



Annotated Bibliography

XII. Sickle Cell Disease and Thalassemia ii. Thalassemia



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D. Iron Overload and Chelation

1. Oral chelators deferasirox and deferiprone for transfusional iron overload in thalassemia major: new data, new questions.

Neufeld EJ. Blood. 2006;107:3436-41. [Abstract](#)

In a "Perspective" article, the author summarizes the results of the reports by Cappellini et al ([citation #3](#)), Borgna-Pignatti et al ([citation #6](#)) and Pennell et al ([Citation #2](#)) and points out some of their strengths and weaknesses and suggests where this work leaves the field.

The novel oral chelator deferasirox was recently approved by the Food and Drug Administration (FDA); a randomized clinical trial demonstrates that deferasirox at 20 to 30 mg/kg/d can maintain or improve hepatic iron in thalassemia as well as deferoxamine. A randomized trial based on cardiac T2* magnetic resonance imaging (MRI) suggests that deferiprone can unload myocardial iron faster than deferoxamine. Retrospective epidemiologic data suggest dramatic reductions in cardiac events and mortality in Italian subjects exposed to deferiprone compared with deferoxamine.

The author considers how data from these 3 studies can best be applied to current practice. The main take-home messages are (1) Cappellini et al show that at 20 to 30 mg/kg/d, deferasirox can keep most *but not all* patients in even or negative iron balance in rough equivalence with moderate doses of DFO "normal". (2) Pennell et al prove that deferiprone was able to improve not only T* in asymptomatic patients, but these investigators also provided circumstantial evidence that their patients with a "normal" left ventricular ejection fraction (LVEF) had subclinical disease, based on improvements in LVEF with chelators. (3) Borgna-Pignatti et al provide the strongest evidence to date that deferiprone should be considered cardioprotective in comparison with DFO.

But these studies have not yet addressed some crucial questions:

What is the optimum deferasirox dose for patients with high iron intake? Some patients with high transfusion burdens will probably have rising ferritin levels and hepatic iron contents (HICs) if treated with the approved doses of 20 to 30 mg/kg/d. Thus, higher doses or combination regimens with DFO may be necessary.

What is the proper role for deferiprone? Based on side-effect profile alone, the author's opinion is that deferiprone is likely to remain a "second-line" drug to deferasirox and DFO. Nevertheless, deferiprone may have a crucial role in combination with DFO for significant cardiac dysfunction from iron overload. If deferasirox is successfully used where patients used to be noncompliant with DFO, its main success will be to prevent the need for such rescue therapy altogether.

What shall we tell our patients? The author considers the approval of deferasirox as a major advance and treatment option. Perhaps surprisingly, many DFO users with good compliance and HICs in the safe ranges are choosing to switch until more data become available. Certainly, further research is crucial.

[Comment: Longevity for β -thalassemia patients has been significantly prolonged by iron chelation therapy with DFO but recent studies indicate that even with good compliance, the life span is still significantly shorter than normal (See ii. Thalassemia A. Clinical Aspects, [citation #1](#), and [citation #3](#)) Also, the need for chronic transfusion therapy has not been changed by chelation. In thalassemia major the lifelong need for medical care can have a major impact on physical and physical and psychosocial well-being and quality of life (QoL) of patients and their families (See ii. Thalassemia B. Bone Marrow and PBSC Transplantation, [citation #1](#).) Crucial information that will ultimately emerge from further studies with oral chelators is whether life span can be further extended. In the meantime, patients and/or the families of children with thalassemia major who are considering a hematopoietic cell transplant for definitive cure will need to make their decision without the availability of such data.]

2. Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. Pennell DJ, Berdoukas V, Karagiorga M, Ladis V, Piga A, Aessopos A, Gotsis ED, Tanner MA, Smith GC, Westwood MA, Wonke B, Galanello R. Blood. 2006;107:3738-44. [Abstract](#)

A randomized controlled trial was performed in 61 patients previously maintained on subcutaneous deferoxamine. The primary end point was the change in myocardial siderosis (myocardial T2*) over 1 year in patients maintained on subcutaneous deferoxamine or those switched to oral deferiprone monotherapy. The dose of deferiprone was 92 mg/kg/d and deferoxamine was 43 mg/kg for 5.7 d/wk. Compliance was 94% +/- 5.3% and 93% +/- 9.7%, respectively. The improvement in myocardial T2* was significantly greater for deferiprone than deferoxamine (27% vs 13%; P = .023). Left ventricular ejection fraction increased significantly more in the deferiprone-treated group (3.1% vs 0.3% absolute units; P = .003). The changes in liver iron level (-0.93 mg/g dry weight vs -1.54 mg/g dry weight; P = .40) and serum ferritin level (-181 microg/L vs -466 microg/L; P = .16), respectively, were not significantly different between groups. The most frequent adverse events were transient gastrointestinal symptoms for deferiprone-treated patients and local reactions at the infusion site for deferoxamine. There were no episodes of agranulocytosis. **The authors concluded that deferiprone monotherapy was significantly more effective than deferoxamine over 1 year in improving asymptomatic myocardial siderosis in beta-thalassemia major.**

3. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with β -thalassemia. Maria Domenica

Organ failure due to chronic iron overload represents the major cause of death in patients with β -thalassemia who receive blood transfusions regularly without appropriate chelation therapy. Within 1 to 2 years of initiation of regular blood transfusions, evidence of iron over load is manifest as elevated liver iron concentration (LIC) values and elevated serum ferritin levels. An increased risk of iron-induced cardiac disease is observed in thalassemia patients with LIC values above 15 mg Fe/g dry weight (dw), and in patients with serum ferritin values above 2500 μ g/L.

Deferoxamine mesylate is the current standard for iron chelation therapy. There is clear and consistent evidence in the literature regarding its benefits on both morbidity and mortality and its ability to provide benefit to a variety of organs. Unfortunately, due to challenges of administering deferoxamine by slow subcutaneous or intravenous infusion over 8 to 12 hours, compliance is often poor.

Deferasirox (ICL670) is a once-daily oral iron chelator developed for the treatment of chronic iron overload from blood transfusions. A comparative phase 3 trial was conducted to demonstrate the efficacy of deferasirox in regularly transfused patients with β -thalassemia aged 2 years or older. Patients were randomized and received treatment with deferasirox (n = 296) or deferoxamine (n = 290), with dosing of each according to baseline liver iron concentration (LIC). The primary endpoint was maintenance or reduction of LIC; secondary endpoints included safety and tolerability, change in serum ferritin level, and net body iron balance. In both arms, patients with LIC values of 7 mg Fe/g dry weight (dw) or higher had significant and similar dose-dependent reductions in LIC and serum ferritin, and effects on net body iron balance. However, the primary endpoint was not met in the overall population, possibly due to the fact that proportionally lower doses of deferasirox relative to deferoxamine were administered to patients with LIC values less than 7 mg Fe/g dw. The most common adverse events included rash, gastrointestinal disturbances, and mild nonprogressive increases in serum creatinine. No agranulocytosis, arthropathy, or growth failure was associated with deferasirox administration. **The authors concluded that deferasirox is a promising once-daily oral therapy for the treatment of transfusional iron overload.**

4. Monitoring and treatment of iron overload: state of the art and new approaches. Porter JB. Semin Hematol. 2005;42(2 Suppl 1):S14-8.

Monitoring: The assessment of serum ferritin is widely used to monitor iron, and retrospective patient analysis has demonstrated a positive correlation between consistently elevated levels of serum ferritin (>2,500 μ g/L) and cardiac death. Although serum ferritin can be useful when looking at individual patient responses to treatment, it cannot provide reliable information on specific body iron levels.

Assessment of liver iron content, classically measured by liver biopsy, can be used to predict body iron levels accurately. However, the invasive nature of the technique, together with the need for a relatively large volume of tissue to obtain reliable values is a significant limitation of the routine use of this approach.

Investigational approaches using biomagnetic susceptometry and magnetic resonance imaging are being assessed in an effort to identify an accurate, low risk and convenient approach to the assessment of patient iron status.

Treatment: Deferoxamine is a parentally administered iron chelator that has been available for more than three decades. In patients requiring life-long chelation therapy, compliance to at least 5 nights per week dosing is crucial.

Deferiprone is an oral iron chelator that is licensed in parts of Europe for use in adult patients for whom deferoxamine is contraindicated. Liver iron is not as well controlled as with deferoxamine and liver iron unfortunately remains at unacceptably high concentrations (>7 mg/g dry weight) in 53% to 88% of patients after 1 to 4 years of continuous treatment, and above the threshold for heart disease in 18% to 65% of patients.

Some clinicians have combined deferoxamine and deferiprone therapy simultaneously or sequentially. The only prospective comparative study showed that deferoxamine alone was superior to either deferiprone alone or combined treatment in the control of serum ferritin.

ICL670 is an oral iron chelator that shows high efficacy and therapeutic safety in preclinical animal studies and is currently in phase III clinical evaluations. It has a long plasma half-life making it a candidate for once-daily oral dosing. Preliminary analyses of data from a prospective randomized 1-year phase II study indicated that ICL670 appears to be as effective as deferoxamine with a good safety profile. Phase II and III randomized multicenter studies in more than 500 patients to compare ICL670 with deferoxamine are ongoing.

5. Iron overload in thalassemia and sickle cell disease. Taher A. Semin Hematol. 2005;42(2 Suppl 1):S5-9.

The authors point out that hematopoietic cell transplantation can effect a cure in patients with thalassemia, particularly children with no evidence of hepatomegaly or portal fibrosis. Published data indicate that such patients may have disease-free survival rates exceeding 90%, 3 years after transplantation.

In an effort to reduce the reliance on repeated transfusion in patients with thalassemia, patients have been treated with hydroxyurea, butyric acid compounds and these agents in combination. While such treatment has produced increases in HbF concentration in some patients, reducing the need for regular transfusions, overall the data appear inconclusive.

Patients with thalassemia (and sickle cell disease) have ineffective erythropoiesis and this results in a drastic increase in plasma iron turnover, 10 to 15 times that of normal subjects. This process stimulates iron absorption, along with the release of iron derived from RBC catabolism into the circulation. Tissue iron overload is a significant problem which is compounded by the need for regular blood transfusions.

In the absence of adequate management iron overload can be fatal, as the accumulation of iron results in progressive dysfunction of the heart, liver, and endocrine systems.

Effective iron chelation therapy plays a key role in management of these patients. However, the potential benefits of deferoxime are limited by poor compliance due to the demanding therapeutic regimen of this agent. Oral chelators have been developed including Deferiprone, an orally active agent. This agent is available in some parts of Europe, although its use is restricted to second-line therapy for patients who are unable to receive deferoxamine.

6. Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major. Borgna-Pignatti C, Cappellini MD, De Stefano P, Del Vecchio GC, Forni GL, Gamberini MR, Ghilardi R, Piga A, Romeo MA, Zhao H, Cnaan A. Blood 2005; 107:3733-3737. **Abstract**

Deferoxamine (DFO) therapy has been associated with improved survival of thalassemia patients. However, cardiac disease continues to be responsible for significant disability, and it causes 70% of the deaths in patients chelated with DFO. In 1995 a new oral chelator, deferiprone, became available for clinical use. The authors compared the occurrence of cardiac disease in patients treated only with DFO and in those whose therapy was switched to deferiprone during the period of observation from January 31, 1995 to December 31, 2003. All patients with thalassemia major, treated in seven Italian centers, born between 1970 and 1993 and who had not experienced a cardiac event prior to January 1995 were included. DFO only was given to 359 patients and 157 patients received deferiprone for part of the time. A total of 3610 patient years were observed on DFO and 750 on deferiprone. At baseline, the two groups were comparable for age and sex, while ferritin levels were significantly higher in patients switched to deferiprone. The median duration of the deferiprone treatment was 4.3 years (range 0.02-8.9 years), for a total of 750 patient years. The median time on DFO since January 1995 until switching to deferiprone was 2.0 years (range 0.06-8.7 years).

Forty-six (31%) patients discontinued deferiprone as a consequence of clinical or laboratory adverse events. The causes for discontinuation were: increase in ferritin levels or in liver iron concentration (21), arthropathy or arthralgia (10), neutropenia (8), agranulocytosis (1), worsening of hepatic insufficiency in a cirrhotic, HCV-positive patient (1). Sixteen (10%) patients discontinued deferiprone for reasons other than adverse events including lack of compliance to the required weekly blood counts (6), end of the deferiprone clinical trial (2), starting on ICL670 clinical trial (3), fear of long-term adverse events (2), or for unknown reasons (3).

Fifty-two cardiac events, including 10 cardiac deaths, occurred during therapy with DFO. No cardiac events occurred during deferiprone therapy or within at least eighteen months after the end of it. On the basis of these data, the authors concluded that, in the setting of a natural history study, deferiprone therapy was associated with significantly greater cardiac protection than deferoxamine in patients with thalassemia major.

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