

Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis

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Background and Objectives. Iron-induced cardiac disease remains the main cause of death in patients with thalassemia major, despite chelation therapy with deferoxamine. Deferiprone is an iron chelator that has the potential to be more effective than deferoxamine in removing intracellular iron from the heart. However, to date, no study has been designed to examine the frequency of cardiac complications and survival as the primary outcomes of a comparative study between these two chelators. This retrospective study assessed the survival and the occurrence of cardiac disease in all patients with thalassemia major treated for at least 4 years with deferiprone or deferoxamine at a single center.

Design and Methods. The patients were, on average, 18.4 years old at the start of the review period and were followed up, on average, for 6 years. At baseline there was no significant difference in the percentage of patients with cardiac disease in the two therapy groups.

Results. At the end of the study, cardiac dysfunction, expressed as worsening of pre-existing cardiac abnormality or development of new cardiac disease, was diagnosed in 2 (4%) of the 54 deferiprone-treated patients and in 15 (20%) of the 75 deferoxamine-treated patients, from the first to the last measurement ($p = 0.007$). The Kaplan Meier analysis of cardiac disease-free survival over the 5-year period was significantly more favorable in the deferiprone group ($p = 0.003$).

Interpretation and Conclusions. None of the patients treated with deferiprone died, while 3 of the patients treated with deferoxamine died because of irreversible worsening of their cardiac condition during the study period. Findings from this study suggest that long-term therapy with deferiprone provides a greater cardio-protective effect against the toxicity of iron overload than does subcutaneous deferoxamine. Formal prospective studies are warranted to confirm this effect.

Key words: thalassemia, chelation, iron, deferiprone, deferoxamine.

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The iron chelator deferoxamine has been available for the treatment of iron overload for more than 3 decades. Deferoxamine use can prolong survival and has been shown to ameliorate hepatic, endocrine and cardiac dysfunction in iron-overloaded patients with thalassemia major.¹⁻⁶ However, cardiac disease remains a frequent cause of morbidity among thalassemia patients^{1,7} and is still responsible for 70% of deaths.⁸ Compliance with regular chelation therapy, as determined by the ability to perform more than 265 deferoxamine infusions per year¹ or maintenance of most serum ferritin values below 2500 $\mu\text{g/L}$, has been identified as an important factor in limiting the incidence of cardiac disease and prolonging the survival among patients with thalassemia major.^{7,9} The age at the start of chelation therapy and the hepatic iron concentration have also been suggested as factors which could affect the development of cardiac disease.^{4,8} Although optimization of subcutaneous deferoxamine infusions (needle, pump, adjustment of daily life) has been achieved in many centers, the cumbersome nature of slow daily subcutaneous infusions of deferoxamine, and the resulting discomfort and adverse effects, have prevented optimal compliance in approximately 50% of patients.^{1,10}

Deferiprone (L1, 1,2-dimethyl-3-hydroxypyrid-4-one) is an orally active chelator, which has been recently approved in Europe for the treatment of iron overload. As a small, lipophilic bidentate molecule, deferiprone would theoretically have the potential to be more effective than deferoxamine in removing intracellular iron from some tissues, as has been demonstrated in the case of red cell membranes.^{11,12} Link *et al.* reported that deferiprone, at concentrations achieved in humans with standard doses, was more effective than deferoxamine in removal of iron from iron-loaded neonatal rat myocytes.¹³

These data from *in vitro* and animal studies are consistent with those from clinical studies that report a low rate of iron-induced clinical complications during deferiprone therapy.¹¹⁻¹⁹ However, to date, no study has been designed to examine the frequency of cardiac complications and survival as the primary outcomes of a comparative study of deferoxamine and deferiprone.

These observations constituted the rationale for designing a study to compare mortality and cardiac morbidity in patients with thalassemia treated long-term with either deferoxamine or deferiprone.

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Design and Methods

Study design

A retrospective analysis was conducted on survival and occurrence of cardiac disease in all patients with thalassemia major treated for at least 4 years with deferiprone or deferoxamine at a single center between 31 January 1995 and 29 March 2001. The medical records of patients aged ≥ 5 years at the time of the start of the review period, with a diagnosis of thalassemia major confirmed by laboratory tests (electrophoresis and/or DNA analysis) and appropriate clinical enrollment criteria (hemoglobin and transfusion dependency) were evaluated. Patients with congenital anemias other than thalassemia major, who were HIV-positive, who had a history of malignancy or who required radiation or chemotherapy were not included in the analysis.

Patients were excluded from the data analysis for the following reasons: chelation therapy with one of the chelators for less than 4 years during the review period; no information available on chelation therapy or cardiac status; only 1 cardiac assessment; age < 5 years at the start of the review period (6 patients); HIV-positive status.

The Regional Ethical Review Board approved the study. All eligible patients or their guardians gave authorization for the review of their medical records.

Patients

All patients received the same transfusion regimen, aimed at maintaining pre-transfusion hemoglobin levels at 9.5–10.0 g/dL and the mean hemoglobin at 12.0 g/dL. A software program, previously designed for thalassemia-oriented clinical records, calculated the annual transfusional iron input on the basis of the net weight and hematocrit of the blood transfused.²⁰

All patients were treated with deferoxamine until January 1995, when some were switched to deferiprone because they were enrolled in clinical trials, or their clinical condition required the drug. For those patients who were treated with deferiprone as part of clinical studies, the major criteria of their inclusion into the studies were age (10 years of age or older), the severity of the body iron load (serum ferritin level > 2000 ng/ μ L or liver iron concentration > 4 mg/g dry weight) and inability to use deferoxamine or unwillingness to continue its use despite medical advice. Exclusion criteria for participating in clinical trials included cardiac disease requiring medication, hepatic insufficiency or renal failure.

Chelation therapy

Deferoxamine (Desferal[®], Novartis Inc.) was prescribed at the dose of 20 to 50 mg/kg/day, as an 8–

12-hour subcutaneous infusion, 4–7 days a week. Three patients in the deferoxamine group had their chelation intensified with intravenous chelation during the study period. Despite the intensive chelation with deferoxamine they were not excluded from the analysis. Compliance with subcutaneous deferoxamine therapy was assessed at each transfusional event by the following:

- comparison of number of infusions reported by the patient with the number prescribed;
- examination of infusion sites;
- number of completed infusions recorded by a special electronic pump (Crono[®], Canè S.r.l., Italy);
- pharmacy records of syringes and needles dispensed.

Deferiprone (Ferriprox[®], Apotex Inc.) was prescribed at the dose of 25–100 mg/kg/day, divided in three doses. Compliance was assessed at each transfusional event by the electronic MEMS[®] cap (Medication Event Monitoring System, Ardex Ltd, Switzerland), which records the time and date of each opening of the deferiprone container. Compliance for patients participating in clinical trials was also measured by monthly counts of the number of deferiprone tablets dispensed and returned.

Regular determinations of serum ferritin level were used to monitor basic iron overload in all patients. The treating hematologist used all the above information during regular interviews with each patient as part of the clinical management of thalassemia and to promote compliance.

Cardiac assessments

A single cardiologist, experienced in hemoglobinopathies but blind to the therapy that the patients were receiving, assessed the cardiac status of all patients. The standard assessment included physical examination, ECG, echocardiogram, and cardiac status based on the criteria of the New York Heart Association (NYHA).²¹ When indicated, a 24-hour electrocardiographic Holter and/or stress test were also performed. The treating physician systematically screened the clinical records of each patient followed at the center. All patients who had had at least two cardiac assessments were evaluated, even if their first assessment was completed after the initiation of the study period. The first assessment was considered as the baseline value for each patient. The records of patients with any abnormal cardiac finding were then reviewed by the cardiologist. A change in shortening fraction (SF) or ejection fraction (EF) values was considered as important if the result at the last echocardiogram changed from normal to abnormal or *vice versa* compared to the first echocardiogram. The thresholds for normality of systolic function were defined as 30% for SF and 55% for EF.

Worsening and improvement of cardiac function

was defined, *a priori*, by one or more of the following criteria:

Worsening

- shifting of congestive heart failure from acute to chronic;
- increase in NYHA class;
- aggravation of arrhythmia requiring medication or a significant change in existing medication, or indication for ablation, or need for a pacemaker;
- shift from normal to abnormal echocardiographic values of systolic function.

Improvement

- shifting from congestive heart failure to asymptomatic;
- decrease in NYHA class;
- reduction of arrhythmia with reversal of medication dependency;
- shift from abnormal to normal echocardiographic values of systolic function or reversal of medication dependency.

In addition to the cardiac assessments, the following clinical and laboratory parameters were included in the evaluation of the two treatment groups:

- gender;
- age at start of the review period;
- age at start of first chelation therapy with deferoxamine;
- serum ferritin;
- transfusional iron input;
- compliance with chelation therapy.

Statistical analysis

A 2-sample t-test or χ^2 test, as appropriate, was performed to compare differences in the study parameters in the two groups of patients. The Kaplan-Meier analysis of heart disease-free survival for patients who were disease-free (NYHA class = 0) at the beginning of the review period was performed using SAS (version 6.12) and the disease-free survival curves were plotted using Statistica 5.5 (Stat-Soft Inc. Tulsa, USA). The incidence of patients with cardiac disease diagnosed at the first cardiac assessment who showed an improvement of their NYHA class during the study was determined and compared between the 2 treatment groups using Fisher's exact test. To examine any potential effect of age on the prevalence and/or progression of iron-induced cardiac disease, a further analysis was conducted, with patients from the 2 therapy arms being matched for age at the start of chelation therapy.

All statistical tests were 2-sided with a type 1 error (α) of 0.05. SAS (version 6.12) was used to conduct all the statistical tests. In all 2-sample t-tests, when the test for equality of variances was significant ($p < 0.05$), the test result based on unequal variances was used to determine the statistical significance of the comparison. Furthermore,

Table 1. Comparison of deferiprone- and deferoxamine-treated patients at the start of the study. Mean values \pm standard deviation are shown. The number of patients for whom the value was calculated is given in brackets if this differed from the original number of subjects.

	Deferiprone (n=54)	Deferoxamine (n=75)	p
Percentage female	44%	49%	0.583
Mean age (years)	17.1 \pm 4.1	19.4 \pm 6.9	0.018
Mean age (years) at start of chelation therapy with deferoxamine	4.5 \pm 2.7 (54)	6.8 \pm 4.7 (72)	0.002
Mean serum ferritin* (μ g/L)	2033 \pm 919 (51)	1809 \pm 1464 (63)	0.328
Percentage of patients with > 50% of serum ferritin results > 2,500* (μ g/L)	24% (51)	15% (60)	0.253
Mean transfusional iron input* (mg Fe/kg body weight/day)	0.464 \pm 0.085 (49)	0.432 \pm 0.110 (61)	0.102
Number (percentage) of patients with abnormal cardiac function	7 (13%)	12 (16%)	0.631

*during the 2 years preceding the study period.

when at least 50% of the cells in the 2 \times 2 contingency table had expected counts of < 5 in the χ^2 test, Fisher's exact test was used to determine the statistical significance.

Results

The clinical records of 168 patients with thalassemia major were screened, and 129 met all of the inclusion and exclusion criteria. Sixteen patients had not had chelation therapy with one of the chelators for at least 4 years during the review period, for 10 patients no information was available on chelation therapy or cardiac assessment, 6 patients had only 1 cardiac assessment, 6 patients were <5 years of age at the start of the review period and one patient was HIV-positive. None of the excluded patients was diagnosed with a change in their cardiac status or died during the review period.

All patients were regularly chelated with deferoxamine prior to the initiation of the study period. At the time of the study initiation both treatment groups were similar for gender distribution and the transfusional iron input received during the preceding 2 years. At baseline patients whose therapy was switched to deferiprone were younger ($p=0.018$) and had initiated chelation therapy with deferoxamine at an earlier age than patients who were maintained on deferoxamine ($p=0.001$) (Table 1).

During the study period the average dose of

Table 2. Comparison of deferiprone- and deferoxamine-treated patients during the study period. Mean values \pm standard deviation are shown and the number of patients for whom the value was calculated is given in brackets if this differed from the original number of subjects.

	Deferiprone (n=54)	Deferoxamine (n=75)	p
Percentage of compliance with chelation therapy	89% \pm 7% (53)	85% \pm 11% (73)	0.011
Mean overall transfusional iron input (mg Fe)/kg/day	0.432 \pm 0.076 (53)	0.408 \pm 0.085 (64)	0.111
Mean serum ferritin (μ g/L) at year 5 of the review period	2142 \pm 957 (49)	2143 \pm 1481 (64)	0.994
% patients > 50% of serum ferritin results > 2500 μ g/L	35%	20%	0.053
Ratio of patients with improvement of cardiac disease	3/7 (43%)	3/12(25%)	0.617
Ratio of patients with onset of cardiac disease	2/47 (4%)	13/63(21%)	0.013
Overall ratio of patients with worsening cardiac status	2/54 (4%)	15/75 (20%)	0.007

deferiprone was 73.7 \pm 11.2 mg/kg/day (range 25–100 mg/kg/day) and the average dose of deferoxamine was 39.2 \pm 4.7 mg/kg per infusion, administered an average of 6 \pm 1 times per week. The weighted mean compliance with deferiprone was 89% (range 66–98%) whereas it was 85% (range 54–99%) with deferoxamine (Table 2).

The mean (\pm SD) transfusional iron load in those patients switched to deferiprone, prior to the switch (0.464 \pm 0.085 mg Fe/kg body weight/day) was higher than the baseline values of those who remained on deferoxamine (0.432 \pm 0.110 mg Fe/kg body weight/day), but the difference failed to reach statistical significance ($p=0.102$). The deferiprone-treated patients continued to receive more iron throughout the study period (an average of 0.432 \pm 0.076 mg Fe/kg body weight/day) than the deferoxamine-treated patients (0.408 \pm 0.085 mg Fe/kg body weight/day), but this trend did not reach statistical significance ($p=0.111$).

The percentage of patients with more than 50% of their serum ferritin values greater than 2500 μ g/L during the study rose from 24% at baseline to 35% by the last year of the study in the deferiprone-treated group, compared with a rise from 15% at baseline to 20% in the deferoxamine-treated group. The difference in the percentage at the end of the study between the two groups was not statistically significant ($p = 0.053$). No significant difference was observed in the mean serum fer-

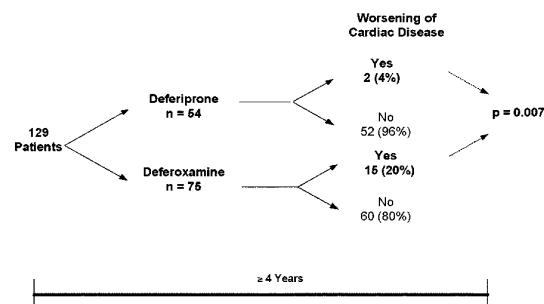


Figure 1. Cardiac function in patients with thalassemia major treated with deferiprone or deferoxamine.

ritin levels between the 2 treatment groups by the end of the study ($p = 0.994$).

Cardiac disease

Seven patients in the deferiprone group and 12 patients in the deferoxamine group had abnormal cardiac function at the first cardiac assessment. The cardiac abnormality was evaluated as NYHA class I in 13 patients (six in the deferiprone group and seven in the deferoxamine group), class II in 3 patients (all in the deferoxamine group), class III in two patients (one in each therapy group), and class IV in one deferoxamine-treated patient. The overall prevalence of cardiac disease at the first assessment was similar for both groups ($p=0.606$). Worsening of cardiac function was diagnosed in none of the patients treated with deferiprone and in 4 (33%) of the patients treated with deferoxamine. An improvement of the NYHA cardiac disease class was observed in 3 (43%) of the 7 deferiprone-treated patients and in 3 (25%) of the 12 deferoxamine-treated patients with cardiac disease diagnosed at the first assessment ($p=0.617$).

Newly diagnosed cardiac disease occurred in 2 (4%) of the 47 deferiprone-treated patients and in 13 (21%) of the 63 deferoxamine-treated patients who were free of cardiac disease at their first cardiac assessment. All but 2 of the 15 patients were classified as having NYHA class I disease. One remaining patient was classified as having NYHA class II, while the other one was classified as having NYHA class I and then worsened to class III; both patients were treated with deferoxamine.

Overall, cardiac dysfunction, expressed as worsening of pre-existing cardiac abnormality or development of new cardiac disease, was diagnosed in 4% of deferiprone-treated patients and in 20% of deferoxamine-treated patients from the first to the last measurement ($p=0.007$; Figure 1).

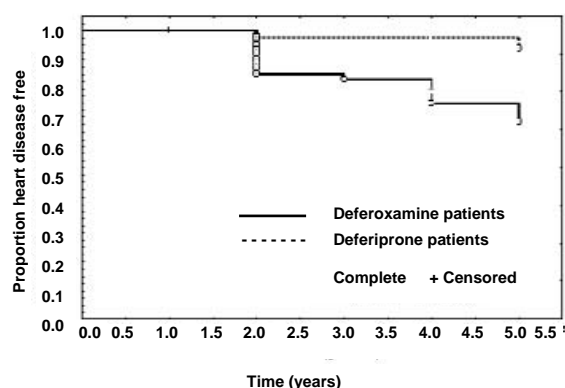


Figure 2. Kaplan-Meier analysis of heart disease-free survival in patients with thalassemia major treated with deferiprone or deferoxamine. Four percent of the deferiprone-treated patients developed cardiac disease compared to 21% of deferoxamine-treated patients over the same period of time ($p = 0.003$).

The Kaplan Meier analysis of cardiac disease-free survival over the 5-year period was significantly more favorable in the deferiprone group ($p = 0.003$) (Figure 2).

To determine whether the observed difference in the occurrence of cardiac disease between the two treatment groups could have been influenced by differences in age or age at the start of chelation, we conducted a cohort analysis. Forty-seven patients treated with deferiprone were found to have a match from the deferoxamine-arm for the same age at start of chelation therapy. Both cohorts were similar for baseline data, including age at the start of the study (*data not shown*). As in the main analysis, after 5 years of therapy there was no significant difference between the 2 treatment groups in the mean serum ferritin level. Overall, worsening of cardiac disease/development of new cardiac disease was diagnosed in 2 (4%)

deferiprone-treated patients and in 9 (19%) deferoxamine-treated patients from the first to the last measurement ($p = 0.023$). Kaplan-Meier analysis indicated a significant difference ($p = 0.017$) in the cardiac disease-free survival between the 2 groups in favor of those treated with deferiprone.

Survival

None of the 54 patients treated with deferiprone died, while 4 of the 750 patients treated with deferoxamine died during the study period. Three of these patients had cardiac disease at the first assessment of the study period and died because of irreversible worsening of their cardiac condition (Table 3). One death occurred during the second year, whereas the other two occurred during the last year of the review period. The fourth death occurred in a patient with a history of drug addiction but no signs of cardiac disease. This patient died within a few hours of being admitted into a provincial hospital for acute abdominal pain. No cause of death was determined. This death was not included among the deaths in the survival analysis.

Discussion

This is the first published study to compare the development of cardiac disease and survival between subjects with thalassemia major treated with deferoxamine or deferiprone. Patients participating in the study were young, with a mean age of 18.4 years at time of the start of the review period, and were followed up on average for 6 years, a period which corresponds to approximately 25% of their life span at the end of the study. The data revealed that patients who had had their chelation therapy switched to deferiprone were less likely to have developed cardiac disease and if they had had pre-existing cardiac disease, were less likely to have experienced a worsening of that disease.

Table 3. Demographics and clinical information on the three patients who died of cardiac disease.

Age at start review period	Gender	Age at start of first chelation	Chelation therapy during study	Cardiac disease at baseline	Compliance with chelation during review	Hepatic iron concentration closest to time of death	% of serum ferritin > 2500 $\mu\text{g/L}$
26 years	Male	13 years	DFO	Yes (NYHA Class II)	54%	Not available	89%
23 years	Male	8 years	DFO	Yes (NYHA Class II)	73%	3.3 mg/g dry weight	25%
23 years	Female	NA	DFO	Yes (NYHA Class IV)	not available	31.2 mg/g dry weight	Not available

Iron-induced cardiac disease remains the main cause of death in patients with thalassemia major.⁸ In a previous study, we reported that 30% of patients with thalassemia developed cardiac disease by the age of 20 years.¹ In the current study, 19 (15%) patients had cardiac disease at the first assessment of the review period and there was no significant difference in the percentage of patients with cardiac disease in the two study groups. At baseline, all patients were being treated with subcutaneous deferoxamine infusions, an average of 6.2 days per week and, based on the serum ferritin levels over the 2 years that preceded the baseline assessment, the overall patient cohort was considered to be relatively well chelated and at low risk of iron-induced cardiac disease.⁷ However, over the 6-year observation period, there was a significantly greater prevalence of worsening of heart disease among patients maintained with deferoxamine than in patients switched to deferiprone. Newly diagnosed heart disease occurred in 15 (12%) patients, which corresponds to an incidence of 2.0 per 100 patient-years. The incidence was greater in the deferoxamine group. Overall, the probability of worsening cardiac status was about 5-fold higher during deferoxamine therapy than during deferiprone therapy. At the completion of the study, three patients in the deferoxamine-treatment group had died of cardiac disease.

The two groups of patients were similar in most aspects but differed regarding the age at baseline and the age at which chelation therapy had been started. To assess the impact of age on the study results, the analysis was repeated after matching the patients in each arm of therapy for age at start of chelation. Both cohorts were similar for baseline data, including age at the start of the study. The analysis, after this correction, still demonstrated a significantly more favorable outcome in the deferiprone-treated cohort in terms of cardiac disease-free survival and for worsening of pre-existing cardiac disease and indeed the difference was even more pronounced.

According to the literature,¹ a major limiting factor in patients treated with deferoxamine is a lack of compliance. However, in this study, the clinically favorable results in the deferiprone-treated group do not appear to be related to a lack of compliance in the deferoxamine-treated group. Although compliance with oral chelation was higher than that with the subcutaneous infusions, the overall compliance with deferoxamine was only 40% less than with deferiprone, and far above the level normally reported.¹⁰ The observed high compliance in the deferoxamine group is probably due to the regular and intensive attention given to this aspect of management of thalassemia over the

years in this center.²²

Only one patient had an extensive interruption of chelation therapy; a deferiprone-treated patient stopped chelation for approximately one year while being treated for hepatitis C. He was not excluded from the analysis. The three patients who died of cardiac disease were among those with the lowest compliance. There was no difference in compliance between the 2 therapies among patients with a worsening of cardiac disease or new cardiac disease (85% vs 84% for deferiprone vs deferoxamine, $p=0.967$).

The two treatment groups were similar for body iron load, as expressed by mean serum ferritin levels at baseline and at the end of the study. The data from this study illustrate that serum ferritin values were not predictive of development of cardiac disease. Based on reported threshold levels, the deferoxamine therapy group would have been judged to be at lower risk of cardiac disease,⁷ as expressed by sequential ferritin assessments (% of serum ferritin values lower 2500 $\mu\text{g/L}$) (Table 2). Hepatic iron concentration (HIC), which was measured in a fraction of patients in both treatment groups (*data not shown*), was also not predictive of cardiac disease. All HIC values were below 15 mg/g dry weight, a suggested threshold for increased risk of cardiac disease in patients with iron load.⁴

The results of the present analysis are consistent with the prevalence of cardiac disease during long-term treatment with deferoxamine^{3,7,23} and with the paucity of reports of cardiac disease in patients receiving long-term treatment with deferiprone even though the early use of deferiprone was generally restricted to the most severely iron overloaded and non-compliant patients.¹⁴⁻¹⁹

This retrospective study suggests that deferiprone may have a cardioprotective effect. If that is the case, it may be due to the drug's physicochemical characteristics: because of its lipophilicity, neutral charge at pH 7.4, and low molecular weight, deferiprone can readily cross cell-membranes and bind intracellular iron.^{12,13,24} Although the most commonly used dose of deferiprone (75 mg/kg/day) is approximately twice that of deferoxamine (40 mg/kg/day), peak serum concentrations (about 100 μM) are more than 10 times those seen with the injectable chelator (<10 μM). At clinically relevant concentrations, deferiprone exhibited greater iron mobilization than deferoxamine from cultured, iron-loaded heart cells.¹¹ These findings are consistent with the results of clinical studies using quantitative magnetic resonance imaging (qMRI). Previous reports showed that deferiprone treatment in patients with thalassemia led to an increase of heart signal, compatible with a reduction in heart iron load.^{25,26} Comparative qMRI stud-

ies indicated that deferiprone may also be more effective than deferoxamine in increasing the heart signal and improving heart function in patients with iron overload.^{27,28}

Other factors, such as a different sensitivity to iron-induced oxidative damage may play a role in the development of cardiac disease in patients with iron overload.²⁹ Autopsy findings in patients with thalassemia who died of cardiac disease showed a heart iron concentration 10-fold lower than the liver iron concentration.³⁰ Non-transferrin-bound iron (NTBI) has been suggested to be a contributor to iron damage.²⁹ Since deferiprone acts 10 times faster than deferoxamine in mobilizing citrate-bound iron, one major component of the NTBI pool,³¹ it is possible that its greater access to NTBI may have contributed to the preferential results. In addition, the longer half-life of deferiprone, associated with its more frequent dosing (thrice daily) and uninterrupted therapy (7 days a week), may also serve as a factor leading to greater protection than that afforded by the standard regimen of deferoxamine (8–12 hours infusion 5 to 7 days a week) by providing a longer duration of chelation.

This retrospective analysis suggests that, in patients with thalassemia major, long-term therapy with deferiprone results in a greater cardioprotective effect against the toxicity of iron overload than does subcutaneous deferoxamine. Formal prospective studies comparing the incidence of cardiac disease and survival in deferiprone and deferoxamine-treated patients are warranted to confirm these findings.

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Pre-publication Report & Outcomes of Peer Review

Contributions

AP: at most for: a) conception, design and interpretation of data b) for drafting and revising c) final approval. CG: at most for a) design, analysis b) revising c) final approval. EF: is the cardiologist that ran the tests and contributed at most in b) revising c) final approval. FT: at most for a) design, interpretation b) drafting and revising c) final approval. Antonio Piga was primarily responsible for the publication and for each Table and each Figure.

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Disclosures

Conflict of interest: FT is an employee of Apotex Research Inc., Canada. AP, through his institution, have received a research grant from Apotex for carrying out the study. None of the authors had financial support as consulting fees, service on advisory boards, ownership of equity, patent royalties, honorariums for lectures or fees for expert testimony. Before publication, based on the results of this study, Apotex has submitted a patent application for the possible cardioprotective action of deferiprone.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received October 10, 2002; accepted March 24, 2003.

In the following paragraphs, the Editor-in-Chief summarizes the peer-review process and its outcomes

What is already known on this topic

In a recent study in the *Lancet* (*Lancet* 2002; 360:516-2) Pennell and co-workers showed that conventional chelation treatment with subcutaneous desferrioxamine does not prevent excess cardiac iron deposition in two-thirds of patients with thalassemia major, placing them at risk of heart failure and its complications. By contrast, oral deferiprone was found to be more effective than desferrioxamine in removal of myocardial iron.

What this study adds

This study confirms that deferiprone might have a greater cardio-protective effect against the toxicity of iron overload than does subcutaneous desferrioxamine

Caveats

This is a retrospective study and, as such, has intrinsic limitations. The *Lancet* study involved small groups of patients (30 in the desferrioxamine group vs 15 in the deferiprone group). Therefore, as underlined by Piga and co-workers, formal prospective studies are warranted to confirm the superior cardio-protective effect of deferiprone. Deferiprone involves a not negligible risk of agranulocytosis and milder neutropenia (0.4/100 and 2.1/100 patient-years, respectively - *Br J Haematol* 2002;118:330-6). Finally, to summarize a long, complex dispute, according to Nathan and Weatherall (*N Engl J Med* 2002;347:1368-71) published papers would suggest that deferiprone does a poor job of removing iron from hepatic stores in a substantial proportion of treated patients, and that the issue of its safety with respect to hepatic fibrosis has not been resolved.