Removing the Burden—Iron Overload and Deferasirox (ICL670)

a report by
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Transfusions and Toxicity

Long-term red blood cell transfusion therapy is a routine and life-saving treatment for patients with chronic anemias such as thalassemia, sickle cell disease (SCD) and myelodysplastic syndromes (MDS). While the life-threatening consequences of these anemias can be overcome by regular blood transfusions from over many years, this supportive therapy can itself cause undesirable disorders of iron balance. Each unit of transfused blood contains 200–250mg of iron. As the human body has no mechanism for actively clearing excess iron, a regularly transfused thalassemia patient can quickly develop iron overload after 10–20 transfusions.[1]

Iron in blood plasma is bound to transferrin, a dedicated iron-binding protein that minimizes the concentration of 'free' unbound iron. Excess iron leads to saturation of transferrin and results in high plasma levels of non-transferrin-bound iron (NTBI), which is taken up by tissue in a seemingly uncontrolled manner. The presence of stored iron is associated with damage to various tissue types, endocrine dysfunction, cancer and other sequelae. The most serious complication, however, is cardiac disease, which is estimated to be the cause of death in approximately two-thirds of patients with thalassemia major.[2] Unless body iron levels are effectively controlled, regularly transfused patients are likely to suffer significant morbidity and mortality.

Maintaining a Balance

A number of key studies have demonstrated a poor prognosis if iron overload is left untreated.[3] Patients who develop iron overload can, however, be effectively managed by iron chelation therapy. Since the 1960s, iron chelation therapy with deferoxamine (Desferal®, DFO) has been key to improving the prognosis of patients with transfusion-dependent anemias. While the efficacy of DFO has been unequivocally demonstrated over many years of clinical use, studies have shown that patient survival is closely linked to compliance.[4] DFO has poor oral bioavailability and is, therefore, administered as a slow subcutaneous or intramuscular infusion 8–12 hours per day, 5–7 days per week. The burden of this regimen means some patients have difficulty complying with treatment.

Deferasirox (Exjade®, ICL670) is a novel, once-daily, oral iron chelator with very high affinity and specificity for iron. In November 2005, deferasirox was approved by the US Food and Drug Administration (FDA) for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients two years of age and older. Deferasirox tablets are simply dispersed by stirring in a glass of water, orange or apple juice (doses of <1g should be dispersed in 3.5 ounces of liquid and doses of >1g in 7 ounces of liquid). This is particularly convenient for pediatric patients who comprise a large proportion of some anemia populations. Deferasirox is the only oral chelator available in the US that offers 24-hour chelation coverage with a single dose, as shown in *Figure 1*. In this way, it provides uninterrupted protection against labile plasma iron, the toxic component of NTBI.[5]

Compliance and Convenience

As mentioned above, compliance with therapy is a key factor determining the outcome of iron chelation therapy. In the deferasirox trials, 97% of thalassemia patients who switched from infusion with DFO to oral deferasirox preferred deferasirox, compared with 0.7% who preferred DFO.[7] In addition, 84% of DFO-naïve patients found deferasirox convenient or very convenient compared with only 28% of patients treated with DFO. Patients also said that deferasirox had less impact on their daily life and many more patients were willing to continue deferasirox after the end of their study. Similar results have been observed in patients with SCD.[8] This superior satisfaction with, and convenience of, deferasirox versus DFO may translate into improved patient compliance and, therefore, increase the effectiveness of chelation therapy.

The efficacy and safety of deferasirox have been demonstrated in a comprehensive and rigorous multinational clinical trials program. To date, more than

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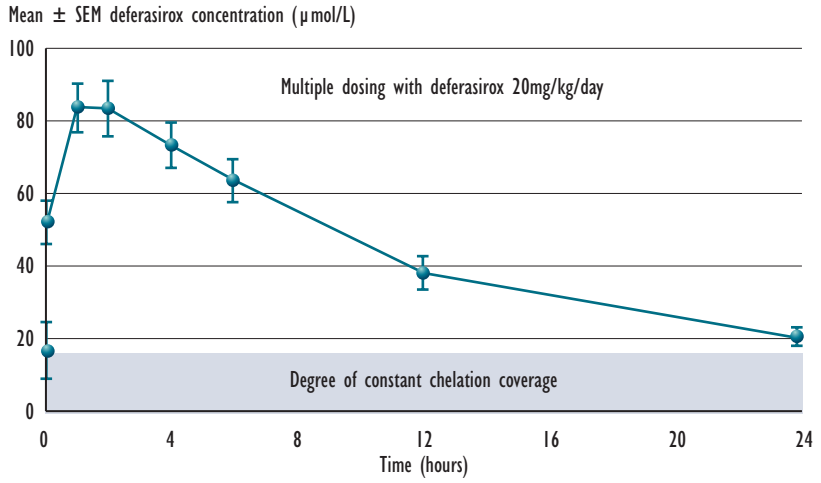
Figure 1: Exjade Offers 24-hour Chelation with a Single Oral Dose



Source: adapted from Daar S, et al., Haematologica *(2006);91:Abstract 31.*

1,000 patients with a range of anemias have received deferasirox, some for up to 3.5 years. In patients with thalassemia, SCD, MDS, and other, rarer anemias, deferasirox has consistently demonstrated stable or falling liver iron concentration at doses of 20–30mg/kg/day over one year. These effects were mirrored by changes in serum ferritin levels. The results of the core studies demonstrate that deferasirox is effective across a wide range of ages; preliminary data from the long-term extension trials are also extremely encouraging.

The response to deferasirox is dependent on both dose and the rate of transfusional iron intake.[9] In patients with low transfusional requirements (<2 units of blood/month), deferasirox 10mg/kg/day is able to maintain iron balance, while in patients with intermediate requirements (2–4 units of blood/month), deferasirox 20mg/kg/day maintains or reduces iron balance. Deferasirox 30mg/kg/day decreases iron balance in most patients, irrespective of transfusional iron intake. This shows that deferasirox dosing is flexible and can be individually tailored to meet a patient's need.

Safety First

In the studies mentioned here, deferasirox was generally well tolerated across a wide range of ages and transfusion-dependent anemias. Deferasirox is, however, contraindicated in patients with hypersensitivity to deferasirox or to any of its other components. The most common adverse events (AEs) following deferasirox therapy were mild to moderate, transient, dose-related gastrointestinal disturbances (nausea, vomiting, diarrhea, abdominal pain), increases in serum creatinine, and skin rash. These typically resolved spontaneously without discontinuation of treatment. Some AEs required treatment to be temporarily disrupted, although most patients were rechallenged after the event resolved. In the pivotal multicenter, randomized, active-controlled phase III clinical trial, Study 107, serious AEs were reported in 9.1% of patients in the deferasirox arm and 8.6% of patients in the DFO arm.[10]

In cases of skin rashes of mild to moderate severity, deferasirox may be continued without dose adjustment, since the rash often resolves spontaneously. For more severe rashes where interruption of treatment may be necessary, deferasirox may be reintroduced at a lower dose and gradually escalated after resolution of the rash; additionally, a short period of oral steroid administration may be considered.

Non-progressive increases in serum creatinine were noted within the first four weeks of treatment in 38% of deferasirox-treated patients in clinical trials, compared with 15% of DFO-treated patients. These increases were dose-related and within the normal range in 94% of patients. There were no cases of moderate to severe renal insufficiency or renal failure, and no patients permanently discontinued therapy due to creatinine rises. Most of these non-progrssive creatinine increased resolved spontaneously, while the rest were generally reversible with dose reduction or interuption. Dose adjustments should be made where necessary to manage serum creatinine, which should be assessed before initiating therapy and monitored monthly thereafter to determine whether dose modification or discontinuation is necessary.

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In the 107 study, intermittent proteinuria (urine protein/creatinine ratio >0.6mg/mg) occurred in 18.6% of deferasirox-treated patients, compared with 7.2% of DFO-treated patients; close monitoring of proteinuria is, therefore, recommended. A total of 5.7% of study patients treated with deferasirox developed elevations in liver enzyme (SGPT/ALT) levels more than five times the upper limit of normal at two consecutive visits, compared with 1.7% of patients treated with DFO. As a precaution, therefore, it is recommended that liver function also be monitored monthly, and if there is an unexplained, persistent or progressive increase in serum transaminase levels, treatment with deferasirox should be interrupted or discontinued.

Auditory (high-frequency hearing loss and decreased hearing) and ocular (lens opacities, cataracts, elevations in intraocular pressure and retinal disorders) disturbances were reported in <1% of patients who received deferasirox; auditory and ophthalmic testing (including slit lamp examinations and dilated fundoscopy) are nonetheless recommended before the initiation of deferasirox therapy, then every 12 months. If disturbances are noted, dose reduction or interruption should be considered.

Summary

Patients with untreated transfusional iron overload are likely to suffer significant morbidity and mortality. Registered by the FDA in the US in November 2005, deferasirox is the only iron chelating agent that offers 24-hour protection against iron overload and related consequences with once-daily oral dosing. A comprehensive program of clinical trials has demonstrated the efficacy of deferasirox in adult and pediatric patients across a range of transfusion-dependent anemias, and has shown that deferasirox is generally well tolerated. These trials also showed that oral deferasirox is preferred over the demanding regimen of DFO infusions, and may lead to better patient compliance, resulting in an improved prognosis for a wide range of patient groups. ■

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