Optimal Use of Iron Chelators in Pediatric Patients

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Abstract: Regular red cell transfusion therapy is used in the treatment of children with various hematologic disorders. These transfusions cause progressive iron loading, which if untreated results in endocrinopathies, cardiac arrhythmias, congestive heart failure, hepatic fibrosis, and premature death. Iron chelation therapy is used to prevent iron loading, remove excess accumulated iron, and detoxify iron. Three chelators have received US Food and Drug Administration approval: deferoxamine, deferasirox, and deferiprone, although deferiprone is approved only as a second-line agent. These chelators differ in their modes of administration, ability to remove iron from different organs, and adverse effect profiles. Chelation therapy should be individualized, taking into account the child's and family's preferences, adherence, adverse effects, ongoing transfusional iron intake, and the degree of cardiac and hepatic iron loading.

Transfusional Iron Overload

Regular red cell transfusions are used in the management of numerous hematologic disorders in childhood, including β-thalassemia major, sickle cell disease (SCD) and other hemolytic anemias, and Diamond Blackfan anemia (DBA) and other bone marrow failure syndromes. Typical transfusion regimens involve the administration of 10–15 mL/kg of packed red blood cells every 3–5 weeks to maintain a trough hemoglobin level of 9–10 g/dL in children with thalassemia and to maintain the hemoglobin S level below 30% in children with SCD. Each milliliter of pure packed red cells (hematocrit 100%) contains approximately 1.08 mg of iron. Because humans lack physiologic mechanisms to excrete excess iron, chronic red cell transfusion therapy will lead to progressive iron accumulation in the absence of chelation therapy. Chelation therapy is necessary to remove this iron accumulation to prevent or treat its associated toxicity.

Toxicity Related to Iron Overload

Iron usually is bound to proteins within the body because free iron is toxic. Ferritin is the main storage complex of iron and is found principally in the liver, reticuloendothelial cells, and red cell precursors.

In the plasma, iron normally is bound to transferrin. In iron overload states, however, nontransferrin-bound iron (NTBI) forms are present once transferrin is about 70% saturated.[1] Labile plasma iron (LPI), a form of NTBI, can be taken up into cells where the iron can participate in the generation of free radicals that cause lipid peroxidation, organelle damage, and fibrosis, resulting in organ damage. The organs most susceptible to iron-related injury include the heart, liver, and endocrine organs.

Cardiac toxicity includes congestive heart failure and atrial and ventricular arrhythmias and is the leading cause of death related to iron overload in patients with thalassemia major.[2] Iron-related heart disease uncommonly occurs in younger children with thalassemia major, but may become evident in the teen years.[3] Iron-associated heart disease also occurs less commonly in transfused individuals with SCD, even at older ages,[4] which may at least in part be owing to lower levels of NTBI found in these patients.[5] However, younger children with transfusion-dependent DBA may be at risk for cardiac toxicity.[6]

Excess iron deposition in the liver leads to inflammation, fibrosis, and cirrhosis.[7] Iron also is toxic to the endocrine organs, leading to growth failure, growth hormone deficiency, delayed puberty,[8] hypogonadotropic hypogonadism, insulin-dependent diabetes mellitus, osteopenia, hypothyroidism, and hypoparathyroidism.[3] Endocrinopathies uncommonly become evident in children with thalassemia major before 15 years of age,[3] although growth delay and osteopenia are seen at earlier ages.[9] Iron-associated endocrinopathies also occur less commonly in patients with SCD than in patients with thalassemia.[10] However, endocrinopathies may occur at younger ages in chronically-transfused children with DBA; one report exists of a child with hypothyroidism at 8.7 years of age.[6] Iron-related organ toxicity likely results from cumulative exposure to iron, and so even if organ toxicity does not become evident until older ages, good control of iron burden in younger children is important.

Monitoring Iron Burden

Multiple methods of assessing the degree of iron overload exist, and each method has benefits and limitations (Table 1). In clinical practice, combinations of the different techniques and serial measurements are used to assess iron burden and to adjust chelation therapy.

The serum ferritin level can be measured with an inexpensive blood test. Levels can be measured frequently, and can be used to monitor trends in iron burden over time. Sustained ferritin levels above 2,500 µg/L are associated with an increased risk of cardiac toxicity and death in patients with thalassemia,[11,12] but low serum ferritin levels do not guarantee the absence of heart disease.[13] Infection, inflammation, and ascorbate deficiency can either raise or lower serum ferritin levels, limiting the utility of this test. This is particularly relevant for patients with SCD, in whom serum ferritin levels are more variable and may not correlate well with transfusional iron loading and liver iron concentration.[14] Serum ferritin levels also underestimate liver iron concentration in patients with nontransfusion-associated iron overload, such as thalassemia intermedia.[15]

The liver iron concentration is a good indicator of total iron burden in transfusion-associated iron overload.[16] Levels in excess of 15 mg Fe/g dry weight of liver are associated with an increased risk of cardiac complications and death in patients with thalassemia major.[11,12] However, significant cardiac iron loading may exist despite adequate liver iron levels owing to differential rates of iron loading and unloading in these organs.[17,18] Therefore, parallel assessment of cardiac iron is particularly important in the management of chelation.

Liver biopsy has been considered the "gold standard" for accurate iron measurement and allows for direct assessment of histology. However, this technique is invasive and carries risks of bleeding, bile leak, and pain, and requires anesthesia in young children. An additional limitation is that fibrosis and inadequate sample size may lead to an underestimation of the liver iron concentration.[16,19]

Magnetic resonance imaging (MRI) assessments of liver iron have largely replaced liver biopsy in the management of patients.[20] Results using R2 MRI correlate well with liver iron levels obtained by biopsy, and the technique is reproducible across different scanners.[21] Other approaches using T2* or R2* MRI also are promising for determining liver iron content.[17,22]

Cardiac iron levels also can be estimated using MRI, most commonly with T2* measurements. Cardiac T2* values above 20 ms are considered normal, while levels below 10 ms indicate severe cardiac iron loading and are associated with an increased risk of heart failure and arrhythmias.[13,17] In patients with thalassemia, cardiac iron loading usually is not evident in the first decade of life[23]; therefore, assessment of cardiac MRI in children with thalassemia generally can be started at approximately 10 years of age. Children with SCD usually do not need such monitoring until their later teens. In contrast, chronically transfused children with DBA may have evidence of cardiac iron loading at younger ages,[6] and testing beginning at 5 years old may be warranted. Most young children (<8 years old) require sedation for MRI studies, and the risks of sedation need to be weighed against the importance of the information to be gained from the study.

MRI techniques also can be used to estimate iron loading in other organs, including the pancreas and the pituitary gland, although these techniques are not currently in widespread clinical use. Elevated pancreatic iron

Table 1. Methods of Assessing the Degree of Iron Overload

Measurement	Age Considerations	Monitoring Frequency	Test Result	Recommendation
Ferritin	No age restriction; begin monitoring upon diagnosis and/or upon starting transfusions	Quarterly; more frequently as needed to assist with chelation adjustments or if ferritin falls below 1,000 µg/L	<500 µg/L	Reduce chelation dose, monitor closely for toxicities
			1,000 µg/L on 2 consecutive tests	Start chelation if patient not currently taking chelation or continue current regimen
			>1,500 µg/L consistently in patient taking chelation	Assess adherence, intensify chelation regimen
Liver Iron Concentration (MRI)	Start after 2 years of transfusion therapy; may postpone until age ≥5 years old if ferritin well controlled and transfusion history known	Annually; consider every 6 months if LIC >15 mg to assist with chelation adjustment	≤2 mg/g dw and normal cardiac T2*	Reduce chelation, monitor closely for toxicities
			>2 to <7 mg/g dw or 7 to <15 mg/g dw and falling and normal cardiac T2*	Continue chelation regimen
			7 to <15 mg/g dw and not falling, ≥15 mg/g dw	Assess adherence, intensify chelation (increase dose or combination therapy)
Cardiac T2*	Recommended for children ≥10 years; consider monitoring earlier for children with Diamond Blackfan anemia (≥5 years old); consider initiating monitoring later in children with sickle cell disease (teens)	Annually; consider every 6 months if T2* <20 ms to assist with chelation adjustment	20 ms	Continue chelation regimen
			10 to <20 ms	Assess adherence, intensify chelation (increase dose or combination therapy)
			<10 ms	Assess adherence, intensify chelation; consider combination therapy with deferiprone if available

dw=dry weight; LIC=liver iron concentration; MRI=magnetic resonance imaging.

(R2* >100 MHz) is associated with an increased risk of glucose dysregulation, although the correlation is not precise.[24] Pancreatic iron loading also may be an early indicator of increased risk of developing cardiac iron loading.[25] Pituitary iron loading and pituitary volume loss are associated with hypogonadism.[26]

Goals of Chelation

The overall goal of chelation therapy is to limit iron loading from ongoing transfusions and to remove excess accumulated iron. Chelators also detoxify iron by binding nontransferrin-bound iron forms, which can protect vulnerable organs such as the heart from damage. Constant exposure of iron to a chelator is optimal for this use. Chelation therapy also can prevent the development of iron-associated organ dysfunction. Once iron-related organ toxicity has developed, chelation therapy can reverse some but not all of the complications.[27,28]

Chelation therapy is dosed to maintain the liver and cardiac iron in an acceptable range and to match ongoing transfusional iron loading. Typically, the goal is to keep the liver iron concentration between 2 and 7 mg/g dry weight, which is slightly higher than the normal range of 0.17–1.8 mg Fe/g dry weight seen in nontransfused individuals.[29] Corresponding ferritin goals are to maintain a level between 500 and 1,500 ng/mL. In addition, chelation should be adjusted to keep the cardiac T2* >20 ms. The average transfusional iron intake is 0.3–0.4 mg/kg/day; higher transfusional iron intakes generally require the use of higher chelator doses.[30]

In recent years, some centers have used more aggressive chelation regimens to achieve "normal" body iron

stores in adults with red cell transfusion dependence.[28,31] With such an approach, cardiac dysfunction and endocrinopathies, including hypothyroidism, hypogonadism, and noninsulin-dependent glucose intolerance, were reversed in a subset of patients.[28] Nonetheless, the risk of toxicity with deferoxamine (Desferal, Novartis) is increased among patients with lower iron burdens, which is especially relevant for young children.[32] It is unclear if similar toxicities are seen with deferiprone (Ferriprox, ApoPharma) and deferasirox (Exjade, Novartis) at lower body iron levels.[28,33] Nonetheless, aggressive chelation to normalize iron burden is not generally recommended in growing children.

Starting Chelation Therapy

Chelation therapy is generally initiated in children with thalassemia major who are 2 years of age or older, who have been receiving 1–2 years of chronic transfusions, and whose serum ferritin level is above 1,000 ng/mL on 2 separate measurements obtained in steady-state.

Choice of Chelator

Three chelators are currently approved by the US Food and Drug Administration (FDA): deferoxamine, deferasirox, and deferiprone. An additional oral chelator, FBS0701, is in phase II clinical trials. Deferiprone is only approved for use in patients with transfusion-dependent thalassemia who have failed treatment with another chelator. A variety of factors differentiate the currently available iron chelators, including the mode of administration, the dosing schedule, the chelator's ability to remove iron from different organs (ie, heart, liver), and adverse effects of the drugs. These factors should be considered when choosing a chelator regimen. The sections below describe the properties of the different chelators, and an overview is provided in Table 2.

Deferoxamine

Deferoxamine was the first FDA-approved iron chelator, and it has been used in routine clinical practice for more than 40 years.[34] Because the drug has poor oral bioavailability and a short half-life,[35] it must be administered parenterally, typically as a continuous infusion of 25–50 mg/kg given over 8–12 hours, 5–7 days per week, either subcutaneously or intravenously. Daily administration over longer durations of up to 24 hours often is used for patients with cardiac iron loading or iron-related cardiac toxicity to ensure continuous exposure of the iron to the chelator.

Deferoxamine induces substantial urinary and fecal iron excretion,[36] and regular administration of this drug has been shown to lower serum ferritin levels.[37-39] Deferoxamine effectively removes iron from the liver in patients with transfusion-dependent anemias,[37,40,41] and can prevent other organ toxicities such as diabetes and other endocrinopathies.[34,42] Importantly, cardiac iron also is removed by deferoxamine,[27] and the regular use of deferoxamine reduces the incidence of cardiac complications in transfusion-dependent patients with thalassemia.[11,34,39] In addition, deferoxamine, usually given in higher doses up to 60 mg/kg/day as a continuous intravenous infusion, can reverse cardiac complications.[43]

The most common adverse effect associated with deferoxamine is irritation and swelling at the infusion site. Allergic reactions also may occur. High-frequency hearing loss and ophthalmological toxicities, including changes in visual acuity and color vision, retinal pigmentation, abnormal visual evoked potentials, night blindness, and lens opacities have been reported with deferoxamine use.[44] Routine screening for audiologic and ophthalmologic toxicity is warranted. Ophthalmologic and audiologic toxicity is more likely to occur when the deferoxamine dose is high relative to the iron burden. The risk of these side effects can be minimized by maintaining the ratio of deferoxamine dose (mg per kilogram of body weight) to the serum ferritin level at less than 0.025.[32]

Deferoxamine-induced bone toxicity includes injury to the growth plate of long bones, cartilage damage, vertebral compression, rickets-like lesions, and genu valgum.[45-48] Bone changes and growth failure are more common when the iron burden is low.[49] For this reason, deferoxamine often is not started until after age 3 years, and lower doses of 25–30 mg/kg/day are administered to young children. Growth velocity, seated height, and bony changes should be monitored regularly.

Deferoxamine use has been associated with an increased risk of infection with *Yersinia* and *Klebsiella* species.[50,51] Therefore, deferoxamine should be held for febrile episodes, and infection with *Yersinia* and *Klebsiella* species should be investigated for any unexplained fevers. Acute neurotoxicity and acute pulmonary toxicity—with respiratory distress, hypoxemia, and a diffuse interstitial pattern on chest radiograph—both have been reported with the administration of very high doses of deferoxamine (10–20 mg/kg/h).[52,53] Therefore, using such high doses generally is not recommended.

Deferiprone

Deferiprone was introduced into clinical trials in the 1980s and received FDA approval as a second-line agent in 2011. Deferiprone is administered orally in 3 divided doses, given its relatively short half-life.[54,55] The typical daily dose is 75–99 mg/kg.

Urinary iron excretion with deferiprone at doses of

Table 2. Properties of Iron Chelators

Property	Deferoxamine	Deferiprone[109]	Deferasirox[110]
Usual Dose	25–50 mg/kg/day	75–99 mg/kg/day	20–40 mg/kg/day (transfusion-associated iron overload) 10–20 mg/kg/day (nontransfusion-associated iron overload)
Frequency	8- to 24-hour infusion	3 divided doses daily	Once daily
Route	Subcutaneous or Intravenous	Oral tablet (solution available in some countries)	Tablets for oral suspension, to be taken on an empty stomach
Excretion	Urinary, some fecal	Urinary (primarily)	Fecal
Adverse Effects	Local site reactions Ocular disturbances Auditory disturbances Growth retardation and bony changes Neurological disturbances* Respiratory distress syndrome* Increased risk of *Yersinia* and *Klebsiella* infection	Agranulocytosis (ANC <0.5 × 10^9/L) Neutropenia (ANC=0.5 to <1.5 × 10^9/L) Gastrointestinal symptoms Change in appetite Skin rash Elevated hepatic enzymes Arthralgia and arthropathy Decreased plasma zinc	Ocular disturbances Auditory disturbances Gastrointestinal symptoms Skin rash Elevated serum creatinine Elevated hepatic enzymes Proteinuria Renal Fanconi syndrome Gastrointestinal bleeding Hepatic failure† Renal insufficiency and failure†
Special Monitoring	Ophthalmic exam annually Audiometry annually Knee radiographs in growing children Sitting height	Complete blood count with white blood cell differential weekly Hepatic enzymes Plasma zinc concentration	Ophthalmic exam annually Audiometry annually Hepatic enzymes and bilirubin monthly (also obtain 2 weeks after drug initiation) Creatinine monthly Urinalysis monthly
Approved Indications in United States	Acute iron intoxication Chronic iron overload associated with transfusion-dependent anemias	Transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate	Transfusional iron overload Chronic iron overload in nontransfusion-dependent patients (if serum ferritin >300 mcg/L and LIC ≥5 mg Fe/g dw)
Main Contraindications	Severe renal disease, anuria	Not recommended for patients with bone marrow failure syndromes	Severe hepatic impairment Elevated creatinine or reduced creatinine clearance Platelet counts <50x10^9/L
Pediatric Considerations	Recommended dose in children is ≤40 mg/kg/day Generally not recommended for children <3 years	Limited information on use in children	Recommended for children ≥2 years with transfusional iron overload Recommended for nontransfusion-dependent children ≥10 years
Challenges to Optimal Use	Adherence	Not currently approved for transfusional iron overload for other anemias Adherence with weekly lab testing Cost	Gastrointestinal symptoms with higher doses Cost

*Associated with higher doses of drug.

†More common in elderly patients with hematologic malignancies, low platelet counts and/or other cytopenias, and liver disease.

ANC=absolute neutrophil count; LIC=liver iron concentration.

75 mg/kg is similar to that induced by deferoxamine at a dose of 50 mg/kg.[56,57] Serum ferritin levels have generally been shown to improve[58-61] or stabilize[62-64] with deferiprone use, although a small proportion of patients demonstrated a significant increase in serum ferritin levels while taking deferiprone.[60,61,63,64] Similarly, studies have shown variable ability of deferiprone to lower liver iron levels, with improvement in some patients but with rising liver iron content in other patients treated at doses of 70–75 mg/kg daily.[59,63,65] Using higher doses of deferiprone of 83–100 mg/kg has led to a better reduction in serum ferritin and liver iron concentration in some patients.[66,67]

Deferiprone appears to be particularly efficacious at removing cardiac iron. Retrospective studies have demonstrated better cardiac T2* values[68] and reduced cardiac morbidity and mortality[69,70] among patients treated with deferiprone compared with deferoxamine. Furthermore, in a randomized, controlled trial of β-thalassemia patients with moderate cardiac siderosis (T2*, 8 to <20 ms) and normal left ventricular ejection fraction, a significantly greater improvement in cardiac T2* values and left ventricular function was seen with deferiprone compared with deferoxamine.[71]

Neutropenia (absolute neutrophil count, 500 to <1,500 × 10^9/L) and agranulocytosis (absolute neutrophil count, <500 x 10^9/L) are the most serious side effects associated with deferiprone, occurring with an incidence of approximately 2.1–5.4 per 100 patient-years and 0.4–0.6 per 100 patient-years, respectively.[60,62] Neutropenia is usually reversible with discontinuation of the drug, but often recurs with reinstitution of therapy.[60,72] Therefore, blood counts should be monitored weekly and obtained at the time of all febrile events, and deferiprone should be held if the child is febrile or infected. Treatment with deferiprone is not recommended for patients with underlying bone marrow failure syndromes such as DBA; these patients may be more likely to develop cytopenias.[73,74]

Gastrointestinal symptoms including nausea, vomiting, diarrhea, and abdominal pain have been reported in up to 33% of patients[64] and often improve after the first few weeks of treatment without discontinuing therapy.[60,62] Arthropathy with pain and/or swelling of the ankles, knees, and other large joints can develop early or late in treatment and has been reported to occur at variable rates of 4–38.5%.[60,64,75] Radiographic and MRI findings include subchondral bone changes and patellar beaks that may persist after cessation of deferiprone.[76] Deferiprone-associated arthropathy often is transient and resolves with discontinuation of the drug.[62,77,78] Transient elevations in alanine aminotransferase (ALT) also may develop, and usually resolve even if deferiprone is continued without dose adjustment.[60,75] Additionally, subclinical zinc deficiency develops in about 15% of patients with thalassemia major treated with deferiprone, warranting periodic monitoring of zinc levels in children and supplementation if indicated.[79]

Deferasirox

Deferasirox was the first oral iron chelator approved for use in the United States. The drug is supplied as orally-dispersible tablets that must be dissolved in a large glass of water or juice and taken once daily on an empty stomach.[80] Deferasirox at doses of 20–30 mg/kg/day causes a similar reduction in liver iron concentration and ferritin levels as deferoxamine.[37] Up to 30% of patients treated with deferasirox at doses above 30 mg/kg/day do not achieve satisfactory iron balance, which may be attributable to adherence difficulties or to individual variation in drug exposure.[81] Dividing the daily deferasirox dose into 2 doses given about 12 hours apart may improve iron excretion in poor responders,[82] although the drug currently is not labeled for twice-daily dosing.

Studies have found that treatment with deferasirox also can improve cardiac iron levels,[83] although patients who have very high liver iron levels may not respond as well.[84] In these studies, left ventricular ejection fraction also did not improve with deferasirox treatment,[84,85] and whether deferasirox can reverse cardiac disease is not yet clear. Reversal of cardiac dysfunction with deferasirox treatment has been reported in a couple of cases.[86,87]

The adverse effect profile of deferasirox generally is similar across disease states.[37,41,88] Gastrointestinal disturbances including nausea, vomiting, and abdominal pain occur in approximately 15.2–28% of patients,[37,89] and may be dose-limiting. In one follow-up study, gastrointestinal adverse effects were less commonly reported in patients <16 years (15.8%) than in patients ≥16 years (29.1%).[90] Nephrotoxicity includes mild elevations in serum creatinine levels in about one-third of patients, and intermittent proteinuria.[37,41] Monthly monitoring of renal function and urinalysis is recommended. Elevations in ALT occur in approximately 1–6% of patients, including elevations above 5 times the baseline value that necessitate holding the drug.[37,41,91] Liver function tests should be obtained 2 weeks after drug initiation, and monthly thereafter. Transient, diffuse, maculopapular skin rashes have been reported in approximately 10% of patients receiving deferasirox.[37,41,89,92] Rare serious side effects include renal Fanconi syndrome, renal failure, fulminant hepatic failure, and gastrointestinal bleeding.[93-96] Cataracts or lenticular opacities and audiotoxicity were reported at low rates, similar to deferoxamine.[37,41]

Long-term follow-up studies of deferasirox in general have not shown an adverse effect on pubertal development and growth in children.[97] One study found that children younger than 12 years had slightly decreased

growth compared with a control population, but it is not clear whether this was associated with deferasirox use or the underlying anemia.[90]

Combination Chelation Therapy

Combination chelation therapy should be considered when iron burden is not well controlled on monotherapy, when cardiac iron loading is present, or when drug toxicities prevent adequate dosing of a single agent. Treatment with 2 chelators may improve adherence, improve organ-specific iron removal, minimize/reduce toxicity, and enhance iron removal if an additive or synergistic effect occurs. Most published data of combination chelation regimens involve treatment of patients in their teens and older.

The most extensively studied chelator combination is that of deferiprone and deferoxamine, which is used in a variety of dosing regimens.[66,98,99] A significant reduction in serum ferritin levels and liver iron concentration has been demonstrated with this 2-drug combination.[98-100] In addition, 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 has been proposed, whereby deferiprone, a smaller molecule, enters cardiac myocytes, binds iron, and then transfers it to deferoxamine for excretion.[101,102] In a large, randomized, placebo-controlled trial of deferoxamine monotherapy compared with deferoxamine and deferiprone for the treatment of patients with mild to moderate cardiac iron loading (cardiac T2*, 8–20 ms), cardiac T2* and cardiac function improved to a greater extent with the combination therapy than with deferoxamine monotherapy.[100] In a nonrandomized trial, combination deferoxamine and deferiprone therapy also led to an improvement in cardiac T2* and left ventricular ejection fraction in patients with severe myocardial siderosis and myocardial dysfunction.[103]

Limited data on the combination of deferoxamine and deferasirox are available. Iron balance studies support an additive or possibly synergistic effect when the 2 drugs are given together.[104] In a pilot study, 22 patients older than 8 years with transfusion-dependent thalassemia and severe iron overload and/or evidence of organ dysfunction were treated with deferoxamine and deferasirox.[105] A significant reduction in liver iron concentration and ferritin levels was seen after 1 year of treatment, and all 6 patients with abnormal cardiac T2* at baseline showed improvement. In addition, no unexpected adverse events were reported, including no increased hepatic or renal toxicity. Additional safety and efficacy data are needed before clinical recommendations for the combination of deferasirox/deferoxamine can be made.

Combination therapy with the 2 oral chelators, deferasirox and deferiprone, would be particularly desirable, but data regarding such therapy are limited. In a pilot study of 15 adult patients with thalassemia major and well-controlled iron burden treated with the combination of deferasirox and deferiprone, a significant reduction in serum ferritin and liver iron concentration was seen after 12–24 months of therapy.[31] There was no increase in adverse effects over the rate expected with monotherapy.[31] Further studies assessing the combination of deferasirox and deferiprone in patients with high iron burdens, cardiac iron loading, and organ dysfunction are needed.

Other Oral Chelators in Development

FBS0701 is a new oral chelator administered once daily. In a phase II study of 2 dose levels, 16 and 32 mg/kg/day (salt form), the mean liver iron concentration rose by 3.1 mg/g dry weight with the low dose, while a minimal reduction of 0.3 mg/g dry weight was seen with the higher dose.[106] A total of 29% of patients who received the lower dose and 44% of patients who received the higher dose achieved a reduction in liver iron concentration. Gastrointestinal side effects including nausea, vomiting, abdominal pain, and diarrhea were each noted in <5% of patients. Importantly, serum creatinine levels did not increase. Eight patients (16%) had a rise in ALT, but 3 of these patients acquired hepatitis C infection during the study and the remaining 5 had abnormal transaminases at baseline. Data on cardiac iron removal are not yet available. A second phase II study using higher doses of the medication (50 and 75 mg/kg/day, salt form) in adults is ongoing,[107] and a phase II study in children with transfusional iron overload also is ongoing.[108]

Summary

Children who are receiving regular red cell transfusions require iron chelation therapy. Three iron chelators, deferoxamine, deferiprone, and deferasirox, have undergone extensive study and are in clinical use worldwide, although deferiprone is approved only as a second-line agent in North America, and limited data on use in children are available. The chelator properties, including tolerability, efficacy at both cardiac and liver iron removal, adverse effect profile, and patient/family preference should be considered in tailoring each child's chelation plan. Trends in ferritin and liver and cardiac iron burden, along with ongoing transfusional iron intake, should be used to adjust the dosing and type of chelator. In growing children, the risks of overchelation need to be balanced with the risks of cumulative iron exposure.

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