

## Iron Chelator Therapy

a report by

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Iron plays a vital role in the metabolic processes of all living organisms. It is involved in oxygen transport, DNA synthesis, and energy generation. As with many nutritional metals, an excess of iron is dangerous, and therefore within the body iron equilibrium is carefully regulated. Unlike other metals, however, iron is highly conserved in the body and is heavily recycled. Extracellular iron is insoluble, unless bound by the glycoprotein transferrin. Within tissue it is stored in ferritin, typically in the liver, bone marrow, and spleen. Non-transferrin-bound iron (NBTI) is toxic and has been described in most forms of iron overload. The iron excretion process is essentially non-existent; aside from bleeding events, iron is lost only through the shedding of cells from the skin and intestinal tract.<sup>1</sup> Therefore, physiological prevention of iron overload occurs through regulation of iron uptake. The presence of iron excess can lead to organ damage.

### Iron Overload

An excess of iron in the body can cause damage in two ways. Large iron deposits—particularly in the liver, heart, and endocrine organs—can damage the tissue and disrupt the normal functioning of the body. The most serious complication is cardiac disease, estimated to be the cause of death in approximately two-thirds of patients with thalassemia major.<sup>2</sup> Furthermore, unbound, freely circulating iron can catalyze the formation of highly reactive hydroxyl radicals.<sup>3</sup> These have the potential to damage cellular lipids, nucleic acids, proteins, and carbohydrates, resulting in wide-ranging impairment of cellular function and integrity.<sup>4</sup> This process leads to tissue damage and, ultimately, to significant morbidity and mortality.<sup>5</sup> Iron intoxication or iron overload can happen gradually, through slow accretion over time from dietary sources or blood transfusions, or acutely, often caused by a large single dose of an iron-rich supplement. Gradual iron overload can be a consequence of certain conditions, and is classified as either primary or secondary depending on whether it results from a congenital defect in iron homeostasis or is secondary to other genetic or acquired disorders and/or their treatment. Primary disorders of iron overload include various types of hereditary hemochromatoses. Secondary conditions include anemias, such as beta-thalassemia and sickle cell disease, or those that can lead to anemia, such as myelodysplasia.<sup>6</sup> Such conditions can lead to transfusion dependency and thus result in an additional intake of excess iron. Only around 10–20 blood transfusions are required for a patient to develop iron overload. This type of iron overload will be the focus of this article.

### Measuring Iron Levels

Iron overload is assessed by measuring liver iron concentration (LIC) and serum ferritin levels. The latter is the traditional indicator of choice for total body iron stores as it is a relatively inexpensive test and is easy to perform. Treatment is normally initiated when serum ferritin levels exceed 1,000ng/ml.

However, serum ferritin is not necessarily the most reliable marker, since it is also an acute-phase reactant and may be elevated owing to inflammation, for example.<sup>8</sup> Total body iron is determined by measuring LIC using liver biopsy. LIC values greater than 7mg Fe/g dry weight (dw) have been reported in the literature to be associated with an increased morbidity and mortality. This test, however, is quite invasive and carries inherent risks. Thus, non-invasive techniques have been developed to measure LIC, including magnetic resonance imaging (MRI) scans.<sup>9</sup> As already indicated, however, the majority of fatalities from iron overload in beta-thalassemia patients are due to iron-induced cardiac dysfunction. LIC can also be measured using a superconducting quantum interference device (SQUID), which has been shown to be equivalent to biochemical determinations taken from biopsy, but there are still limited numbers of these devices currently available for routine clinical use.<sup>10,11</sup> Neither serum ferritin nor LIC levels correlate with cardiac iron content, so a dedicated MRI T2\* has been developed where a score of less than 20ms indicates ventricular dysfunction.<sup>12</sup>

### Available Iron Chelators

Several studies have highlighted the potential danger of leaving iron overload untreated.<sup>13</sup> As noted, there are no innate primate mechanisms for iron removal, but there are compounds developed by microbes that can bind to iron and create an inert molecule that can be excreted through the normal routes. These microbial siderophores are iron chelators (from the Greek for claw—so-called because that is what the molecular structure resembles). Efficiency can be limited, however, because most of the body's iron stores are bound by ferritin within the cells and are thus not directly chelatable. Once iron has been deposited in organs other than the liver, most notably the heart, removal by chelation is slow and inefficient. A negative balance needs to be established to draw iron out, which will necessitate a near continuous chelator plasma presence. From the 1960s until the late 1990s, the only chelator available, and thus the only way to treat iron overload, was deferoxamine (DFO; Desferal®), developed from a microbial siderophore.<sup>14</sup> It is a hexadentate chelator, binding iron on a 1:1 ratio, excreted in bile and urine.<sup>15</sup> It is, however, also highly hydrophilic, making it poorly absorbable in the gastrointestinal tract and giving it a very short plasma half-life of around 12 minutes.<sup>16</sup> These properties require DFO to be administered via subcutaneous infusion for up to 12 hours per day, five to seven days a week. Such cumbersome requirements mean that although DFO is an effective iron chelator, compliance with therapy and thus patient outcomes are often suboptimal.

Attention has therefore turned toward the development of an orally available chelator. The first to be developed was deferiprone (Ferriprox®), also known as L1; it is a bidentate chelator that binds iron on a 3:1 basis. It has a moderate

half-life at around three hours, so must be taken three times per day. It is not available in the US, but is licensed for use in Europe as a second-line treatment for iron chelation in patients for whom DFO is not effective/suitable or for those who are allergic to DFO. There is some evidence that deferiprone is more effective than DFO at removing iron from cardiac tissue, but also that it may cause liver fibrosis; these results remain controversial.<sup>17</sup> In addition, there are concerns about neutropenia and agranulocytosis.<sup>18</sup> In those countries where it is approved, use of deferiprone requires strict monitoring of white blood cells.

The most recent compound to become available is deferasirox (Exjade®, formerly ICL670A), a rationally designed tridentate chelator that binds 2:1 with iron. Unlike the existing chelators, it is in the bis-hydroxyphenyl-triazole class. It was approved by the US Food and Drug Administration (FDA) in November 2005 for the treatment of chronic iron overload caused by blood transfusions (transfusional hemosiderosis) for patients aged two years and older. Like deferiprone, deferasirox is orally available, but with a much longer half-life of eight to 16 hours. This permits a once-daily administrative regimen, with the tablets dissolved in water or orange or apple juice; this is particularly important for pediatric patients, who account for a large proportion of some anemia populations. In animal trials, deferasirox showed highly potent activity, with iron clearance four to five times that of DFO.<sup>19</sup> In a multinational phase III randomized trial, deferasirox was compared with DFO over one year in pediatric and adult patients with beta-thalassemia receiving regular blood transfusions. The primary end-point was to prove the non-inferiority of deferasirox.<sup>20</sup> The trial randomized patients to deferasirox (n=296) or DFO (n=290). The initial dose of either drug was based on the initial LIC level, although those in the DFO arm remained on their existing dose, which was often higher than would have been prescribed *de novo* in the trial. This dose uncertainty may have contributed to the failure of the trial to reach its primary end-point, particularly concerning patients with mild to moderate iron overload in whom the administered levels of deferasirox were too low compared with DFO. Nevertheless, it is important to note that with appropriate dosing deferasirox maintained or reduced iron burden. In patients with LIC values greater than 7mg Fe/g dw, the success rates were similar for both drugs. Moreover, in the highest-risk group of frequently transfused patients, receiving two to four units per month, once-daily deferasirox 20mg/kg maintained LIC, neutral iron balance, and stable serum ferritin levels.<sup>20</sup>

Perhaps the most important element of any new chelator therapy, given the issues with DFO, is compliance. In the trials of deferasirox, 97% of thalassemia patients who switched from infusion with DFO to the new drug preferred it compared with 0.7% who preferred DFO.<sup>21</sup> In addition, 84% of DFO-naïve patients found deferasirox convenient or very convenient compared with only 28% of patients on DFO. Deferasirox was also considered to have less impact on daily life, and more patients were willing to continue treatment with it after the end of the study. In terms of adverse events, the most common symptoms reported in the deferasirox arm of the trial were abdominal pain, nausea, vomiting, diarrhea, constipation, and skin rash. These tended to be of mild to moderate severity, and were often

transitory. In clinical trials, increases in serum creatinine >33% on ≥2 consecutive occasions have occurred in about 36% of patients. The increases were dose-dependent and occurred mainly with daily doses of 20–30mg/kg, whereas lower doses of 5–10mg/kg were better tolerated. Subsequently, it is recommended that particular attention be given to monitoring serum creatinine in patients who are at increased risk of complications, have pre-existing renal conditions, are elderly, have comorbid conditions, or are receiving medicinal products that depress renal function. These patients should be monitored weekly during the first month after initiation or modification of therapy, and monitored monthly thereafter. Dose reduction, interruption, or discontinuation should be considered for increases in serum creatinine.<sup>22</sup> While most evidence has been gathered for the benefit of deferasirox in treating iron overload as a result of transfusions in patients with thalassemia, there is mounting evidence that it also has utility to treat iron overload as a result of myelodysplastic syndromes.<sup>23</sup>

### Future Development

Other new chelators are in development. One strategy involves attaching DFO to hydroxyethyl starch to create S-DFO—a high-molecular-weight compound with a longer circulation time. A phase Ib study involving four transfusion-dependent patients with beta-thalassemia showed that weekly transfusion of doses at 150, 300, 600, and 900mg/kg resulted in significant urinary iron excretion, and there were only minor adverse events.<sup>24</sup> Another new compound in development is deferitron, an orally active tridentate compound in the ferrithiocin class of chelators. A phase II clinical trial designed to compare the safety and iron excretion properties of DFO and deferitron has recently been completed, and results are pending.

### Summary and Conclusions

Iron metabolism is finely balanced in the human body. Blood transfusions are life-saving interventions for conditions such as thalassemia and myelodysplastic syndromes, but have an attendant problem of their own: additional iron intake. There is no effective way for the body to rid itself of excess iron. Iron overload, involving the build-up of iron in organs and the creation of damaging hydroxyl radicals, can lead to significant morbidity and mortality if not kept in check. For more than 40 years, chelator therapy has helped patients to reduce their iron levels and avoid the worst effects of iron toxicity. The gold standard treatment, deferoxamine, has a very limited serum half-life, however, and needs to be transfused over a long period of time. Therefore, while effective, compliance rates are low, leading to suboptimal results. An alternative, orally available chelator, deferiprone, developed more than a decade ago, is not licensed for use in the US. There is a new chelator available, however: deferasirox, licensed in 2005. Deferasirox is an orally available chelator with a long plasma half-life, and the first once-daily compound for the treatment of iron overload caused by transfusion. So far the compound appears to be effective and well-tolerated and, critically, has fewer compliance issues than deferoxamine. While trials are still ongoing concerning its long-term effects and efficacy in removing iron deposited in the cardiac tissue, it is a valuable addition to the iron overload armamentarium. ■

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