A Randomized, Placebo-Controlled, Double-Blind Trial of the Effect of Combined Therapy With Deferoxamine and Deferiprone on Myocardial Iron in Thalassemia Major Using Cardiovascular Magnetic Resonance

M.A. Tanner, MRCP; R. Galanello, MD; C. Dessi, MD; G.C. Smith, MSc; M.A. Westwood, MD; A. Agus, MD; M. Roughton, MSc; R. Assomull, MRCP; S.V. Nair, MRCP; J.M. Walker, MD; D.J. Pennell, MD

Background—Cardiac complications secondary to iron overload are the leading cause of death in β-thalassemia major. Approximately two thirds of patients maintained on the parenteral iron chelator deferoxamine have myocardial iron loading. The oral iron chelator deferiprone has been demonstrated to remove myocardial iron, and it has been proposed that in combination with deferoxamine it may have additional effect.

Methods and Results—Myocardial iron loading was assessed with the use of myocardial T2* cardiovascular magnetic resonance in 167 patients with thalassemia major receiving standard maintenance chelation monotherapy with subcutaneous deferoxamine. Of these patients, 65 with mild to moderate myocardial iron loading (T2* 8 to 20 ms) entered the trial with continuation of subcutaneous deferoxamine and were randomized to receive additional oral placebo (deferoxamine group) or oral deferiprone 75 mg/kg per day (combined group). The primary end point was the change in myocardial T2* over 12 months. Secondary end points of endothelial function (flow-mediated dilatation of the brachial artery) and cardiac function were also measured with cardiovascular magnetic resonance. There were significant improvements in the combined treatment group compared with the deferoxamine group in myocardial T2* (ratio of change in geometric means 1.50 versus 1.24; \( P = 0.02 \)), absolute left ventricular ejection fraction (2.6% versus 0.6%; \( P = 0.05 \)), and absolute endothelial function (8.8% versus 3.3%; \( P = 0.02 \)). There was also a significantly greater improvement in serum ferritin in the combined group (−976 versus −233 μg/L; \( P < 0.001 \)).

Conclusions—In comparison to the standard chelation monotherapy of deferoxamine, combination treatment with additional deferiprone reduced myocardial iron and improved the ejection fraction and endothelial function in thalassemia major patients with mild to moderate cardiac iron loading. (Circulation. 2007;115:1876-1884.)

Key Words: deferiprone ■ deferoxamine ■ endothelium ■ heart failure ■ magnetic resonance imaging ■ thalassemia ■ trials

Beta-thalassemia major (TM) affects ≈60 000 births per year worldwide. A mutation in the β-globin gene causes defective erythropoiesis, which in its homozygous form results in a severe anemia, rendering the individual dependent on lifelong blood transfusions. The subsequent development of iron overload can result in cardiomyopathy, and heart failure remains the leading cause of death in TM.1,2 Although treatment with the parenteral iron chelator deferoxamine has improved morbidity and mortality, long-term survival remains poor, with data from the United Kingdom showing 50% of patients dead by the age of 35 years.3

Received August 1, 2006; accepted January 24, 2007.

From the Cardiovascular Magnetic Resonance Unit (M.A.T., G.C.S., M.A.W., R.A., D.J.P.) and Health Services Research Unit (M.R.), Royal Brompton Hospital, London, UK; Ospedale Regionale per le Microcitemie, Cagliari, Italy (R.G., C.D., A.A.); and Department of Cardiology, University College Hospital, London, UK (S.V.N., J.M.W.).


Correspondence to Dr Dudley Pennell, Professor of Cardiology, Royal Brompton Hospital, Sydney St, London SW3 6NP, UK. E-mail d.pennell@ic.ac.uk

© 2007 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org
use of better-tolerated chelators as a total or partial replacement for deferoxamine could pave the way for improvement in cardiovascular mortality.

Cardiovascular magnetic resonance (CMR) permits the quantification of myocardial iron through the measurement of T2*, which is highly sensitive to tissue iron concentration and has been validated in the United Kingdom and independently in the United States. The high reproducibility of T2* measurement makes the technique ideal for longitudinal follow-up studies to determine optimal treatments for reducing myocardial iron. CMR is established as the gold standard for quantifying LV function and can also assess the effects of iron loading on endothelial function as measured from brachial arterial reactivity, which may contribute to cardiovascular pathology in TM. Therefore, CMR is the technique of choice for studies of the effects of iron chelators on the cardiovascular system in TM.

Deferiprone is an orally administered iron chelator that has been approved for use as second-line chelation therapy in Europe since 1999. Initial concerns regarding an increased risk of hepatic fibrosis have proved unfounded, and there are now considerable clinical trial data to suggest that deferiprone is superior in removing myocardial iron compared with deferoxamine; this position has been strengthened with data showing improved outcomes in patients on deferiprone. Conversely, deferiprone may be less effective in removing hepatic iron than deferoxamine. Because of the relative merits of the 2 drugs, the issue of combined therapy has been proposed, but few randomized data are available for the cardiovascular system for this maneuver. We therefore initiated a randomized, placebo-controlled, double-blind trial to test the hypothesis that the combined therapy of deferoxamine and deferiprone would result in greater reduction in cardiac iron loading than deferoxamine alone, using myocardial T2* as the primary end point.

Methods

Overall Study Performance

A London-based mobile 1.5-T CMR scanner (Sonata, Siemens, Erlangen, Germany) with specialized cardiovascular capability was transported 3 times to Cagliari, Italy, for this research. Patient recruitment was from 12 thalassemia centers on the island of Sardinia, with patients undergoing local hematologist management but traveling to Cagliari for regular visits and CMR scans. After baseline CMR scans, randomization to treatment groups was performed. The study protocol was approved by ethics committees in London and Cagliari. Patient information and consent forms were in Italian, and all patients gave written informed consent.

Study Protocol

The inclusion criteria for patient entry into the trial were as follows: diagnosis of TM currently maintained on subcutaneous deferoxamine monotherapy; age >18 years; maintenance of pretransfusion hemoglobin >9 g/dL; myocardial T2* between 8 and 20 ms (mild to moderate myocardial siderosis); and confirmation of effective contraception throughout the trial. Exclusion criteria were as follows: patients who have previously received deferiprole for a total of >6 months over the last 5 years; patients with previous reaction to deferiprole; neutropenia (absolute neutrophil count <1.5 x 10^9/L) at screening; thrombocytopenia (<50 x 10^9/L) at screening; liver enzymes >3 times upper limit of normal; and implant incompatible with MR (such as pacemaker), claustrophobia, or other condition making CMR impossible or inadvisable.

The baseline screening was performed by CMR in 167 eligible patients with TM (75 men, 92 women; age range, 18 to 42 years; mean age, 30±5.3 years). Patients without cardiac iron loading (myocardial T2* >20 ms; n=59) were excluded. Subjects with severe cardiac siderosis (T2* <8 ms; n=22) were also excluded on the basis that it was not ethical to offer such patients placebo, and they were offered best medical therapy based on current practice according to the decision of the caring hematologist. Patients with mild to moderate cardiac iron loading who satisfied the trial entry criteria (myocardial T2* 8 to 20 ms; n=86) were invited for further detailed assessment by MR. Of these, 74 patients agreed to return for the full MR protocol, and 65 were subsequently randomized to receive either deferoxamine plus deferiprole (combined group; n=32) or deferoxamine plus placebo (deferoxamine group; n=33). The 9 patients who were not randomized consisted of 2 who were unsuitable (1 adverse response to glycerol trinitrate with frequent ventricular ectopy, 1 atrial fibrillation) and 7 who expressed the concern that although they were willing to participate, they would prefer to defer to participation of others. The overall patient numbers throughout the trial are shown in Figure 1.

The primary end point of the trial was defined as the change between treatment groups from baseline to 12 months in myocardial T2*. The secondary end points were the change from baseline to 12 months in liver T2*, serum ferritin; LV volumes and function; brachial artery reactivity (endothelium dependent and independent); B-type natriuretic peptide (BNP) (Biosite Diagnostics Inc, San Diego, Calif) as a marker of heart failure; compliance with chelation treatments; and adverse events.

Iron Chelation Management and Randomization

Normal clinical management of deferoxamine therapy was performed by the hematologist in accordance with local standard clinical practice and guidelines. Current standard treatment for iron loading is subcutaneous deferoxamine (40 to 50 mg/kg body wt) for as many nights per week as the patient will tolerate (ideally a minimum of 5). In addition to the standard deferoxamine treatment, patients were randomized to deferiprole at a dose of 75 mg/kg body wt or placebo with identical appearance. Neither the patients nor the hematologists were aware of the treatment allocation (double-blind).

Cardiovascular Magnetic Resonance

CMR was performed at baseline and after 6 and 12 months of treatment. Myocardial T2* was assessed with the use of a single breath-hold multiecho technique that can be completed in 5 minutes, as previously described. In brief, a single 10-mm-thick short-axis midventricular slice of the LV was acquired at 8 echo times (2.6 to 16.7 ms, with 2.02-ms increments) with standard shimming in a single breath-hold. For analysis, a full-thickness region of interest was chosen in the LV septum. The signal intensity of this region was measured for each image with the use of in-house designed software (CMRtools, Cardiovascular Imaging Solutions, London, UK). Ventricular volumes were determined with the use of steady state free precession cine, with contiguous short-axis slices from base to apex, as previously described. Ventricular volumes were also analyzed with the use of CMRtools. For the assessment of endothelial function, flow-mediated dilatation (FMD) of the brachial artery was examined by a validated CMR technique. This was performed at baseline and 12 months only for logistical reasons. A 2-cm surface coil was placed over the brachial artery. The brachial artery was occluded for 5 minutes by inflating a blood pressure cuff on the forearm to 20 mm Hg above systolic pressure. On release, the artery was scanned immediately and at 1 to 5 minutes after cuff deflation. The cross-sectional area of the artery was calculated at baseline and 1 to 5 minutes after cuff deflation. The cross-sectional area of the artery was calculated at baseline and at maximal dilatation, and the resulting FMD was expressed as percent change in area. For assessment of endothelium-independent dilatation, the percent change in brachial artery area was measured before and 3 minutes after sublingual administration of glyceryl trinitrate (400 µg).
Serum Ferritin
Serum ferritin was measured at baseline and every 2 months. Serum was separated, labeled, and stored frozen at -20°C and was measured by microparticle enzyme immunoassay (Abbott AXSYM System).

Safety Assessments
Patients were monitored weekly for absolute neutrophil count and any adverse events. Serum alanine aminotransferase levels were measured every 2 months, serum zinc levels were measured at baseline and every 6 months, and serum creatinine levels were measured at baseline, 6 months, and 12 months.

Statistical Analysis
Power calculations showed that the study would have an 80% power at a significance level of 0.05 to detect a change in the primary end point of myocardial T2* of 0.75 SD with a sample size of 55 patients, which, allowing for a 15% patient dropout, indicated that we should randomize 65 patients. Differences between groups for all continuous parameters at baseline were analyzed by the unpaired t test. Because tissue iron is related linearly to the inverse of T2*, this measure was log-transformed before analysis for normalization. It was also necessary to log-transform serum ferritin levels to achieve normality. Data are presented as mean±SD, except for the T2* and ferritin data, which use the geometric mean (anti-log of the mean of the log data) plus or minus the coefficient of variation (CV), equivalent to the variance of the mean in log scale. Between-group analysis from baseline to 12 months was performed with the use of a mixed-effects model, with baseline readings and treatment group entered as fixed effects and patients considered a random effect. Trend analysis over time within groups for continuous parameters was performed with a mixed model with time as a fixed effect. In the case of FMD, in which measurement at only 2 time points was available, ANCOVA was used with treatment, and baseline measures were entered as covariates. Proportions of patients between the treatment groups were compared by Fisher exact test. Deferoxamine compliance was calculated as the percentage of completed infusions, as determined by the Crono pumps, divided by the number of infusions prescribed. Deferiprone/placebo compliance was measured through pill counting at the bimonthly visits. Statistical analysis was performed with the use of SPSS version 10.0 (SPSS, Inc, Chicago, Ill) and STATA 9.2 (StataCorp, College Station, Tex). A probability value of 0.05 was the threshold used for statistical significance.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Characterization
The baseline characteristics are shown in the Table. The groups were well matched for all measures at baseline, including the primary end point of myocardial siderosis.

Deferoxamine Dosing
At baseline, both groups were well matched for the prescribed dose of deferoxamine (Table). The mean dose of deferoxamine in all randomized patients (deferoxamine and combined groups) before trial entry was 36.4±11.1 mg/kg per day for 5.5 d/wk (equivalent to 40.5 mg/kg for 5 d/wk). This is in accord with the 40 to 50 mg/kg per day for 5 d/wk from clinical recommendations. During the trial, the dose prescribed for deferoxamine in the deferoxamine group was equivalent to 43.4 mg/kg per day for 5 d/wk (2.5±9.2 mg/kg per day; P=0.1 versus pretrial maintenance dose for the deferoxamine group only). In comparison, the dose prescribed in the combined group during the trial was significantly lower at 34.9 mg/kg per day for 5 days (P=0.02 versus deferoxamine group).

Deferiprone Dosing
At baseline, no patient was taking deferiprone. During the trial, the dose prescribed for deferiprone was 75 mg/kg per day for all patients.

Compliance
Compliance with deferoxamine was similar in both groups (combined 91.4±12.7% versus deferoxamine 92.6±12.7%; P=0.7). Compliance with deferiprone was less than compliance with placebo (82.4±18.1% versus 89.8±7.2%; P=0.04).
Myocardial Iron
In the combined treatment group, myocardial T2* improved significantly (indicating reduced myocardial iron) from a baseline of 11.7 ms to 14.7 ms at 6 months and 17.7 ms at 12 months (ratio of geometric means 1.50; CV 13%; P<0.001; Figure 2). In the deferoxamine group, myocardial T2* changed from a baseline of 12.4 ms to 14.5 ms at 6 months and 15.7 ms at 12 months (ratio 1.24; CV 16%; P<0.001). The between-group difference (39%) was significantly in favor of the combined treatment group (95% CI, 20% to 61%; P<0.001).

Liver Iron
In the combined group, liver T2* improved significantly from a baseline of 4.9 ms to 9.5 ms at 6 months and 10.7 ms at 12 months (ratio of geometric means 2.07; CV 37%; P<0.001; Figure 3). In the deferoxamine group, there was a significant change in liver T2* from a baseline of 4.2 ms to 4.9 ms at 6 months and 5.0 ms at 12 months (ratio 1.20; CV 50%; P=0.01). The between-group difference (39%) was significantly in favor of the combined treatment group (95% CI, 20% to 61%; P<0.001).

Cardiac Function and Volumes
There was a significant difference between treatment groups with respect to changes in LV ejection fraction over 12 months. In the combined group, LV ejection fraction increased from 65.8±6.2% at baseline to 68.4±4.7% at 12 months, and in the deferoxamine group, LVEF increased from 64.7±6.5% to 65.3±6.0% (absolute percent difference between groups, 1.17%; 95% CI, 0.0% to 2.35%; P=0.05;
Figure 4). There was no significant difference between treatment groups in terms of end-diastolic volume and end-systolic volume. End-diastolic volume decreased from 124.9 ± 30.5 to 119.1 ± 31.8 mL over 12 months in the combined group and changed from 127.5 ± 37.4 mL at baseline to 126.4 ± 35.5 mL in the deferoxamine group (difference between groups, -3.83 mL; 95% CI, -20.23 to 12.55; \( P = 0.7 \)). End-systolic volume decreased from 43.3 ± 16.1 to 38.3 ± 13.3 mL in the combined group, and end-systolic volume changed from 46 ± 18.9 to 44.7 ± 17.2 mL over 12 months in the deferoxamine group (\( P = 0.3 \)). There was a significant correlation between improved ejection fraction and baseline myocardial T2* in all study patients with baseline T2* < 10 ms (\( r = 0.67, \ P < 0.01 \)) but no significant correlation in the entire study group. For the 8 patients treated with deferiprone with baseline myocardial T2* < 10 ms, the ejection fraction rose by 4.9% over 12 months. Seven patients were treated with placebo with baseline myocardial T2* < 10 ms, and in this group the ejection fraction fell by 0.1% over 12 months (\( P = 0.05 \) for the difference between groups).

**Brachial Artery Reactivity**

In the combined treatment group, endothelial-dependent FMD improved significantly (baseline 10.0 ± 7.7% versus 18.8 ± 9.3% at 12 months; \( P < 0.001 \); Figure 5). There was no significant change in FMD in the deferoxamine group (baseline 10.0 ± 9.5% versus 13.3 ± 9.8% at 12 months; \( P = 0.1 \)). The between-group difference was significantly in favor of the combined treatment group, with a treatment effect of 5.9% (95% CI, 0.99% to 10.8%; \( P = 0.02 \)). There was no significant change in endothelium-independent glyceryl trini-
Adverse Events and Subject Withdrawals

Gastrointestinal symptoms (nausea, vomiting, or abdominal pain) were the most common adverse event, occurring in 38% of patients in the combined group and 24% of patients in the deferoxamine group ($P=0.2$). These were generally mild in severity, although they were more likely to be recurrent ($>$2 episodes) in the combined group compared with the deferoxamine group (19% versus 3%; $P=0.05$). Other adverse events included reactions at the deferoxamine infusion site, occurring in 3% of the combined group and 6% of the deferoxamine group. Joint problems, including pain and/or swelling, occurred in 9% of the combined patients and in 18% of the deferoxamine group ($P=0.3$). In the combined group, there was 1 episode of agranulocytosis, which recovered without complication with the use of granulocyte colony-stimulating factor. There were 2 episodes of neutropenia ($1.0$ to $1.5 \times 10^9/L$) in the combined group. Both episodes resolved after discontinuation of the drug, and neither of these subjects was withdrawn from the study. In total, there were 7 patient withdrawals: 6 in the first month of treatment and 1 after 6 months of treatment; there were 4 in the combined group (agranulocytosis [n=1], reduction of myocardial T2* to $<8$ ms [n=1], gastrointestinal symptoms [n=1], and personal reasons [n=1]) and 3 in the deferoxamine group (atrial fibrillation [n=1] and personal reasons [n=2]).

Discussion

The cardiomyopathy resulting from iron toxicity is the single most important cause of death in individuals with TM.$^{1,2,4}$

Despite treatment with the most widely used iron chelator deferoxamine, a significant proportion of patients have myocardial iron loading.$^{5,6}$ Therefore, a logical step toward an improvement in cardiac mortality is to optimize the treatment of myocardial siderosis. Although deferoxamine is an important chelator$^{24}$ with a very high affinity for iron, it is a large and relatively lipophobic molecule that does not readily cross cell membranes. In contrast, deferiprone is small and lipophilic and readily crosses cell membranes, thereby gaining access to intracellular iron.$^{25}$ These differential properties form the basis of the “shuttle hypothesis,” which proposes that combination therapy has additive or synergistic effects.$^{26}$ There is evidence for this in vitro,$^{27}$ and a number of clinical studies have concluded that combined therapy offers additional benefit in terms of iron loading and cardiac function.$^{28,29}$ Despite these studies, widespread acceptance of the use of combination therapy has not occurred because prospective, randomized, placebo-controlled data have not been available. Our study provides such evidence for the first time. Our study shows that the addition of deferiprone to deferoxamine therapy has favorable effects in the treatment of iron overload in TM and in particular shows that combination therapy results in a significant relative reduction in myocardial siderosis. Although there are currently no published data on the direct prognostic significance of myocardial T2*, there are data demonstrating the adverse effects of a low T2*. Subjects with a very low myocardial T2* are at risk of symptomatic heart failure and ventricular arrhythmias.$^{6,10}$ Myocardial T2* improves in concert with cardiac function in response to intensification of chelation therapy in severe myocardial iron loading.$^{11}$ It is therefore highly probable that an increase in T2* is associated with an improvement in cardiovascular outcome.
A number of changes in secondary outcome measures were also more favorable in the combined group. The relative improvement in liver iron and serum ferritin was significantly greater in the combined group. The superior effects on LV ejection fraction are in agreement with prior combination trial data28,29 and are most obvious in patients with the highest myocardial iron burden (myocardial T2* <10 ms). These patients have LV ejection fractions that are subnormal relative to thalassemia patients with no myocardial iron loading,30 and therefore their rise in ejection fraction represents relief of subclinical LV dysfunction.12 Of additional considerable interest was the significant relative improvement in endothelial function in the combined treatment group. Endothelial dysfunction has previously been described in patients with TM.14 Our results support this finding with a mean FMD of the combined treatment group. Endothelial dysfunction has been linked with TM results in large improvements in endothelial function. In TM, endothelial dysfunction has been linked to increased arterial stiffness.14 This is highly relevant to the management of those patients in whom the interactions between vasculature and ventricle are likely to play a significant role in the development and progression of heart failure. Relief of endothelial dysfunction in patients with heart failure might therefore be beneficial. Although optimization of chelation therapy improves endothelial function, there are other therapeutic options, such as isosorbide dinitrate, that stimulate nitric oxide signaling,33 to increased arterial stiffness.14 This is highly relevant to the management of those patients in whom the interactions between vasculature and ventricle are likely to play a significant role in the development and progression of heart failure. Relief of endothelial dysfunction in patients with heart failure might therefore be beneficial. Although optimization of chelation therapy improves endothelial function, there are other therapeutic options, such as isosorbide dinitrate, that stimulate nitric oxide signaling,33 which might provide additional protection from heart failure and cardiovascular complications.

The baseline cross-sectional findings of the cohort screened for this study have been reported previously.6 These findings showed that BNP was inadequate as a predictor of myocardial iron loading. The present study now demonstrates in addition that serial measurements of BNP show no significant change in either of the treatment groups, despite large improvements in myocardial siderosis in the combined group. These results suggest a very limited role for BNP as a convenient surrogate marker for myocardial iron.

Although compliance to deferoxamine was very similar in both groups, the actual prescribed dose was significantly lower in the combined group. Thus, despite lower deferoxamine dosing in the combined group, these subjects still demonstrated improved iron clearance. The likely explanation for the disparity in dosing between groups is that hematologists would be expected to lower the dose of deferoxamine in response to falling serum ferritin, which occurred more frequently in the combined group (ferritin <500 µg/L was seen in 1 patient in each group at baseline but at 6 months occurred in 11 of 32 [34%] in the combined group but in only 1 of 33 [3%] in the deferoxamine group; P=0.001).

Compliance with deferiprone was lower than compliance with deferoxamine (82.4% versus 89.8%; P=0.04). On further analysis of individual cases, it was clear that the majority of cases of poor chelation (compliance <75%; n=8) were associated with adverse events. There were 2 cases of transient neutropenia, 3 cases of elevated alanine aminotransferase, and 2 cases of gastrointestinal intolerance, and 1 subject requested a drug “vacation.” In all cases, adverse effects in response to deferiprone were transient and responded to either dose reduction or temporary drug cessation. These adverse events have been documented in previous studies of deferiprone monotherapy and combined therapy.12,20,28,29 Overall, in the entire combination treatment group, there were 2 cases of neutropenia and 1 case of agranulocytosis. It is not clear whether this represents a higher than expected level of toxicity because of the small number involved. Therefore, although the superior efficacy of combined therapy has been clearly demonstrated, the incidence of adverse events requires further scrutiny.

Limitations
The results of the present study apply to adults with mild to moderate myocardial iron loading and may not necessarily be applicable to patients with severe cardiac siderosis or symptomatic heart failure. Combined therapy was better than monotherapy as currently practiced (40 mg/kg per day for 5 d/wk) and was a safe, consistent, and well-tolerated mechanism to ensure negative iron balance in the liver, heart, and endothelium; similar data do not exist for higher-dose deferoxamine therapy, which is an alternative strategy. However, a further advantage of combined treatment is that the deferoxamine treatment can be administered less often and for a shorter duration, which helps patient compliance.

Conclusions
In comparison to the standard chelation therapy of maintenance subcutaneous deferoxamine, combined therapy including deferiprone demonstrates superior reduction in myocardial iron and improved ventricular and endothelial function. This therapy is likely to translate into an improvement in cardiovascular mortality and should be considered in patients whose deferoxamine monotherapy fails to achieve adequate control of myocardial iron.

Acknowledgments
We would like to thank the following colleagues from the Sardinian thalassemia centers involved in the trial: Simona Piras, Martina Pibiri, S. Mulas (Ospedale Civile, Alghero); G. Tocco (Ospedale Sirai, Carbonia); N. Landis (Ospedale F. li Crobu, Iglesias); I. Contu, P. Cannas (Ospedale Civile, Lanusei); G. Puggioni (Ospedale San Francesco, Nuoro); A. Zaccarelli (Ospedale Civile, Olbia); A. Carta (Ospedale Civile San Martino, Oristano); G. Bertrand (Ospedale A. Segni, Ozieri); M.G. Batzella (Ospedale Civile, San Gavino); G. Sechi (Centro Trasfusionale, Sassari); D. Gallisai (Clinica Pediatrica, Sassari, and “Fondazione L. Giambrone” Sassari). We also thank Mohammed Khan for statistical advice and analysis and the following colleagues for their important contributions: David Firmin, Taigang He, Steve Collins, Tim Cannell, Ray Hughes, Niall Keenan, and Craig Broberg.
Sources of Funding

Funding was received from CORDA, Royal Brompton, and Harefield Hospital Charitable Funds, the Cooley’s Anemia Foundation, Apoptex, the UK Thalassaemia Society, and the University College London Special Trustees Charity. The funding sources played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

Disclosures

Dr Pennell had full access to all the data in the study and had final responsibility for the decision to submit for publication. The authors are solely responsible for the conduct, data storage, data analysis, and reporting of this trial. Dr Pennell is a consultant to, has received speaker’s honoraria and research support from, and has participated in chelation drug research with Apoptex. He is also a consultant to and is participating in chelation drug research with Novartis. He is a consultant to Siemens Medical Solutions and a director of Cardiovascular Imaging Solutions. Dr Galanello has received speaker’s honoraria and research support from Apoptex and Novartis. Ms Smith is a consultant to and is participating in chelation drug research with Novartis. Dr Walker has received research support from Novartis and speaker’s honoraria from Apoptex. Dr Westwood has received speaker’s honoraria from Apoptex. Drs Assomull and Nair are supported by the British Heart Foundation. The remaining authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

Thalassemia is the most common single gene disorder worldwide. Lifelong transfusion dependence causes damaging tissue iron accumulation. Excess iron can be removed with chelation, and deferoxamine has been used since the late 1960s, but this is difficult, typically requiring a subcutaneous injection schedule for 8 hours for 5 nights per week to achieve iron balance. Deferoxamine improves life expectancy, but in recent cohorts half of the patients still die before the age of 35 years, with 70% of patients dying of heart failure. Addressing this premature cardiac mortality was difficult until 2001, when a new cardiac iron measurement technique based on magnetic relaxation of myocardial T2* was reported. Myocardial T2* is normally 40 ms, with a lower limit of normal of 20 ms. Increased iron causes faster relaxation that shortens the T2* value to <20 ms, with values <10 ms indicating severe myocardial siderosis, which is strongly associated with heart failure. Research is now focused on the manner in which to treat patients effectively once myocardial siderosis is identified. Deferiprone is a small neutral molecule that has good access to myocyte iron and is known to be effective in removing cardiac iron as monotherapy. In the present study, deferiprone was added to deferoxamine in a randomized placebo-controlled trial. Myocardial iron improved significantly more with the combination than with deferoxamine alone. Therefore, combination therapy is superior to deferoxamine monotherapy in removing myocardial iron, and it should be considered for patients with myocardial siderosis and may be valuable in more severe myocardial siderosis associated with heart failure.
A Randomized, Placebo-Controlled, Double-Blind Trial of the Effect of Combined Therapy With Deferoxamine and Deferiprone on Myocardial Iron in Thalassemia Major Using Cardiovascular Magnetic Resonance

_Circulation_. 2007;115:1876-1884; originally published online March 19, 2007; doi: 10.1161/CIRCULATIONAHA.106.648790
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/115/14/1876

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/