

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

Ellis J. Neufeld

For nearly 30 years, patients with transfusional iron overload have depended on nightly deferoxamine infusions for iron chelation. Despite dramatic gains in life expectancy in the deferoxamine era for patients with transfusion-dependent anemias, the leading cause of death for young adults with thalassemia major and related disorders has been cardiac disease from myocardial iron deposition. Strategies to reduce cardiac disease by improving chelation regimens have been of the highest priority. These strategies have included development of novel oral iron chelators

to improve compliance, improved assessment of cardiac iron status, and careful epidemiologic assessment of European outcomes with deferiprone, an oral alternative chelator available for about a decade. Each of these strategies is now bearing fruit. 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. These developments herald a new era for iron chelation, but many unanswered questions remain. (Blood. 2006;107:3436-3441)

© 2006 by The American Society of Hematology

Introduction

In this issue of *Blood*, there are reports of 2 randomized clinical trials and a large retrospective epidemiology study that represent crucial advances in the field of oral agents to treat transfusional iron overload in thalassemia.¹⁻³ Here I will summarize the results of these studies, point out some of their strengths and weaknesses, and propose one hematologist's view of where this work leaves the field.

Three iron chelators: parenteral versus oral

Deferoxamine

Deferoxamine (DFO; Desferal and generic) has been the standard iron chelator since the 1970s. DFO is both safe and effective for transfusional hemosiderosis. A hexadentate chelator, it binds iron tightly, and the iron-DFO complex is excreted in both urine and stool. DFO is administered as long parenteral infusions because the plasma half-life is short (minutes) and it is not active orally. Thus, it is given as an overnight subcutaneous infusion 5 to 7 nights/wk. The DFO-iron chelate is charged and does not readily enter and leave cells.⁴ Parenteral administration and the daily nuisance of an infusion pump hinder optimal compliance. Nevertheless, in the DFO era, over the past generation, dramatic strides in survival of thalassemia patients have occurred.⁵

Deferiprone

Deferiprone (Ferriprox and others) is an orally active hydroxypyridineone first used in humans in 1987. Deferiprone is a bidentate

chelator (3 molecules surround one iron ion). An advantage of this compound is that the iron(III) chelate of deferiprone carries no net charge and therefore can penetrate membranes easily, allowing removal of potentially toxic iron from tissues.⁶ Many *Blood* readers are aware of a controversy over the safety of deferiprone that arose in the late 1990s because of an observation of hepatic fibrosis during a clinical trial.⁷ However, in subsequent studies this problem has not been a significant toxicity issue for deferiprone.⁸ The history of deferiprone and this safety debate were well summarized in a 2003 *Blood* "Perspective."⁹ Deferiprone often causes gastrointestinal symptoms. Idiosyncratic side effects that are potentially severe include erosive arthritis (common in patients in South Asian countries, from 5% to >20%) and neutropenia (up to 5% of patients), including severe agranulocytosis (up to 0.5% of patients); close monitoring is required. Typical dosage for deferiprone is 75 mg/kg/d in 3 divided doses, up to 100 mg/kg daily.^{3,10}

Deferasirox

Deferasirox (ICL670, Exjade) belongs to a new class of oral tridentate chelator, N-substituted bis-hydroxyphenyltriazoles. Deferasirox, the result of a concerted discovery program, underwent extensive safety testing and clinical trials including preclinical studies,¹¹ initial phase 1 and iron balance studies,¹² phase 2 efficacy studies in adult¹³ and pediatric¹⁴ thalassemia patients, patients with a variety of anemias or unable/noncompliant with DFO,¹⁵ and the phase 3 clinical trial discussed here.¹ With a plasma half-life of 8 to 16 hours, once-daily dosing permits circulating drug at all times to

From the Division of Hematology/Oncology, Children's Hospital, Boston, MA; and the Dana Farber Cancer Institute and Harvard Medical School, Boston, MA.

Submitted February 28, 2006; accepted March 03, 2006. Prepublished online as *Blood* First Edition Paper, March 7, 2006; DOI 10.1182/blood-2006-02-002394.

Supported in part by the National Heart, Lung, and Blood Institute (NHLBI) Thalassemia Clinical Research Network grant U01-HL065260.

Supported by research funding from Novartis for deferasirox clinical trials and serves, unpaid, on the Study Monitoring Committee for a manufacturer-sponsored clinical study of deferasirox.

Reprints: Ellis J. Neufeld, Division of Hematology, Children's Hospital, Karp 08210, 300 Longwood Ave, Boston, MA 02115; e-mail: ellis.neufeld@childrens.harvard.edu.

© 2006 by The American Society of Hematology

scavenge non-transferrin-bound “labile plasma iron,”¹⁶ the chemical species responsible for tissue damage in iron-overloaded subjects, by means of toxic oxygen intermediaries.¹⁷ Deferasirox-iron complexes are excreted in the stool.

The 3 compounds are compared in Table 1 to properties of an ideal chelator. One “theoretical” advantage with real clinical import is access of chelators to intracellular iron, particularly in cardiac myocytes. In cultured heart muscle, deferasirox and deferiprone have rapid access to intracellular iron pools, whereas DFO does not.¹⁸ Nevertheless, high-dose continuous DFO, administered via central catheter, can dramatically reverse cardiac toxicity of iron overload.⁴ High-dose continuous DFO has been the “standard” initial therapy for cardiac iron overload.

Clinical assessments of chelator efficacy and novel noninvasive measures of iron overload

Trials to test chelator effectiveness necessarily require a choice of a primary outcome measure. Potential “hard” end points or surrogates are summarized in Table 2. Different outcomes were chosen for the 3 studies discussed here. (1) Hepatic iron content (HIC) by liver biopsy was used for the deferasirox-versus-DFO trial.¹ Liver biopsy has been the “gold standard” for iron balance studies, but the technique is invasive, expensive, and subject to variability within and between research subjects. (2) The epidemiologic study of deferiprone examines onset of symptomatic cardiac disease as the primary outcome measure.² This is a compelling end point because iron-related cardiac disease is a major clinical problem. (3) For their comparative trial of DFO and deferiprone, Pennell and colleagues³ used the cardiac magnetic resonance imaging (MRI) parameter T2* (pronounced “T-2-star”). Iron concentration in tissues (in this case, the myocardium of the cardiac septum) is inversely related to T2*. Low T2* values (< 8 ms compared with normal [> 20 ms]) are related to risk of heart failure and death in iron-overloaded thalassemia patients.²⁰ T2* reports initially raised concerns about whether it is a good surrogate for cardiac iron

concentration²⁵ for technical reasons as well as the paradox that liver iron correlated poorly with cardiac T2*. These points have largely been settled. In an iron-overload gerbil model, T2* is indeed inversely related to myocardial iron measured directly.²⁶ The poor correlation of T2* with hepatic iron is now understood on a kinetic basis. The liver can be readily unloaded by aggressive chelation much more rapidly than can the heart, giving rise to patients with low T2* values (heart still iron loaded) while the liver has been unloaded to values previously thought of as “safe.”²⁷

Randomized clinical trial of deferiprone versus deferoxamine

Pennell et al³ compared oral deferiprone to subcutaneous DFO in 61 thalassemia major patients without symptomatic heart failure. The entry criteria required T2* to be abnormal (< 20 ms) but not “severe” (< 8 ms) and left ventricular ejection fraction (LVEF) to be greater than 56%. Technical details of the single-breath-hold T2* method were previously published.²⁸ Superconducting quantum interference device (SQUID; Table 2) was used to measure HIC at baseline and 12 months. Compliance was closely monitored. The primary outcome measure was change in myocardial T2* at 6 and 12 months. The rate of rise in T2* was significantly higher to deferiprone (mean dose 92 mg/kg/d) than to DFO (mean dose of 43 mg/kg, 5.7 d/wk). In addition, there was a greater increase in LVEF in the deferiprone group compared with the deferoxamine group, all within the “normal” range. Mean HIC fell slightly in each group. Gastrointestinal symptoms and joint pain were common side effects. This prospective trial validates the prior retrospective series of Anderson et al²⁹ that had been controversial.²⁵ A potential weakness of the trial is the use of the surrogate T2* as primary outcome, because the clinical significance of a few more milliseconds within the mildly abnormal range is unknown if taken alone. However, taken together with *in vitro* data and with the epidemiologic data of Borgna-Pignatti et al,² this trial provides

Table 1. Comparison of available iron chelators to an ideal chelation drug

	“Ideal chelator”	Deferoxamine	Deferiprone	Deferasirox
Route of administration	Oral	Parenteral, usually subcutaneous or intravenous	Oral	Oral
Plasma half-life	Long enough to give constant protection from labile plasma iron	Short (minutes); requires constant delivery	Moderate (< 2 hours). Requires at least 3-times-per-day dosing	Long, 8-16 hours; remains in plasma at 24 h
Therapeutic index	High	High at moderate doses in iron-overloaded subjects	Idiosyncratic side effects are most important	Probably high in iron-overloaded subjects*
Molar iron chelating efficiency; charge of iron (III) complex	High, uncharged	High (hexadentate); charged	Low (bidentate); uncharged	Moderate (tridentate); uncharged
Important side effects	None or only in iron-depleted subjects	Auditory and retinal toxicity; effects on bones and growth; potential lung toxicity, all at high doses; local skin reactions at infusion sites	Rare but severe agranulocytosis; mild neutropenia; common abdominal discomfort; erosive arthritis	Abdominal discomfort; rash or mild diarrhea upon initiation of therapy; mild increased creatinine level
Ability to chelate intracellular cardiac and other tissue iron in humans	High	Probably lower than deferiprone and deferasirox	High in clinical and <i>in vitro</i> studies	Insufficient clinical data available; promising in laboratory studies

*Nephrotoxicity observed in non-iron-loaded animals has been minimal in iron-overloaded humans, but effectiveness is demonstrated only at higher end of tested doses, as discussed in Cappellini et al.¹

Table 2. Example of outcome measures for chelator trials and their application for clinical practice now and in the future

Outcome	Advantages	Disadvantages	Current status in clinical practice, 2006	Future status in clinical practice
Death	Hard outcome; compelling for studies	Cannot be monitored for individuals in clinical practice	Cardiac disease is leading cause of death in thalassemia major	Remains ultimate outcome
Cardiac events	Hard outcome, compelling	Late event for individuals	Critical marker of clinical status	Remains crucial outcome
HIC by liver biopsy, both as intrinsic outcome and as surrogate for risk of cardiac disease and death ¹⁹	Gold standard to date; accurately reflects total body iron status; best assessment of fibrosis, hepatitis	Invasive and uncomfortable for patients; heterogeneous tissue iron cannot be assessed; less reliable for iron content in fibrosis or cirrhosis	Remains a critical tool but may not be so golden considering variability and new alternatives; imperfect surrogate for cardiac iron	Use may decline if R2 MRI becomes widely available
Cardiac iron by T2*; surrogate for risk of heart failure due to iron ^{20,21}	Noninvasive measure of cardiac iron status. T2* < 8 ms associated with high risk of heart disease.	Not widely available; not yet proven that improved T2* by chelation improves cardiac disease or death from iron	Very helpful for patient assessment and follow-up at sites where study is available	Widespread use likely, if improvement correlates with improved clinical outcomes
HIC by MR; R2 "Ferriscan" approved by FDA, other methods under study	Noninvasive, potentially more accurate ²⁴	As of 2006, not widely available	Ferriscan requires commercial license; few United States sites signed on to date	Use likely to increase if commercial hurdles are overcome
HIC by SQUID ^{22,23}	Validated in clinical studies in comparison to liver biopsy	Expensive instruments, limited availability (4 in world); not directly comparable to biopsy because of calibration variability	Good alternative to biopsy for patients who live close to instruments	Likely to wane except for study settings if MRI methods become widespread and useful
Serum ferritin level; surrogate measure of HIC	Noninvasive, inexpensive	Highly variable; acute-phase reactant and affected by liver disease; single measures inadequate for assessment of current status	Widely available and used; running average over 6 months reliable for trends	Likely to remain as a first-line monitoring tool between more expensive HIC assessments

HIC indicates hepatic iron content; and SQUID, superconducting quantum interference device.

important further evidence that, despite the concerns about deferiprone chelation efficiency based on 3:1 stoichiometry, deferiprone is probably better *in vivo* at improving myocardial iron than DFO (at the doses used).

Efficacy of a new oral iron chelator

Phase 3 trial results for deferasirox in a randomized controlled comparison trial with DFO are reported by Cappellini and colleagues.¹ The trial involved nearly 600 patients (half were 16 years of age or younger) with transfusion-dependent β -thalassemia. The study was designed as a noninferiority trial, measuring hepatic iron by biopsy at baseline and after one year of therapy. Success was defined as either maintenance or improvement in HIC (depending on the baseline levels). Based on the study results, the United States Food and Drug Administration (FDA) approved the drug for transfusional iron overload for patients older than 2 years of age in November 2005. The drug is still under regulatory review in Europe.

This report deserves careful scrutiny from hematologists who care for patients with thalassemia and other disorders of transfusional iron overload. The dose choices for DFO and for deferasirox were based solely on baseline HIC at study entry. The decision to use this baseline value and the choice of what are now known to be relatively low deferasirox doses caused the study to fail to meet its overall primary end point (ie, at low doses of deferasirox, 5-10 mg/kg/d, increased HIC was observed). However, at doses of 20 to 30 mg/kg/d, the doses for HIC greater than 7 mg/g dry weight, noninferiority of deferasirox compared with DFO was established, with 60% versus 59% achieving a successful outcome, respectively. Assessed by ferritin concentration, 20 mg/kg/d deferasirox was sufficient to maintain mean ferritin levels over 52 weeks,

whereas 30 mg/kg yielded a reduction in ferritin level. In retrospect, several design decisions contributed to the mixed outcome of "failure" at low doses and success at higher doses. For example, results from an earlier phase 2 trial of deferasirox in children,¹⁴ which also used low doses that proved ineffective, were not available in time to guide the phase 3 trial. As well, additional factors proved important in deferasirox efficacy. For example, transfused iron burden was shown to be a strong predictor of the iron response at a year.^{30,31} Likelihood of failing to achieve iron balance was much higher for patients receiving more than 0.5 mg/kg/d iron.³¹ Adverse drug reactions in deferasirox trials have included modest rise in creatinine level, rarely clinically significant. Increased transaminases were observed occasionally. Common side effects of deferasirox include transient gastrointestinal symptoms in 15% and rash in 11%.

An epidemiologic assessment of onset of cardiac disease in DFO- or deferiprone-treated patients with thalassemia

Borgna-Pignatti and colleagues² present an interesting retrospective cohort study of cardiac events in Italian thalassemia patients who switched from DFO to deferiprone. The study included more than 500 patients with thalassemia major at 7 large Italian centers who were alive in 1995 and who had neither prior heart disease nor subsequent marrow transplantation. Deferiprone was given to 157 subjects during some period in the subsequent 9 years, whereas 359 received only DFO. Many of the deferiprone patients were initially part of clinical trials, before the drug became available on a compassionate-use basis in 1997 and commercially in 2000. In a time-to-event analysis, the authors noted 52 cardiac events, includ-

ing 10 deaths, in patients while on DFO and 0 events while on deferiprone. The result is dramatic and unexpected, whether one believes that deferiprone would have been given mostly to DFO-intolerant patients or not. Although potential bias could easily arise in a retrospective study of unmatched groups, the authors have examined possible biases in a comprehensive fashion, controlling for as many as possible, and explaining the rest with admirable clarity and near-perfect patient ascertainment. This stunning finding, coupled with similar but less rigorous data from other sites, is hard to ignore. The results confirmed a smaller retrospective analysis of Piga et al.³²

Cost comparison of DFO and deferasirox

Perfect and unbiased cost comparisons among commercial versions of all 3 drugs are not yet possible for any single country, and national price differences abound. Although a rough first-order approximation of price ranking might be deferiprone < deferoxamine < deferasirox, this may not be true in every country (Table 3 provides some comparisons of available costs). Nondrug obligatory costs are important as well: deferiprone therapy requires weekly complete blood count (CBC)/differential count; DFO requires ancillary supplies for infusion. Deferasirox will cost more than twice as much as DFO in the United States. At least until deferasirox, chelators heretofore have not been the major cost of caring for American thalassemia patients; this dubious honor goes to the transfusions themselves.³⁵ But the cost of deferasirox will be a significant new burden even in developed nations with strong health insurance programs, and it will be prohibitive in the developing world, without substantial discounts. An initial attempt at cost-effectiveness analysis was presented in abstract form at the American Society of Hematology 47th Annual Meeting in 2005, wherein the extra cost of the medication was weighed (favorably) against the cost of illness and death from noncompliance and iron overload for DFO.³⁶ This analysis was sponsored by the manufacturer.

Additional recent studies of deferasirox

More than 20 deferasirox abstracts were presented at the 2005 American Society of Hematology Annual Meeting. These included clear evidence from both phase 2 and phase 3 clinical trials that transfusional iron loading (expressed as mg/kg/d of transfused iron) had a dramatic effect on the ability of deferasirox doses to maintain or reduce hepatic iron^{30,31} and presentation of the randomized trial of deferasirox versus DFO in sickle cell disease.³⁷ Porter et al³⁸ demonstrated improved cardiac T2* with deferasirox in patients from their site in the phase 2 and 3 trials. Molar efficiency of DFO and deferasirox was compared by examining net iron balance as a function of input transfusional iron and chelator dose.³⁹ These results have important implications to consider along with the phase 3 trial¹: chelator efficiency and clinical effectiveness in vivo are not a function of chelate stoichiometry alone. Iron removal also depends on achievable plasma concentration, host factors, degree of loading, and rate of accessibility of stored iron to chelator.

Clinical utility of the data from the 3 new studies

How can data from these 3 studies best be applied to current practice?

For treaters and patients, a prudent path would be first to take to heart the main messages of each of the 3 studies. I believe these are the take-home messages. (1) Cappellini et al¹ 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. (2) Pennell et al³ prove that deferiprone was able to improve not only T2* in asymptomatic patients, but these investigators also provided circumstantial evidence that their patients with “normal” LVEF had subclinical disease, based on improvements in LVEF with chelators. Pennell and colleagues have also initiated a randomized, prospective trial of DFO plus placebo versus DFO plus

Table 3. Relative estimated cost of deferaprone, deferoxamine, and deferasirox*

	Deferiprone†		Deferoxamine‡		Deferasirox§	
	25-kg child	60-kg adult	25-kg child	60-kg adult	25-kg child	60-kg adult
Moderate daily dose, mg/kg	75	75	25	25	20	20
Annual cost, \$						
United States	NA	NA	6 760	16 220	16 270	39 000
India	350	840	ND	ND	NA	NA
Italy	2 790	6 700	1 670	4 020	NA	NA
Higher daily dose, mg/kg	100	100	40	40	30	30
Annual cost, \$						
United States	NA	NA	10 810	25 952	24 400	58 500
India	470	1 120	ND	ND	NA	NA
Italy	3 720	8 940	2 680	6 430	NA	NA

AWP indicates average wholesale price; NA, not available; and ND, not determined for this review.

*No published data compare contemporaneous costs in a single country. Deferasirox is available with commercial pricing in the United States only, whereas deferiprone is not available in the United States.

†Deferiprone monitoring includes weekly CBC/differential count compared with monthly CBC for the other drugs; this adds more than \$1000 to the annual drug cost at United States prices. India cost \$0.272/500 mg³³; Italy wholesale \$2.04/500 mg. Costs based on exchange rates 47 rp/\$US and \$US1.20/Euro.

‡Italian costs courtesy of Pharmacy, University of Ferrara, Italy.

§Generic DFO became available after the 2003 Redbook was released. The price now ranges from well below \$14/500 mg for generic DFO to more than \$20/500 mg for brand name (US AWP \$14.81/500 mg vial, without infusion ancillaries; Italy wholesale \$3.67/500 mg). Neither discounts nor markups to AWP are considered for these estimates. Infusion costs (pumps, needles, tubing, diluent) vary widely among United States payers and among states and countries and could add up to a few thousand dollars annually to DFO costs.

¶Price information (AWP \$89/g) courtesy of Novartis Medical Affairs and cited in Cost Effectiveness abstract.³⁴

deferiprone in borderline T2* status; results should soon be published. (3) Borgna-Pignatti et al² provide the strongest evidence to date that deferiprone should be considered cardioprotective in comparison with DFO, albeit in a retrospective setting without formal matching. But these 3 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 HICs if treated with the approved doses of 20 to 30 mg/kg/d.

If so, alternative strategies will be obligatory. These might include higher daily doses (which may cause more diarrhea¹²), twice-daily dosing, or possible combination regimens with DFO. The latter option would offer lower average price than deferasirox alone (and ideally better net iron chelation) but would lose the advantages of an oral drug. A combination of the 2 oral drugs, deferasirox and deferiprone, requires detailed study before it can be safely recommended.

What is the proper role for deferiprone? Based on side-effect profile alone, in my opinion, deferiprone is likely to remain a “second-line” drug to deferasirox and DFO.

This is not to say that deferiprone will not have a crucial role. In particular, deferiprone plus DFO in some combination appears to be the emerging “treatment of choice” for significant cardiac dysfunction from iron overload, as *in vivo*⁴⁰ and *in vitro*⁴¹ evidence support the biochemical rationale.⁴² Deferiprone is currently available only on a compassionate-use basis in the United States. 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? In our thalassemia center, we are presenting the approval of deferasirox as a major advance and treatment option.

After politely receiving this information, however, many DFO users with good compliance and HICs in safe ranges are choosing not to switch until more data become available, because they are doing fine with their pumps and long-term deferasirox data are not yet available. We have not recommended deferasirox to patients with overt myocardial dysfunction because no published data support this use. We now adamantly suggest deferasirox to DFO-noncompliant patients without symptomatic heart disease.

Further research is crucial

Our center is participating in a National Institutes of Health (NIH)-sponsored randomized trial comparing intensive DFO plus deferiprone to DFO plus placebo for patients with low LVEF or symptomatic heart disease, and we tell such patients that continuous-infusion DFO is standard care but that addition of deferiprone on study (or for nonstudy participants as compassionate use) may be advantageous. Additional carefully designed studies are required to answer pressing questions about many drug combinations and treatment scenarios. Examples include both small-scale trials (eg, pilot pharmacodynamic studies of the 3 drugs in various combinations) and large-scale efforts (eg, initiation of a randomized, prospective phase 3 trial comparing deferasirox and deferaprone to assess relative safety, efficacy, and cardioprotection).

We look forward to a future where complications due to iron overload are rare, and our patients certainly look forward to life without “the pump.”

References

- Cappellini MD, Cohen A, Piga A, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with (beta)-thalassemia. *Blood*. 2005;107:3455-3462.
- Borgna-Pignatti C, Cappellini MD, De Stefano P, et al. Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major. *Blood*. 2005;107:3733-3737.
- Pennell DJ, Berdoukas V, Karagiorga M, et al. Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. *Blood*. 2005;107:3738-3744.
- Davis BA, Porter JB. Long-term outcome of continuous 24-hour deferoxamine infusion via indwelling intravenous catheters in high-risk beta-thalassemia. *Blood*. 2000;95:1229-1236.
- Borgna-Pignatti C, Rugolotto S, De Stefano P, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematologica*. 2004;89:1187-1193.
- Hider RC, Zhou T. The design of orally active iron chelators. *Ann N Y Acad Sci*. 2005;1054:141-154.
- Olivieri NF, Brittenham GM, McLaren CE, et al. Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. *N Engl J Med*. 1998;339:417-423.
- Cohen AR, Galanello R, Piga A, De Sanctis V, Tricta F. Safety and effectiveness of long-term therapy with the oral iron chelator deferiprone. *Blood*. 2003;102:1583-1587.
- Hoffbrand AV, Cohen A, Hershko C. Role of deferiprone in chelation therapy for transfusional iron overload. *Blood*. 2003;102:17-24.
- Taher A, Sheikh-Taha M, Sharara A, et al. Safety and effectiveness of 100 mg/kg/day deferiprone in patients with thalassemia major: a two-year study. *Acta Haematol*. 2005;114:146-149.
- Hershko C, Konijn AM, Nick HP, Breuer W, Cabantchik ZI, Link G. ICL670A: a new synthetic oral chelator: evaluation in hypertransfused rats with selective radioiron probes of hepatocellular and reticuloendothelial iron stores and in iron-loaded rat heart cells in culture. *Blood*. 2001;97:1115-1122.
- Nisbet-Brown E, Olivieri NF, Giardina PJ, et al. Effectiveness and safety of ICL670 in iron-loaded patients with thalassaemia: a randomised, double-blind, placebo-controlled, dose-escalation trial. *Lancet*. 2003;361:1597-1602.
- Piga A, Galanello R, Cappellini MD, et al. Phase II study of ICL670, an oral chelator, in adult thalassaemia patients with transfusional iron overload: efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) after 18 months of therapy [abstract]. *Blood*. 2003;102:121a. Abstract 412.
- Piga A, Galanello R, Foschini ML, et al. Once-daily treatment with the oral iron chelator ICL670 (Exjade (R)): results of a phase II study in pediatric patients with beta-thalassaemia major [abstract]. *Blood*. 2004;104:983a. Abstract 3614.
- Porter J, Vichinsky E, Rose C, et al. A phase II study with ICL670 (Exjade(R)), a once-daily oral iron chelator, in patients with various transfusion-dependent anemias and iron overload [abstract]. *Blood*. 2004;104:872a. Abstract 3193.
- Daar S, Taher A, Pathare A, et al. Plasma LPI in beta-thalassemia patients before and after treatment with deferasirox (Exjade (R), ICL670) [abstract]. *Blood*. 2005;106:758a. Abstract 2697.
- Rachmilewitz EA, Weizer-Stern O, Adamsky K, et al. Role of iron in inducing oxidative stress in thalassemia: can it be prevented by inhibition of absorption and by antioxidants? *Ann N Y Acad Sci*. 2005;1054:118-123.
- Glickstein H, El RB, Shvartsman M, Cabantchik ZI. Intracellular labile iron pools as direct targets of iron chelators: a fluorescence study of chelator action in living cells. *Blood*. 2005;106:3242-3250.
- Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. *Blood*. 1997;89:739-761.
- Anderson LJ, Holden S, Davis B, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. *Eur Heart J*. 2001;22:2171-2179.
- Pennell DJ. T2* magnetic resonance and myocardial iron in thalassemia. *Ann N Y Acad Sci*. 2005;1054:373-378.
- Brittenham GM, Sheth S, Allen CJ, Farrell DE. Noninvasive methods for quantitative assessment of transfusional iron overload in sickle cell disease. *Semin Hematol*. 2001;38:37-56.
- Sheth S. SQUID biosusceptometry in the measurement of hepatic iron. *Pediatr Radiol*. 2003;33:373-377.
- St Pierre TG, Clark PR, Chua-anusorn W, et al. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. *Blood*. 2005;105:855-861.
- Brittenham GM, Nathan DG, Olivieri NF, Pippard MJ, Weatherall DJ. Deferiprone versus desferrioxamine in thalassaemia, and T2* validation and utility. *Lancet*. 2003;361:183; author reply 183-184.
- Wood JC, Otto-Duessel M, Aguilar M, et al. Cardiac iron determines cardiac T2*, T2, and T1 in the gerbil model of iron cardiomyopathy. *Circulation*. 2005;112:535-543.
- Wood JC, Tyszkja JM, Carson S, Nelson MD, Coates TD. Myocardial iron loading in transfusion-dependent thalassemia and sickle cell disease. *Blood*. 2004;103:1934-1936.
- Westwood M, Anderson LJ, Firmin DN, et al. A

- single breath-hold multiecho T2* cardiovascular magnetic resonance technique for diagnosis of myocardial iron overload. *J Magn Reson Imaging*. 2003;18:33-39.
29. Anderson LJ, Wonke B, Prescott E, Holden S, Walker JM, Pennell DJ. Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in beta-thalassaemia. *Lancet*. 2002;360:516-520.
 30. Greenberg P, Dine G, Ganser A, et al. Deferasirox (Exjade (R), ICL670) demonstrates dose-related effects on body iron levels related to transfusional iron intake in transfusion-dependent anemia [abstract]. *Blood*. 2005;106:757a. Abstract 2694.
 31. Cohen A, Masera G, Zoumbos N, et al. Effect of iron intake on control of body iron in patients with thalassemia major treated with deferasirox (Exjade((R)), ICL670) [abstract]. *Blood*. 2005;106:242a. Abstract 822.
 32. Piga A, Gaglioti C, Fogliacco E, Tricta F. Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. *Haematologica*. 2003;88:489-496.
 33. Gomber S, Saxena R, Madan N. Comparative efficacy of desferrioxamine, deferiprone and in combination on iron chelation in thalassemic children. *Indian Pediatr*. 2004;41:21-27.
 34. Delea TE, Sofrygin O, Thomas SK, Baladi JF, Phatak PD, Coates TD. Cost-effectiveness of once-daily oral chelation therapy with deferasirox (Exjade (R), ICL670) versus infusional deferoxamine in transfusion-dependent thalassemic patients [abstract]. *Blood*. 2005;106:389a. Abstract 1341.
 35. Renfro JL, Forbes P, Braunstein J, Neufeld EJ. Relationship of transfusion and iron-related complications to cost of care in thalassemia [abstract]. *Blood*. 2005;106:631a. Abstract 2240.
 36. Delea TE, Thomas SK, Baladi JF, Phatak PD. Cost-effectiveness analysis of oral iron chelation therapy with deferasirox (Exjade (R), ICL670) versus infusional chelation therapy with deferoxamine in patients with transfusion-dependent myelodysplastic syndrome [abstract]. *Blood*. 2005;106:484b-485b. Abstract 5585.
 37. Vichinsky E, Fischer R, Fung E, et al. A randomized, controlled phase II trial in sickle cell disease patients with chronic iron overload demonstrates that the once-daily oral iron chelator deferasirox (Exjade((R)) ICL670) is well tolerated and reduces iron burden [abstract]. *Blood*. 2005;106:95a. Abstract 313.
 38. Porter JB, Tanner MA, Pennell DJ, Eleftheriou P. Improved myocardial T2* in transfusion dependent anemias receiving ICL670 (Deferasirox) [abstract]. *Blood*. 2005;106:1003a. Abstract 3600.
 39. Porter J, Borgna-Pignatti C, Baccarani M, et al. Iron chelation efficiency of deferasirox (Exjade (R), ICL670) in patients with transfusional hemosiderosis [abstract]. *Blood*. 2005;106:755a. Abstract 2690.
 40. Mourad FH, Hoffbrand AV, Sheikh-Taha M, Koussa S, Khoriaty AI, Taher A. Comparison between desferrioxamine and combined therapy with desferrioxamine and deferiprone in iron overloaded thalassaemia patients. *Br J Haematol*. 2003;121:187-189.
 41. Link G, Konijn AM, Breuer W, Cabantchik ZI, Hershko C. Exploring the "iron shuttle" hypothesis in chelation therapy: effects of combined deferoxamine and deferiprone treatment in hypertransfused rats with labeled iron stores and in iron-loaded rat heart cells in culture. *J Lab Clin Med*. 2001;138:130-138.
 42. Grady RW, Giardina PJ. Iron chelation: rationale for combination therapy. In: Dadman DG, Bergeron RJ, Brittenham GM, eds. *Iron Chelators: New Development Strategies*. Ponte Vedra Beach, FL: Saratoga; 2000:293-310.

Erratum

In the article by Orabona et al entitled "Toward the identification of a tolerogenic signature in IDO-competent dendritic cells," which appeared in the April 1, 2006, issue of *Blood* (Volume 107:2846-2854), throughout the paper "CTL0-4-Ig" should have been "CTLA-4-Ig".