for further long-term (>3 years) studies to determine the proportion of individuals treated with deferiprone in whom hepatic iron overload is adequately controlled. Randomised trials designed to compare deferiprone and deferasirox therapy will help to refine presently available knowledge regarding optimal use of these drugs. Long-term survival and safety data for deferiprone and deferasirox therapy of young individuals are needed, including investigations to determine the molecular basis of adverse events of oral chelation therapy such as agranulocytosis, arthralgias, elevated hepatic transaminase levels and elevated serum creatinine concentrations.

4.4 MDS and Rare Anaemias

Prospective studies are needed to delineate which MDS patients will survive long enough to develop clinically significant iron overload and, therefore, potentially benefit from chelation therapy. Greater insight into the optimal selection of oral chelators and treatment schedules for patients with rare forms of anaemia is needed.

4.5 Development of New Iron Chelation Drugs

Three unlicensed chelation drugs for which some animal and limited clinical trial data have been reported include parenterally administered starch deferoxamine polymers; the orally administered compound deferitrin (GT56-252), and L1NAII, also an oral agent.[5,147-149]

5. Conclusions

Iron overload disorders are common worldwide, and cause significant morbidity and mortality in children and adults. Successful management requires early diagnosis and safe, effective treatment to deplete target organs of iron and to maintain iron depletion despite increased iron absorption and periodic transfusions. At present, many patients without anaemia can be treated satisfactorily with phlebotomy, while most patients with anaemia require chelation therapy. The availability and use of oral iron chelators can improve the overall health and survival of transfusion-dependent patients, and may represent acceptable treatment options for some patients presently managed with phlebotomy.

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Correspondence: Dr *James C. Barton*, Southern Iron Disorders Center, Suite G-105 Ambulatory Care Center, 2022 Brookwood Medical Center Drive, Birmingham, AL 35209, USA.
E-mail: ironmd@dnamail.com