Combined therapy with deferiprone and desferrioxamine in thalassemia major

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Background and Objectives. Effective and convenient iron chelation remains one of the main targets of clinical management of thalassemia major. The combined treatment with desferrioxamine and deferiprone could have an increased chelation efficacy and sometimes allow drug doses and toxicity to be reduced and the number of days of desferrioxamine infusion to be decreased, improving compliance and quality of life.

Design and Methods. We used combined therapy with desferrioxamine and deferiprone to treat 79 patients with severe iron overload (serum ferritin higher than 3000 ng/mL) who had low compliance with subcutaneous desferrioxamine.

Results. Total therapy exposure was 201 patient-years. Three patients developed agranulocytosis and seven mild neutropenia. Other adverse effects were nausea, vomiting, abdominal pain, increased concentrations of liver transaminases and joint pain. The efficacy of combined therapy was evaluated in 64 patients treated for at least 12 months. Ferritin decreased from 5243±2345 to 3439±2446 ng/mL, $p<0.001$). Mean urinary iron excretion during combined therapy was double that with desferrioxamine or deferiprone monotherapy. In 20 patients receiving heart therapy at baseline, left ventricular ejection fraction increased from 48.6±9% to 57±6% ($p=0.0001$) over 12 to 57 months, without modifying the cardiac treatment.

Interpretation and Conclusions. Continuous deferiprone treatment with intermittent administration of subcutaneous desferrioxamine is a practical and effective procedure to decrease severe iron overload in patients with thalassemia major. This study also shows that the combined therapy is associated with an improvement in heart function.

Key words: thalassemia, iron overload, combined therapy, desferrioxamine, deferiprone.

Haematologica 2005; 90:1309-1314

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Homozygous β^0-thalassemia usually becomes symptomatic as a severe, progressive anemia during the second six months of life. Regular blood transfusions are necessary in these patients to prevent the serious consequences and cardiac decompensation caused by the marked anemia. The recommended transfusion scheme leads to the transfusion of 100-200 mL/kg/year of pure red cells, which is equivalent to 0.3-0.6 mg of iron per kg body weight per day. The lack of a natural mechanism to eliminate the excessive iron causes its accumulation in organs. When the iron-binding capacity of defensive proteins such as transferrin and ferritin is exceeded, iron can generate harmful free radicals and cause tissue and multiorgan damage.[1] Prevention of iron toxicity, and consequently of iron-induced morbidity and mortality, is the main objective of iron chelation therapy in transfusion-dependent patients. Chelation therapy with desferrioxamine, the most widely used iron chelator, has been associated with a significant decrease in the rate of iron-induced complications and with a dramatic increase in survival of transfusion-dependent thalassemia patients.[2-4] However, despite the availability of desferrioxamine in most developed countries, one third of the patients develop an excessive body iron load because of the difficulties in complying with the self-administered subcutaneous infusions 5-6 days a week.[4] Therefore, it is not surprising that a proportion of chelated patients continue to develop iron-induced complications and/or die from iron-induced cardiac disease.[4-6]

The development of a safe and effective oral chelator has been the goal for many years. Deferiprone, first synthesized in 1982, is a bidentate chelator which forms a 3:1 chelator/iron complex excreted mainly in the urine.[7-8] The most serious deferiprone-related adverse event is agranulocytosis, which occurs in 0.6/100 patients

for each year.[9] Other common side effects are transient gastrointestinal symptoms, arthropathy and a transient rise in serum transaminases.[9-10]

The combined use of both chelators has been suggested to increase iron chelation effectiveness. Wonke *et al*. first reported that combined therapy of daily deferiprone with subcutaneous desferrioxamine administered 2-6 days per week resulted in a decrease in serum ferritin concentrations in five patients treated for 7-15 months.[11] A statistically significant reduction of ferritin serum values associated with a higher mean urinary iron excretion were observed in other studies.[12-14] The present study aims at evaluating the efficacy, with special attention to effects on heart function, and safety of long-term combination therapy in a large group of transfusion-dependent patients with severe iron overload. To our knowledge, this is the largest study on this combination therapy in terms of both number of patients and duration of follow-up.

Design and Methods

Patients

Transfusion-dependent thalassemia patients over 10 years of age with severe iron overload (serum ferritin higher than 3000 ng/mL) were considered for combined chelation therapy. All patients but one had been prescribed subcutaneous infusions of desferrioxamine at doses of 40-50 mg/kg 5-6 days a week, but showed poor compliance (less than 50% of the prescribed dose) and refused intensive intravenous chelation despite extensive advice on the importance of chelation. One patient was being treated with high doses of desferrioxamine (60 mg/kg/day) via a Port-a-Cath. Criteria for exclusion from the study were severe liver and kidney disease, pregnancy or lactation, previous serious adverse events with desferrioxamine or deferiprone, a history of neutropenia, or positivity for human immunodeficiency virus. Seventy-nine patients (44 females and 35 males) were enrolled in the study between March 2000 and November 2003. All patients were homozygotes for β^0-thalassemia and were receiving regular packed red cell transfusions every 2 to 3 weeks. The mean age at enrollment was 23±5 years (range 12-35) and eight patients were under 18 years. Sixty-four patients (81%) were positive for hepatitis C virus (HCV).

Methods

A complete blood count and white cell differential were obtained every 7-10 days using an electronic cell counter (Gene S or LH700-Beckman Coulter). If the neutrophil count fell below 1.5×10^9/L, therapy with deferiprone was temporarily interrupted and the complete blood count was repeated within 24 hours. If neutropenia was confirmed, deferiprone was discontinued. Serum ferritin was measured on venous blood samples every 2 months using an automated immunoassay system (IMMULITE 2000®). Urinary iron excretion induced by monotherapy with desferrioxamine or deferiprone or by the combination of both chelators was measured by atomic absorption spectrophotometry on a 24-hour urine specimen prior to the initiation of the trial and every 2 to 3 weeks for the first 6 months of the study. Atomic absorption spectrophotometry was also used to measure zinc levels every 3 months, while alanine aminotransferase (ALT) levels were determined monthly with standard methods. Heart function was monitored once or twice a year by echocardiography, measuring the left ventricular ejection fraction. Adverse events and compliance were checked at each transfusion visit.

Study design

The study was designed according to the standards of Good Clinical Practice and it was approved by the Hospital Ethics Committee. Informed consent was obtained from all study participants.

Treatment

Chelation treatment was tailored to the needs of the individual patients. Deferiprone was prescribed daily, at a dose of 70-80 mg/kg in three divided oral administrations. Desferrioxamine was given subcutaneously at 40±10 mg/kg/day over 10-24 hours/day, 2 to 6 days/week according to the ferritin level: 6 days per week when the ferritin was >5000 ng/mL, 4-5 days/week when the level was 3000-5000 ng/mL. As the ferritin value decreased, the prescription was modified: desferrioxamine was suggested for 3-4 days/week when the ferritin level was 2000-3000 ng/mL, or 2-3 days/week for values <2000 ng/mL.

The patient who had been on treatment with high doses of desferrioxamine via a Port-a-Cath had the dose of desferrioxamine reduced to a mean of 27 mg/kg/day because of glycosuria and proteinuria associated with elevated doses of this chelator. A simultaneous regimen was suggested, but almost all the patients preferred to perform the desferrioxamine infusions at night and take deferiprone during the day.

Statistical methods

A paired t-test was performed to examine the changes in serum ferritin and ALT levels between baseline and last results, and to compare left ventricle ejection fraction before and after combination therapy. Urinary iron excretion during monotherapy with desferrioxamine or deferiprone was compared to that during the combined chelation regimen by analysis of variance (ANOVA). The χ^2 test was used to compare the

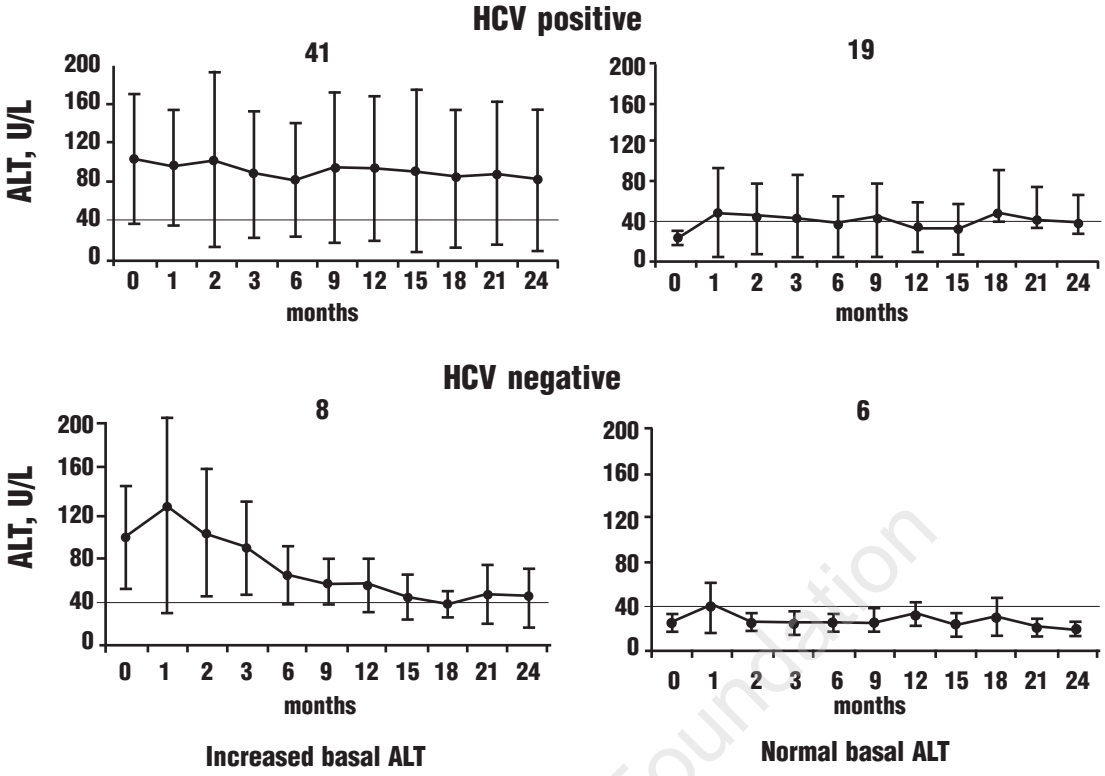

Figure 1. ALT values according to HCV status and basal level. The numbers on top of each figure indicate the number of patients.

incidence of agranulocytosis and neutropenia between patients on monotherapy with deferiprone to those on combination therapy. The ferritin levels were examined in all patients treated with combination therapy for at least one year and ALT in those treated for at least 3 weeks. A type 1 error (α) of 0.05 was used to assess statistical significance in all tests.

Results

Seventy-nine patients were treated with combination therapy: 64 for at least 1 year and 45 for at least 2 years (24-56 months). Total drug exposure was 201 patient years, with an average of 2.5±1.4 years per patient.

Adverse events

Twenty-five patients (32%) experienced nausea, most frequently during the first weeks of combination treatment. Nausea was associated with vomiting or abdominal pain in 10% and 9% of the patients, respectively. One patient discontinued therapy after 10 months because of recurrent vomiting. In all the other patients, gastrointestinal symptoms resolved without discontinuation of the treatments. Some patients reported improvement of gastrointestinal symptoms when deferiprone was taken after meals instead of fasting. In other patients, the dose of deferiprone was temporarily reduced and then gradually increased without recurrence of the gastrointestinal symptoms.

Out of 64 patients tested, 26 (40%) had low serum zinc values. Zinc values normalized with zinc sulfate supplementation (200 mg twice a week). Glucose metabolism was evaluated in 32 patients receiving the combination therapy: 5 had diabetes and 11 impaired glucose tolerance. There was no difference in the incidence of zinc deficiency between patients with diabetes or impaired glucose tolerance and patients with normal glucose tolerance.

ALT levels were evaluated in 74 patients (60-HCV positive and 14 HCV-negative) in an intent-to-treat analysis. Overall, there was a slight but significant decrease of ALT values from those recorded at baseline (74.7±63.2 U/L) to those at the last determination (59±62 U/L; p=0.01). A detailed analysis of ALT values according to HCV status and basal level is reported in Figure 1. Forty-one HCV-positive patients with increased ALT at baseline (76±66 U/L) showed a not significant decrease in ALT levels (67±65 U/L, p=0.20). In 19 HCV-positive patients with normal ALT values at baseline, there was a mild and transient increase in the first 3 months of treatment. No significant changes were observed in HCV-negative patients with normal baseline levels, but a significant decline was observed in

Table 1. Adverse events in patients with thalassemia major during combination therapy with deferiprone and desferrioxamine.

Adverse events	*% of patients*
Agranulocytosis	3.8
Neutropenia	8.8
Increased ALT*	18.0
Nausea	32.0
Vomiting	10.0
Abdominal pain	9.0
Zinc reduction	40.0
Joint symptoms	2.5

**ALT values greater than twice the baseline within the first 6 months of treatment.*

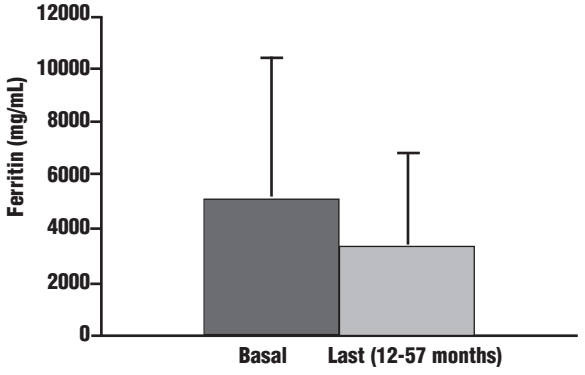

Figure 2. Mean ferritin levels in patients on combination therapy.

mean value in the eight HCV-negative patients with elevated ALT values at baseline (from 97±46 U/L to 43±26 U/L; p=0.005). Two patients (2.5%) developed joint problems. One patient with serum ferritin above 10,000 ng/mL developed bilateral painful knee swelling and pain in the hand joints after a few weeks of combined therapy. Symptoms and signs disappeared upon increasing the days of desferrioxamine infusion from 2 to 7 per week. The second patient had repeated episodes of knee pain and synovitis when the ferritin level was 2300 ng/mL. These symptoms persisted despite interruption of deferiprone treatment.

Three patients (3.8%), all female, developed agranulocytosis in the first year of combined treatment (occurrence rate 1.5/100 patients/year). Seven additional patients (four females and three males) developed mild neutropenia (occurrence rate 3.5/100 patients/year) between 36-148 weeks from beginning the combined therapy. All the patients who developed agranulocytosis or mild neutropenia were HCV-positive and had not undergone splenectomy. Agranulocytosis resolved within 4-14 days after granulocyte colony-stimulating factor administration, without any sign of infection. One male patient who experienced mild neutropenia with signs of hypersplenism (enhanced blood consumption and low platelet count) was rechallenged after splenectomy, without recurrence of neutropenia during 28 months of combination therapy. The adverse events observed during combined therapy are summarized in Table 1.

Withdrawals

Thirty-four patients dropped out of the study after 1-38 months of treatment. Thirteen patients (13%) withdrew because of adverse events, including agranulocytosis (three patients), neutropenia (seven patients), gastrointestinal problems (one patient), increased levels of ALT (one patient) and arthropathy (one patient). In addition, eight patients withdrew because of a medical decision: programmed pregnancy in one case, treatment with drugs known to produce neutropenia in three patients, tendency to low neutrophil count or poor compliance with the prescribed therapy in four patients. Finally, 13 patients withdrew voluntarily, because of difficulties in performing weekly monitoring of their neutrophil count or for personal reasons. Five restarted combination therapy some months after the withdrawal.

Efficacy

The efficacy of combined therapy was evaluated in 64 patients treated for at least 12 months (range 12–57 months). Ferritin levels decreased from 5243±2345 ng/mL to 3439±2446 ng/ml, p<0.001) during the combined treatment (Figure 2).

The urinary iron excretion induced by monotherapy with desferrioxamine or deferiprone, or by combination of both chelators was determined in 45 patients, for a total of 749 determinations. The mean urinary excretion during combined therapy (0.84±0.48 mg/kg) was double that during desferrioxamine monotherapy (0.42±0.23 mg/kg) or deferiprone monotherapy (0.44±0.37 mg/kg) (p<0.0001). The combined use of oral deferiprone and intravenous desferrioxamine via a Port-a-Cath in one patient induced an average (mean of 19 24-hour urine determinations) urinary iron excretion of 1.71 mg/kg/day and was associated with a decrease of the serum ferritin from 6570 to 1520 ng/mL over a 27-month period.

Three patients had two sequential liver iron evaluations by SQUID (Centro Microcitemia, University of Turin, Italy), which showed a decrease in liver iron concentration from 12.9±7.5 mg/g dry weight to 7.0±3.6 mg/g dry weight, after 12-24 months of combined therapy.

Heart function

The effect of combined therapy on cardiac function was evaluated by determining the left ventricular ejection fraction in 44 patients on treatment for at least 1

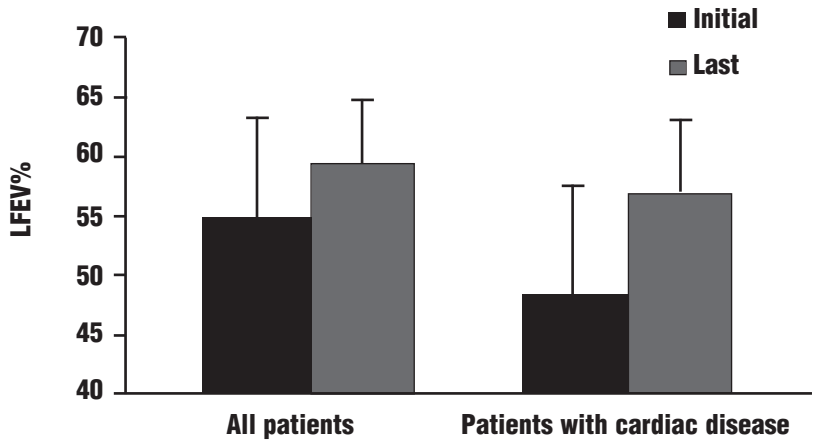

Figure 3. Left ventricular ejection fraction before and after combined iron chelation.

year and who had an echocardiogram performed within 6 months prior to initiation of the study. Overall, the combined therapy was associated with a change in left ventricular ejection fraction from 54.7±8.6% at baseline to 59.6±5.1% ($p \leq 0.0001$). Twenty out of 44 patients were receiving heart therapy at the time of initiation of combined chelation. In these patients, the ejection fraction increased from 48.6±9% to 57±6% ($p=0.0001$) over 12 to 57 months (mean 31±11 months) of study, without the cardiac treatment having been modified (Figure 3).

Discussion

Recently, a number of *in vitro* and *in vivo* studies have suggested that the simultaneous use of desferrioxamine and deferiprone is associated with an additive or even synergistic iron excretion in patients with thalassemia major, and that combined therapy could decrease iron overload in patients who had previously been unable to achieve a satisfactory response to deferiprone or desferrioxamine alone.[12-17] It has been suggested that deferiprone, with a low molecular weight, acts as an intracellular chelating shuttle and the large and hydrophilic molecule of desferrioxamine serves as an extracellular iron sink.[18] In our study we evaluated the safety and efficacy of the combined treatment in a large group of patients for an extended period of time (up to 57 months). Transient gastrointestinal symptoms were the most frequent side effects, as observed during monotherapy with deferiprone.[19] The reduction in ALT levels observed in HCV-negative patients with high basal ALT may have been due to a more efficient chelation and consequent reduction of liver cytolysis.[20] Joint problems during combined therapy appear to occur less frequently than with the use of deferiprone alone, suggesting a possible decrease in the intra-articular labile iron pool.[19,21-23] Our data did not confirm that zinc excretion is particularly increased in patients with diabetes or impaired glucose tolerance, as reported in a study investigating the use of deferiprone alone.[24] The incidence of agranulocytosis, which is the most serious complication during chelation therapy with deferiprone, was higher in our study than in a multicenter study involving 187 patients on long-term treatment with deferiprone alone (1.8% vs 0.5%, $p=0.04$).[19] No difference was observed in the frequency of milder neutropenia (8.8% vs 4.8%, $p=0.19$). Studies with larger numbers of patients are required to clarify whether or not combination therapy is associated with a higher incidence of agranulocytosis than is monotherapy with deferiprone. Agranulocytosis and neutropenia were reversible once deferiprone was discontinued. Data from our study confirm a relationship between spleen status and female sex, as in idiosyncratic agranulocytosis caused by other drugs.[25] Careful monitoring of blood count, a critical aspect in the follow-up of patients treated with only deferiprone, is also essential in patients receiving combination therapy.

The resolution of glucose and protein loss that had been associated with desferrioxamine in the patient previously treated with high doses of this drug indicates that combined use of lower doses of the two chelators can limit dose-dependent toxic effects of these chelators. Using magnetic resonance imaging, Olivieri *et al.*[26] reported improvement in T2 relaxation time in the heart, believed to be associated with decreased iron content, in thalassemic patients treated with deferiprone but not in patients treated with desferrioxamine. In more recent studies, significantly higher magnetic resonance imaging values, presumed to reflect lower cardiac iron and higher mean ejection fraction, were reported in patients treated long-term with deferiprone as compared to patients treated with desferrioxamine.[27] In a retrospective study evaluating survival and cardiac disease in 129 patients treated for at least 4 years with desferrioxamine or deferiprone, deferiprone was associated with a greater cardioprotective effect than was desferrioxamine.[28] Our study

shows an improvement in contractile heart function during combined therapy in patients who had previously had a worsening ejection fraction during therapy with desferrioxamine alone. Until now, continuous intravenous desferrioxamine was the only treatment thought to be effective in improving cardiac function in thalassemic patients with heart disease. However, continuous parenteral chelation is cumbersome, not well accepted by patients and increases the risk of infection and thrombosis.[29-30] Long-term prospective trials are also needed to compare the ability of desferrioxamine alone to that of combined therapy in resolving iron-induced heart damage.

In conclusion, combined therapy results in better compliance since patients need desferrioxamine infusions fewer days per week. The combined therapy is effective in inducing negative iron balance in all patients and in reducing body iron load.

Finally, this study also showed that combined therapy was associated with an improvement in cardiac function.

RO and RG designed the study and wrote the manuscript. All authors contributed to the analysis and interpretation of data and gave final approval of the revised version.

This study was supported by grants from Regione Sardegna (L.R.11,1998). The authors wish to thank Prof. Antonio Cao for his continuous advice and Nora Rayners and Franca Rosa Demartis for editorial assistance.

RG received research support from Apotex and Novartis and speakers' honoraria from Apotex.

Manuscript received February 12, 2005. Accepted August 9, 2005.

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