

Iron Overload and Iron Chelation Therapy in Pediatric Patients

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Abstract

Iron overload is an unfortunate clinical consequence of repeated blood transfusions that can cause significant organ damage, morbidity, and mortality in the absence of proper treatment. Pediatric patients with transfusion-dependent pathologies face the additional risk of growth failure and poor sexual development owing to iron build-up in the anterior pituitary gland. Iron chelation therapy is necessary for the removal of excess iron, but treatment efficacy and success are highly dependent on patient compliance. Deferoxamine is a well-established but inconvenient therapy requiring parenteral administration over extended periods of time. Patient compliance can be improved with use of the oral iron chelators deferasirox and deferiprone. Long-term data have shown deferasirox to have a good safety and efficacy profile in pediatric patients.

Keywords

Iron overload, hemoglobinopathies, pediatric, iron chelator, compliance

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Hemoglobinopathies such as thalassemia and sickle cell disease (SCD) impose a significant burden on global healthcare, with >300,000 afflicted infants born each year and approximately 5% of the global population carrying a potentially pathological hemoglobin gene.¹ The anemia resulting from these conditions is commonly managed by red blood cell (RBC) transfusions in addition to treatment targeting the underlying disease. Chronic transfusions are routinely used in thalassemia patients to prevent life-threatening anemia, and studies have shown that regular transfusions in children with SCD can significantly reduce the risk for primary and secondary stroke, hospitalizations, vaso-occlusive events, acute chest syndrome, and growth failure.²⁻⁴

The Clinical Significance of Iron Overload

Although the benefits of regular RBC transfusions in patients are increasingly recognized, this approach also has the clinical consequence of iron overload, often presenting as a secondary disease among transfusion-dependent patients. Because each unit of transfused RBCs contains 200–250mg of iron, repeated transfusions can rapidly overwhelm the body's iron-binding capacity of transferrin such that iron overload can develop after as few as 10 transfusions.^{5,6} With no mechanism for active excretion of excess iron, iron overload presents a serious and potentially fatal condition. Without therapeutic intervention, non-transferrin-bound iron (NTBI), formed by a weak complex between excess iron and other proteins or low-molecular-weight organic

molecules, circulates through the body and preferentially deposits in the liver, spleen, myocardium, and endocrine organs. This leads to progressive damage and functional impairment of these organs and, ultimately, significant morbidity and mortality.^{7,8} Iron overload is particularly harmful in children, as the accumulation of excess iron in the anterior pituitary gland can interfere with normal endocrine function, leading to growth failure and adverse effects on sexual maturation.⁹

Assessment of Iron Burden in the Body

The iron load in the body can be measured using several methods, including liver biopsies and serum ferritin levels. As over 70% of excess iron deposits in the liver in iron overload,¹⁰ liver iron content has been accepted as the most accurate quantitative means of determining whole-body iron concentration. However, liver biopsy is not indicated for routine assessment due to its invasive nature. Although serum ferritin levels are much more conveniently and easily assessed, they can be influenced by inflammation, ascorbate levels, and intercurrent diseases, and therefore may not accurately reflect total body iron stores.¹¹⁻¹⁵ This in turn can hinder the physician's ability to determine optimal iron chelation therapy. Non-invasive techniques such as superconducting quantum interference device (SQUID) and magnetic resonance imaging (MRI) are increasingly being used to monitor iron chelation therapy, resulting in improved management of iron overload.¹⁶⁻¹⁹ SQUID measures changes in magnetic flux, directly

correlating the paramagnetic response to the amount of iron stored in a certain volume of tissue. In MRI, the hemosiderin molecules in iron disrupt the local magnetic field; a greater iron deposit causes quicker signal decay rates. These decay rates are measurable and proportional to tissue iron concentration, allowing for an indirect evaluation of iron load in an entire organ.^{18,19} The ability to measure and quantify the iron burden in the body is crucial for determining the extent of iron chelation therapy; the timely removal of excess iron from the body is necessary in order to maintain safe levels of iron in the body, limit bodily exposure to NTBI and its toxicities, and prevent the clinical consequences of long-term iron overload.

Current Options in Iron Chelation Therapy for Pediatric Patients

At present, two iron chelation therapies are available to patients in the US with transfusion-dependent hemoglobinopathies: deferoxamine and deferasirox. Deferiprone is a third option for patients in many countries outside of the US.

Deferoxamine

Deferoxamine (Desferal, Novartis Pharma AG) is the current standard of care in iron chelation therapy, with over 40 years of clinical experience and an established effect on long-term survival and morbidity in thalassemia patients, and decades of clinical use demonstrate its excellent safety and efficacy profile for pediatric patients with thalassemia.²⁰⁻²² Furthermore, there is evidence to suggest that continuous deferoxamine infusions over the long term may be able to reverse iron-induced heart failure.²³ However, its poor oral bioavailability and short half-life in plasma necessitates parenteral administration, either subcutaneously as an eight- to 12-hour overnight infusion at least five days a week or as a 24-hour continuous intravenous infusion. Deferoxamine can also cause visual and auditory neurotoxicities.^{24,25} The prolonged and burdensome administration, coupled with the adverse effects, can become a cause of low compliance, particularly in adolescent patients. Poor compliance has significant implications for the outcome of chelation therapy and survival in iron-overloaded pediatric patients, as many of these patients will require iron chelation therapy for the duration of their lives.²⁶ With this in mind, more convenient, well-tolerated, and effective oral iron chelators have since been developed to improve patient compliance.

Deferasirox

The first oral iron chelator introduced to the US was deferasirox (Exjade, Novartis Pharma AG), which is additionally licensed in Europe and other regions for the treatment of iron overload. Its long half-life of 11–19 hours maintains plasma levels within the therapeutic range over a 24-hour period, allowing for a convenient once-daily oral administration and offering a viable option over deferoxamine and its associated problems with compliance.^{27,28} The pharmacokinetics of deferasirox in pediatric patients is similar to that in older patients: once-daily dosing is able to control freely circulating plasma iron during a 24-hour period, preventing potential damage by NTBI.²⁹ *In vitro* and animal studies currently suggest that deferasirox can enter cardiac tissue and remove cardiac iron.³⁰ Clinical studies have shown the ability of deferasirox to significantly reduce cardiac iron burden after 12 months of treatment and maintain low cardiac iron levels for two years.³¹ Preliminary data

also show that after six months of deferasirox treatment, thalassemia patients experienced significant improvements in cardiac MRI T₂*, liver iron concentration, and labile plasma iron, with 93% of patients achieving a negative cardiac and liver iron balance.^{32,33} Dosing recommendations for deferasirox are identical for pediatric and adult patients, taking into account changes in weight over time, with a recommended starting dosage of 20mg/kg bodyweight.³⁴ Monthly monitoring of serum ferritin upon initiating therapy is advised, with adjustments of deferasirox dosage in steps of 5 or 10mg/kg bodyweight every three to six months to a maximum of 40mg/kg bodyweight on the basis of serum ferritin levels if necessary; this allows for individualized therapy according to a patient's specific response and therapeutic goals. Some patients have a suboptimal response to deferasirox, which may be based on transfusion burden and variable bioavailability. Therefore, close monitoring of the iron stores and deferasirox dosing are indicated in all patients.³⁵

The efficacy, safety, and tolerability of deferasirox were assessed in five pivotal clinical studies in a number of patients with transfusion-dependent anemias, of whom nearly half were children.^{28,36-39} Deferasirox was shown to induce significant and dose-dependent reductions in liver iron concentration and serum ferritin levels after one year of treatment across patients with a range of severe chronic anemias.³³⁻³⁸ Patients from four earlier trials with deferasirox were eligible for a four-year extension trial;⁴⁰ after 42 months, a subgroup analysis of 434 pediatric patients showed that the median serum ferritin level fell below baseline following a continued dose-dependent effect on serum ferritin levels.⁴¹ Significantly, these patients experienced normal physical and sexual development with deferasirox treatment.⁴¹

The safety profile is similar for pediatric and adult patients.^{37,39} Commonly reported drug-related adverse events in pediatric patients include mild, transient diarrhea and vomiting (4.4%), abdominal pain and nausea (3.9%), and mild or moderate skin rash (5.5%).⁴² Deferasirox-associated gastrointestinal events generally resolved on their own, but approximately 0.5% of patients discontinued therapy due to severe gastrointestinal symptoms. Therapy that is interrupted due to severe diarrhea can be reinstated at 10mg/kg/day after the diarrhea has cleared, with a gradual dosage escalation of 5mg/kg each week until the target dosage is achieved. Monthly monitoring of patient creatinine levels is recommended. Studies have reported mild and non-progressive increases in serum creatinine >33% above baseline in 38% of adult patients receiving deferasirox, although these increases were generally within the normal range, rarely exceeding twice the upper limit of normal (ULN).²⁸ Only a small percentage of pediatric patients (4.2%) exhibited increases in serum creatinine >33% above baseline, many of which resolved spontaneously. A one-year study comparing deferasirox with deferoxamine in pediatric and adult patients with SCD found no increased risk for renal damage with deferasirox, with similar transient increases in creatinine above the ULN (2.3 and 3.2%, respectively).³⁸ Long-term data have not shown any increased or unexpected adverse events with deferasirox therapy in pediatric or adult patients, and there have been no reports of progressive increases in serum creatinine.^{40,41,43,44} Post-marketing reports have included cytopenias and cases of acute renal failure.^{34,45} However, the reported cytopenias were

in patients with pre-existing hematological disorders requiring concomitant medication, providing an unreliable causal relationship with deferasirox.³⁴ Further, these post-marketing reports are from a population of uncertain size where concomitant medication may not be disclosed, and it is therefore difficult to estimate the frequency or establish a causal relationship with deferasirox.³³ Regular monitoring of liver function and blood counts are advised as a precaution.

Deferiprone

Taken three times a day, the orally available deferiprone (Ferriprox, Apotex Inc.) has a demonstrated ability to reduce or maintain body iron stores,⁴⁶ and there is evidence to suggest that deferiprone may be better able to chelate cardiac iron and protect against iron cardiotoxicity than deferoxamine.^{47–50} The combination of deferoxamine plus deferiprone has also been investigated in the attempt to optimize body iron removal, and studies have documented considerably greater urinary excretion of iron with simultaneous use of the drugs than either drug as monotherapy.^{51,52} The combination of deferoxamine and deferiprone may also reduce the risk for developing cardiac disease and improve cardiac function;^{53–56} this is an area currently under investigation. Preliminary data suggest survival is improved in patients treated with combination deferoxamine/deferiprone therapy.⁵⁷ Long-term safety data for the combination of deferiprone and deferoxamine are being studied, and careful monitoring on a regular basis is necessary.

Deferiprone monotherapy is associated with the adverse effects of gastrointestinal symptoms, joint pain, and liver dysfunction, but the most serious adverse effects are neutropenia and agranulocytosis.^{58,59} A safety study of deferiprone in 44 children <6 years of age with thalassemia major has reported similar results to the drug's overall safety profile; commonly reported adverse events were gastrointestinal (27% of patients), joint symptoms (9%), and neutropenia (4%).⁶⁰ Although no cases of agranulocytosis were reported in this specific study even after a median duration of 13 months,⁶⁰ there are documented agranulocytosis-associated deaths in pediatric patients.⁶¹ Weekly assessment of white blood cell count is therefore required for patients receiving deferiprone therapy. While licensed in Europe and other regions for iron overload, deferiprone is not licensed in the US or Canada, and is available in these countries only under a compassionate-use program. It is currently being reviewed by the FDA.

Satisfaction in Iron Chelation Therapy

Decades of deferoxamine use in clinical practice have established its safety and efficacy profile in pediatrics; however, there remains an issue with compliance in transfusion-dependent patients, particularly in those with thalassemia in whom lack of compliance can greatly affect survival.⁶² The demanding therapeutic regimen of deferoxamine can also reduce quality of life; over 50% of patients with thalassemia have said that deferoxamine often or very often disrupts or prevents their

activities, and 65% of patients have admitted to disliking the treatment.⁶³ By comparison, 80% of patients with SCD and 93% of patients with thalassemia found deferasirox to be more convenient than deferoxamine, with a greater proportion of patients reporting satisfaction with deferasirox.^{64,65} Data comparing compliance between the thrice-daily oral chelator deferiprone with deferoxamine in patients with thalassemia have shown median improvements in compliance of 11.4% from baseline with deferiprone and declines of 4.3% from baseline with deferoxamine.¹⁶ These results have prompted researchers to speculate that the more convenient dosing of deferasirox may further improve compliance versus deferoxamine by 16%, with an estimated compliance of 74%.⁶⁶ Patients have indeed shown higher compliance with deferasirox therapy over deferoxamine: in one study, the ratio of the administered to intended doses of therapy was 1.16 and 0.97 for deferasirox and deferoxamine, respectively.³⁸

Conclusions

Compliance with iron chelation therapy is a crucial point to consider, as more often than not children with transfusion-dependent hemoglobinopathies require lifelong iron chelation therapy for the treatment of iron overload. Without proper treatment, pediatric patients with iron overload face the risk of delayed sexual and physical maturation, liver and heart disease, and reduced life expectancy. The current standard of care is the parenterally administered deferoxamine, a stringent regimen in which the regular and prolonged infusions can be burdensome, particularly in pediatric patients. Deferoxamine remains the gold standard for iron chelation therapy, with a long safety record. Patients whose iron stores are well controlled with deferoxamine should have the option to continue this therapy. The oral chelators deferiprone and deferasirox are now available in many parts of the world. Deferiprone has the potential to decrease cardiac disease, but there are concomitant risks of developing neutropenia. The once-daily dosing of deferasirox has proved to be efficacious in reducing iron load, while also presenting a safe and convenient alternative for most patients with transfusion-dependent anemias. ■



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