Role of deferiprone in chelation therapy for transfusional iron overload

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Introduction

Before 1987, iron chelation therapy for patients with thalassemia major and other refractory anemias requiring regular transfusions depended almost entirely on one drug, deferoxamine. The drug has dramatically increased survival in patients with thalassemia major in countries where it is readily available.1,2 Although many other compounds had been tried as iron-chelating agents in experiments with animals and humans, none had proved sufficiently effective and free of side effects to warrant further development and widespread clinical use. Throughout the world, however, most patients with thalassemia major still do not receive adequate chelation with deferoxamine because of its high cost and the lack of compliance with the arduous regime of self-administered subcutaneous infusions at least 5 days a week.3,4 In Malaysia, for instance, deferoxamine is available to only a few of the 5000 patients with thalassemia major.5 Toxic or allergic side effects also develop in a minority of patients. Death from iron overload, usually from cardiac failure, continues to occur in patients in poor countries, where deferoxamine is unaffordable, and in more developed countries, where failure of compliance in at least one third of the patients enables excessive iron accumulation.6,7

The orally active iron chelator deferiprone (1,2 dimethyl-3-hydroxypyrid-4-1, also known as L1, CP20, Ferriprox, or Kelfer) has emerged from a long, extensive search for new therapies for iron overload. Deferiprone is a synthetic compound first designed in Professor R.C. Hider’s laboratories at the University of Essex.8 In 1987, 2 papers were published showing that deferiprone could achieve effective short-term iron chelation.9,10 Iron excretion levels in the urine, in response to deferiprone in patients with heavy iron overload and with myelodysplasia and thalassemia major, were found to be similar to those obtained with therapeutic doses of deferoxamine. In those studies and a subsequent study in India,11 iron excretion was found to be related to the dose of deferiprone within the range of 25 to 100 mg/kg body weight per day and to the iron load of the patient.

Several groups subsequently confirmed in longer term studies that deferiprone was an orally active iron chelator,12-15 and substantial data concerning the efficacy and toxicity of deferiprone have accumulated over 15 years. The results of these trials and of animal and cell culture studies have been extensively reviewed.16-18 Studies have shown that treatment with deferiprone reduces serum ferritin levels and concentrations in some but not all patients.19,21

Pharmacokinetics

Deferiprone is rapidly absorbed and has a peak plasma level usually within 45 to 60 minutes of ingestion.27-29 Food reduces the rate of absorption but not the amount of drug absorbed.27 Deferiprone forms a 3:1 chelator/iron complex that is excreted together with free drug in the urine. More than 90% of the free drug is eliminated from plasma in most patients within 5 to 6 hours of ingestion. In 2 studies, the mean elimination half-life was 160 minutes and 91 minutes, with a range of 53 to 166 minutes in the latter study.27,29 Deferiprone is inactivated (more than 85%) by glucuronidation; the glucuronide derivative is also excreted in urine. The area under the curve for the free drug in plasma varies considerably among patients and may explain some of the individual variation in response.28 In one study, the long-term administration of deferiprone was associated with a decrease in serum deferiprone trough levels, suggesting that the drug induced its own metabolism or that absorption decreased over time.27 Findings from a subsequent pharmacokinetic study, however, revealed no evidence of a change in absorption, glucuronidation, or clearance with duration or administration.29 Approximately 4% of a single oral
dose is excreted in urine bound to iron in patients with heavy iron load.

Iron excretion

Table 1 shows the results of urine iron excretion in response to deferiprone at doses up to 100 mg/kg per day divided into 2, 3, or 4 subdoses. A study in a large group of previously untreated Indian patients showed that excretion increased substantially with each increment of dose between 25 and 100 mg/kg. Longer term studies have shown no diminution of urine excretion with time in patients in whom iron burden (based on serial serum ferritin levels) is unchanged.

Combined data suggest that urinary iron excretion in response to deferiprone 75 mg/kg is comparable to that with deferoxamine infused subcutaneously over 8 to 12 hours at a dose of 40 to 50 mg/kg. Although one study reported fecal iron excretion with deferiprone ingestion to be 15% to 23% of total excretion, other studies, either published or in abstract form, showed no increase or only negligible increase in fecal iron excretion and no detectable deferiprone in feces. Metabolic balance studies in 13 patients showed that the level of total iron excretion in response to deferiprone (75 mg/kg) was 62% (range, 24%-129%) of that achieved with deferoxamine (60 mg/kg over 8 hours subcutaneously). Although all patients were in net negative balance when treated with deferoxamine, only 6 of 13 were in net negative balance as a result of taking deferiprone. The difference was attributed to fecal excretion of iron in response to deferoxamine. More recent studies from the same group showed that 100 mg/kg deferiprone placed 4 of 6 patients in negative balance compared with 2 of 6 administered the normal therapeutic dose (40 mg/kg) of deferoxamine. Urine iron excretion in response to deferiprone therapy has not been found to be consistently affected by the coadministration of vitamin C or food or by giving the daily dose in 2, 3, or 4 divided doses, though additional studies addressing these issues would be helpful.

Most clinical trials have used a total daily dose of 75 mg/kg divided into 3 subdoses.

Effectiveness

The effectiveness of deferiprone has been assessed by iron excretion, serum ferritin, serum nontransferrin-bound iron, liver iron measured chemically, by superconducting quantum-interference device (SQUID), magnetic resonance imaging (MRI), and, most recently, MRI of cardiac iron. Most of the data are based on the treatment of patients with thalassemia major. Although limited information on other, less severe iron overload states, such as thalassemia intermedia, is also available, the following analysis is restricted to studies of patients receiving regular transfusions.

Serum ferritin

Single or sporadic measurement of serum ferritin alone is a poor indicator of iron burden in the transfusion-dependent patient, particularly if the patient also has hepatitis C infection. Nevertheless, serial studies in individual patients usually give an indication of whether the iron burden in that patient is static, increasing, or decreasing, and the changes in serum ferritin level during chelation therapy generally parallel the changes in liver iron concentration. In addition, the maintenance of serum ferritin levels below 2500 μg/L is associated with improved survival free of cardiac disease in patients with thalassemia. Further studies are needed to clarify the prognostic value of serum ferritin levels in patients treated with deferiprone.

As shown in Table 2, most studies have demonstrated stable or declining mean serum ferritin levels during long-term therapy with deferiprone. A decrease in serum ferritin is most likely in patients with the highest initial serum ferritin values. In the largest study of deferiprone, involving 532 participants, patients beginning with serum ferritin levels higher than 4000 μg/L showed significant and persistent decreases in serum ferritin, whereas patients beginning with serum ferritin levels higher than 2000 μg/L showed no significant change. In a separate study, deferiprone doses from 83 to 100 mg/kg per day produced a significant decrease in ferritin level over 6 months without new side effects in 9 patients considered to be inadequately chelated at the daily dose of 75 mg/kg.

Liver iron

Measurement of liver iron levels has been described as the criterion for the assessment of the efficacy of iron chelation therapy. In a study of 59 patients with thalassemia major treated with deferoxamine, all deaths from cardiac disease occurred in patients with liver iron concentrations greater than 80 μmol/g wet weight, the equivalent of 15 mg/g dry weight. This value has been incorporated into criteria for effective chelation therapy.

Differences in methods used to measure liver iron concentrations and units used to express findings complicate the comparison of studies for serial iron measurements (Table 3). The Toronto group initially reported their experience with deferiprone given to 21 patients for a mean of 3.1 ± 0.3 years. Assessing liver iron concentration by SQUID or biochemical measurement, the investigators found that all 10 patients beginning deferiprone therapy at levels higher than 80 μmol/g wet weight had declines in liver iron concentration during treatment with deferiprone; in 8 of the 10 patients, the liver iron level fell below this threshold. In the remaining 11 patients, the liver iron level was maintained below 80 μmol/g wet weight. In a subsequent report, the Toronto group found that after treatment with deferiprone given for 4.6 ± 0.3 years, mean liver iron concentration decreased from 88.7 ± 12.1 μmol/g wet weight at baseline to 65.5 ± 7.9 μmol/g wet weight at the last reported time point (P = .07). The last liver iron concentration was greater than 80 μmol/g wet weight in 7 of 18 (39%) patients. Highest overall liver iron concentrations in patients receiving long-term therapy with 75 mg/kg deferiprone were encountered in the study by Hoffbrand et al. Ten of 17 (58%) patients treated for 2 to 4 years had levels greater than 15 mg/g dry weight. This study, however, enrolled only patients for whom...
chelation therapy with deferoxamine had previously failed because of lack of compliance or toxicity. Results were from single liver iron determinations. Because serial biopsies were not performed, the initial liver iron concentrations remain unknown and the trend in liver iron cannot be assessed.

Unfortunately, there are few published prospective, randomized trials comparing the effects of deferoxamine and deferiprone on liver iron concentration. Among 20 patients who underwent liver biopsy in a larger randomized study by Maggio et al., the liver iron concentration was 3.36 mg/g dry weight at baseline and 2.34 mg/g dry weight after a mean duration of treatment with deferiprone of 30 months. Among 15 patients treated with deferoxamine for a mean duration of 34 months, the values were 3.52 and 3.17 mg/g dry weight. In contrast, in a study reported in abstract form in 1997, Olivieri and Brittenham reported significant increases in liver iron levels in 19 patients treated with deferiprone for a mean duration of 33 months (8.9-13.7 mg/g dry weight) and no significant change in 18 patients treated with deferoxamine (6.9-7.9 mg/g dry weight).

Cardiac iron

The cardioprotective effect of iron chelation therapy is a critical feature for evaluating efficacy because iron-induced cardiac disease is the leading cause of death in patients with thalassemia major. No noninvasive method of assessing cardiac iron has been correlated directly with tissue iron measurements. Using MRI, Olivieri et al.44 reported improvement in T2 relaxation time, presumed to reflect lower cardiac iron concentrations in patients treated long term with deferiprone than in patients treated with deferoxamine.47 The deferiprone-treated group had significantly longer T2* values (P = .02) and higher mean left ventricular ejection fractions (P = .004) than the deferoxamine-treated group. The prevalence of short T2* values less than 20 milliseconds was significantly lower in the deferiprone group (27% vs 67%; P = .025). The deferiprone group, on the other hand, had longer T2* values. The authors concluded that conventional treatment with deferoxamine did not prevent excess cardiac iron accumulation in two thirds of their patients with thalassemia major and that oral deferiprone was more effective at removing myocardial iron overload.45 The authors found the T2*, but not serum ferritin or liver iron concentration, to be predictive of ventricular dysfunction, and they consider that T2* reflects cardiac iron.46 In a subsequent study, this group has shown significantly shorter T2* values, presumed to reflect lower cardiac iron concentrations in patients treated long term with deferiprone than in patients treated with deferoxamine.47 The deferiprone-treated group had significantly longer T2* values (P = .02) and higher mean left ventricular ejection fractions (P = .004) than the deferoxamine-treated group. The prevalence of short T2* values less than 20 milliseconds was significantly lower in the deferiprone group (27% vs 67%; P = .025). The deferiprone group, on the other hand, had longer T2* values. The authors concluded that conventional treatment with deferoxamine did not prevent excess cardiac iron accumulation in two thirds of their patients with thalassemia major and that oral deferiprone was more effective at removing cardiac iron. These data should be interpreted with caution. First, T2* measurements have not been correlated directly with cardiac iron measured biochemically. Second, the study involved a single measurement of cardiac T2*, and no follow-up information is available regarding trends in this measurement. Third, despite efforts to match the 2 groups, the possibility of a significant difference at the outset cannot be excluded. Fourth, though serum ferritin and hepatic iron concentrations had previously been found to predict myocardial disease and cardiac death,42,48 this study showed no correlation between these variables and cardiac siderosis. Fifth, the cardioprotective effect of deferoxamine in compliant patients is strongly supported by the sharp decrease in cardiac deaths in the thalassemic population with the introduction of subcutaneous deferoxamine therapy1,2,7 and the ability of vigorous

### Table 2. Effect of deferiprone on serum ferritin levels

<table>
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<tr>
<th>Study</th>
<th>No. patients</th>
<th>Length of study, mo</th>
<th>Dose mg/kg</th>
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*A few patients in this study may overlap with patients included in Al-Refaie et al13 and Olivieri et al19.

†NG indicates not given; NS, not significant.

### Table 3. Effect of oral deferiprone therapy on liver iron concentration in patients with thalassemia major

<table>
<thead>
<tr>
<th>Study</th>
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<th>No. patients</th>
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<th>Final</th>
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<td>3.4</td>
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*Some patients underwent initial liver biopsy by SQUID, subsequently by liver biopsy, and vice versa.

†μmol/g wet weight.
deferiprone treatment to benefit most patients with established siderotic cardiomyopathy.49

Death caused by cardiac disease may occur in patients treated with deferiprone. Of 51 patients (deferiprone “failures”) treated by deferiprone, 4 died of cardiac-related causes, and the authors concluded that deferiprone alone, in the face of pre-existing severe myocardial iron overload and continuing need for blood transfusions, cannot reliably protect patients from death from iron overload.33 Similarly, in the study of deferiprone treatment in 532 patients with thalassemia over a 3-year period, 9 patients died of heart failure.40

Continuous intravenous deferoxamine is the recommended treatment for patients with advanced cardiomyopathy. Because this treatment is unable to help some patients,49,50 prospective trials are needed to compare the ability of deferiprone alone with combined therapy with deferoxamine and deferiprone to reverse such damage. Long-term prospective trials comparing the ability of chelation therapy with deferiprone or deferiprone to prevent heart disease are also needed. In a prospective, randomized trial, 71 patients treated with deferiprone and 73 patients treated with deferiprone showed similar and significant improvement in cardiac nuclear magnetic resonance (NMR) signal.21

Combined therapy

Formal balance studies have shown additive or synergistic iron excretion in patients treated simultaneously with deferoxamine and deferiprone.35 The basis for this effect is that deferiprone easily enters cells51-53 and is subsequently able to transfer the intracellularly chelated iron to the stronger iron chelator, deferoxamine, in plasma.35,54,55 Thus, combined therapy may achieve levels of iron excretion that cannot be achieved by either drug alone without loss of compliance or potential toxicity. Combined therapy reduces serum ferritin levels in patients who had previously been unable to achieve satisfactory response to deferoxamine or deferiprone alone (Table 4). This approach to chelation therapy may be an attractive option for those patients who are unable to comply with deferiprone infusions on more than a few days a week and who have inadequate reduction of iron stores with deferiprone alone. To date, this combination therapy has shown no unanticipated side effects when given for periods of a year or more.5,56-58

Sequential (alternating) therapy

A pilot study of sequential therapy was carried out by Aydinok et al.61 Seven children, noncompliant with deferoxamine (serum ferritin range, 2190-17 220 μg/L; mean, 5536 μg/L), were treated with 75 mg/kg oral deferiprone for 4 days followed by 40 to 50 mg/kg subcutaneous deferoxamine for 2 days each week. In addition, they received 40 to 50 mg/kg intravenous deferoxamine every 3 to 4 weeks at the time of transfusion. Compliance with this sequential therapy was excellent. In 6 months the result was a significant (P = .03) decrease in mean hepatic iron level from 26.5 to 21.1 mg/g and a nonsignificant decrease in serum ferritin level from a mean of 5536 to 3778 μg/L. The place of sequential therapy requires long-term prospective trials in larger numbers of patients.

Compliance

An assessment of the effectiveness of iron chelators on the basis of iron excretion must take into account compliance with the prescribed regimen. Most patients treated with deferoxamine do not infuse the chelator 7 days a week, and many do not infuse the chelator for the usual prescribed minimum of 5 days a week.7 Compliance with orally administered deferiprone is likely to be substantially better than with parenterally administered deferoxamine (for a review, see Barman Balfour and Foster18). In one clinical trial, the mean compliance rate assessed with an electronic recording system during 1 to 4.8 years of therapy with deferiprone was 85%.39 Thus, compliance is a critical factor in assessing iron excretion in response to deferoxamine or deferiprone as a predictor of long-term reduction of iron levels.

Adverse effects

Early clinical studies identified agranulocytosis, arthralgia, nausea and other gastrointestinal symptoms, and fluctuating liver enzymes as side effects of deferiprone therapy. Subsequent studies have confirmed these findings and identified their incidence. Zinc deficiency has subsequently been observed in a few patients.

Agranulocytosis

Agranulocytosis has generally been considered the most serious side effect of deferiprone. In a study designed specifically to establish the frequency of agranulocytosis (neutrophil count, 0.0-0.5 × 10⁹/L) and requiring strict monitoring with weekly blood counts, confirmation within 24 hours of all neutrophil counts below 1.5 × 10⁹/L, and discontinuation of the drug if confirmed, agranulocytosis developed in 1 of 187 (0.5%) patients during 1 year of treatment, with an incidence of 0.6 per 100 patient-years.39 Milder neutropenia (absolute neutrophil count, 0.5-1.5 × 10⁹/L) developed in 9 (4.8%) patients. No additional cases of agranulocytosis

<table>
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<th>Study</th>
<th>No.</th>
<th>Duration, mo</th>
<th>DFP dose, mg/kg/d</th>
<th>DFO dose</th>
<th>DFO, days per week</th>
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*One additional patient withdrew after 1 month because of gastrointestinal symptoms.
†Significant improvement in ventricular dimensions and function and increase in myocardial T2 relaxation time.
‡Agranulocytosis in 2 patients reversed.
§Agranulocytosis in 2 patients reversed.
DFP indicates deferoxamine; DFP, deferiprone; UIE, urine iron excretion.
and 7 new cases of mild neutropenia occurred during the next 3 years of treatment in this study, as reported in abstract form. In 532 patients with thalassemia treated for a total of 1154 patient-years, the incidences of agranulocytosis and neutropenia were 0.43 and 2.08 per 100 patient-years, respectively. Agranulocytosis and milder neutropenia have been reversible on discontinuation of the drug, though some patients required temporary treatment with granulocyte–colony-stimulating factor (G-CSF). Milder forms of neutropenia may be related to hypersplenism and intercurrent infections rather than to drug toxicity. The cause of agranulocytosis during therapy with deferiprone is uncertain. Studies in animals suggest a dose-dependent and a time-dependent effect for this class of chelators. Clinical findings in patients with thalassemia, however, seem to be more characteristic of an idiosyncratic response and, as with idiosyncratic agranulocytosis caused by other drugs—such as chlorpromazine and clozairil—more common in females. Careful monitoring of blood counts remains a critical component of therapy with deferiprone and may be especially important for patients receiving higher doses of the drug or combined therapy with deferiprone and deferoxamine. Agranulocytosis hasrecurred in many but not all patients. Therefore, the reintroduction of deferiprone after an initial episode of agranulocytosis is not recommended.

Hepatotoxicity

Most studies of deferiprone have found fluctuations in alanine aminotransferase (ALT) levels, particularly in the first months of treatment. The International Cooperative Group found at least one serum ALT level greater than twice the upper limit of normal in 50 of 84 patients during the first 6 months of therapy. Changes in liver enzymes were mild and transient among the 38 hepatitis C virus (HCV)–negative patients, and persistent elevation occurred in only one patient but returned to pretreatment levels when deferiprone treatment was discontinued. In the first year of the large prospective multicenter trial, mean ALT levels rose significantly at 3 and 6 months and in the intention-to-treat analysis at 9 months. At 12 months, however, ALT levels did not differ significantly from baseline values. Two patients discontinued therapy in the first year because of increased ALT levels. In an extension of the study to 4 years, the mean ALT level was 71 U/L at 48 months in comparison with 61 U/L at baseline (P = .02). Trend analysis of ALT levels after 4 years showed no change during therapy with deferiprone, irrespective of hepatitis C status. No additional patients withdrew from the study because of increased ALT levels in years 2 to 4.

In the study of Ceci et al., ALT levels did not change over time in the analysis of 151 patients who completed 3 years of treatment. Increases and decreases in ALT levels were common. Twelve patients interrupted therapy with deferiprone, and 4 or 5 patients discontinued therapy because of increased ALT levels. In contrast, Olivieri et al. reported a reduction in ALT levels in most patients receiving deferiprone. They attributed fluctuating ALT levels to deferiprone in one patient with antibodies to hepatitis C. There are no published reports of liver failure during therapy with deferiprone.

The issue of deferiprone-associated liver injury has been particularly contentious since the initial report of accelerated liver fibrosis in patients receiving deferiprone. Of 19 patients with thalassemia on long-term deferiprone treatment, 14 could be evaluated for progressive fibrosis based on serial liver biopsy findings. Five patients receiving deferiprone were considered to have progression of fibrosis compared with none in the retrospectively chosen group of 12 patients treated with deferoxamine. The authors estimated the mean time to progression of fibrosis to be 3.2 years. An accompanying editorial emphasized several differences between the patients receiving the 2 chelators. These included higher mean baseline hepatic iron concentration in the deferiprone group (81 μmol/g wet weight) than in the deferoxamine group (35 μmol/g wet weight) and higher median age of the deferiprone group (18.2 years) than the deferoxamine group (13.9 years). Four of 5 patients believed to have progression of fibrosis had antibodies to hepatitis C compared with only 2 of 9 patients without progression. Patients with positive test results for hepatitis C mRNA and liver iron levels greater than 7 mg/g dry weight have been found to have progression of hepatic fibrosis after bone marrow transplantation in the absence of chelation therapy or transfusion. On the other hand, in the absence of hepatitis C, only levels greater than 15 mg/g dry weight were associated with progressive fibrosis. Thus, the combination of hepatitis C infection and iron overload, even at modest levels, as in 4 of Olivieri’s patients, is likely to cause liver fibrosis without any additional factor.

Biopsy specimens with as few as 2 portal tracts were included in the analysis. A letter in response to these findings noted that when the same biopsy specimens were reviewed by another hepatopathologist in a masked manner but excluding specimens with insufficient numbers of portal tracts, no progression of liver fibrosis was found in the patients treated with deferiprone.

The description of increased rates of iron accumulation and hepatotoxicity in iron-loaded gerbils after treatment with dimethyl-3-hydroxypyrid-4-1 (CP94), a compound closely related to deferiprone, has been identified as evidence supportive of the hepatotoxicity and fibrogenic effect of deferiprone. However, CP94 (dimethyl-3-hydroxypyrid-4-1) and deferiprone (dimethyl-3-hydroxypyrid-4-1) are different in their biologic activity. Subsequent studies using deferiprone in iron-loaded gerbils and iron-loaded guinea pigs have shown no indications of increased hepatotoxicity or increase in fibrosis from deferiprone therapy.

The most comprehensive study of hepatic fibrosis has been performed by Wanless et al in 56 patients with repeat liver biopsy after a median of 3.5 years (mean, 3.1 years) of deferiprone therapy. Of 58 patients in the multicenter study of deferiprone with initial (less than 6 months pretreatment) liver biopsy results available, 56 consented to repeat biopsy while still treated with deferiprone. Reasons for performing the initial liver biopsy were variable. At one center, all patients underwent biopsy before entry. At 3 other centers, biopsies were performed in patients with serum ferritin levels lower than 2000 μg/L to determine eligibility for inclusion in the deferiprone study or as incidental biopsies at surgery. A panel coded 112 liver biopsy specimens obtained before and after deferiprone therapy. Fibrosis was scored with the Laennec and Ishak systems. Mean number of portal tracts was 10.2 (range, 2 to 39). Forty-five patients were seropositive and 11 were seronegative for hepatitis C. After a mean interval of 3.1 years, no significant increase was observed in fibrosis scores using either scoring system in the patients seronegative or seropositive for hepatitis C. There was still no significant difference when analysis was limited to the 31 patients with 6 portal tracts or more. The fibrosis score increased by more than one level in one patient with hepatitis C and in no patient without hepatitis C.

This study, representing the largest group of evaluable patients reported so far, shows no evidence of progression of liver fibrosis that may be attributed to deferiprone toxicity. Results of this study
confirm the conclusions of previous smaller studies that failed to implicate deferiprone as a cause of liver fibrosis.\textsuperscript{22,31,78}

Other complications

The International Study Group on Oral Chelators found that the complications most frequently associated with treatment with deferiprone were nausea and other gastrointestinal symptoms, arthralgia (joint pain, effusions in severe cases, and stiffness of muscles), zinc deficiency, and fluctuating liver function tests, especially in anti-HCV-positive patients.\textsuperscript{39} The prospective, multicenter study of 187 patients, the largest clinical study designed to characterize the safety profile of deferiprone,\textsuperscript{39} showed a similar range of drug-related effects during the first year of therapy. Nausea, vomiting, or both occurred in 24% of patients, abdominal pain in 14%, and arthralgia in 13%. Plasma zinc levels also fell significantly from a mean of 14.4 \(\mu\)M to a mean of 13.0 \(\mu\)M. A previous study had shown zinc excretion to be increased, particularly in patients with diabetes or prediabetes receiving deferiprone.\textsuperscript{38} Side effects other than neutropenia rarely required the discontinuation of therapy in the multicenter study. A subsequent analysis after 4 years of treatment demonstrated that gastrointestinal symptoms were reported infrequently after the first year of therapy.\textsuperscript{23}

Arthralgia was one of the earliest reported side effects of deferiprone.\textsuperscript{39} Large joints, especially the knees, are most affected. The incidence of arthralgia was 20% of the 82 patients in the International study\textsuperscript{39} but only 3.9% in a much larger Italian study.\textsuperscript{40} The cause of joint symptoms during deferiprone therapy remains obscure. There is no relation to the presence of antinuclear antibody or rheumatoid factor before or during therapy. Some investigators have proposed chelator-induced transit of iron into the synovial space.\textsuperscript{81} Others have related joint symptoms to higher levels of deferiprone or greater levels of iron overload.\textsuperscript{11} The association of joint problems with higher ferritin levels found in the multicenter safety study after 1 year was not sustained after 4 years.\textsuperscript{23,39} Arthralgia generally resolves after temporary discontinuation of the drug or reduction of the dose, at a median time of 12 days.\textsuperscript{40} It required discontinuation of the drug in 5 of 51 (9.8%) heavily iron-loaded patients in one series\textsuperscript{31} but in only 10 of 522 (1.9%) patients studied for 3 to 36 months by Ceci et al.\textsuperscript{40} Interestingly, joint problems also occur during chelation therapy with deferoxamine, albeit less frequently.\textsuperscript{82}

Drug-related systemic lupus erythematosus was suggested as the cause of death in one patient,\textsuperscript{83} but neither the clinical course nor the laboratory data established this diagnosis with certainty. Monitoring of double-stranded DNA antibodies, antinuclear factor, antihistone antibodies, and rheumatoid factor, CD4 and CD8 counts, and immunoglobulin levels in several studies has not shown significant changes associated with deferiprone therapy.\textsuperscript{13,15,39,84} Neutropenia and systemic vasculitis developed in one patient receiving deferiprone, but no similar cases have been described.\textsuperscript{83} No neurologic side effects are established. Auditory disturbance progressed in 5 of 9 patients switched from deferoxamine to deferiprone therapy because of this side effect.\textsuperscript{84} No patient without visual or auditory disturbance has been reported to acquire these problems de novo while receiving deferiprone.

A potential complication of the availability of deferiprone or other oral chelators is the premature abandonment of successful therapy with deferoxamine for the convenience of an orally active alternative. It is incumbent upon physicians to determine which patients are appropriate candidates for deferiprone, based on the clinical needs of individual patients and the current data regarding safety and efficacy.

Several additional papers have reviewed the characteristics and frequency of deferiprone-associated side effects.\textsuperscript{87-89}

Conclusions

\textit{Life is short and science is long, opportunity is elusive, experiment is dangerous, judgement is difficult.}

Hippocrates\textsuperscript{90}

Patients with thalassemia major and other transfusion-dependent disorders who are able to successfully control iron overload at a safe level with deferoxamine should be encouraged to continue with this approach to chelation therapy. Treatment with deferiprone should be carefully considered for patients unable to use deferoxamine or for patients with an unsatisfactory response to deferoxamine as judged by liver iron and serum ferritin measurements or evidence of cardiac iron overload or iron-induced cardiac dysfunction. At a dose of deferiprone of 75 mg/kg per day, iron stores may decrease in some patients, remain stable in others, and increase in some others. Thus, careful monitoring of iron stores, preferably by measurement of tissue iron and of cardiac function, is important during treatment with deferiprone, as it is with deferoxamine. Enhanced iron excretion can be obtained at higher doses of deferiprone or by combining deferiprone and deferoxamine therapy. Early studies of combined therapy are particularly encouraging, but these approaches have not undergone rigorous long-term testing for complications. Although we have focused on the use of deferiprone for thalassemia major, deferiprone may also have an important role in the treatment of patients with thalassemia intermedia and of patients with other anemias who accumulate iron at lower rates than do those with thalassemia major. As with any drug recently introduced to clinical practice, further studies of the risks and benefits associated with deferiprone therapy should take place, and all patients receiving the drug should be closely monitored.

\textit{Note added in proof.} In a retrospective analysis of 129 thalassemia major patients followed on average for 6 years, development of new cardiac disease was diagnosed in 2 (4%) of 54 deferiprone-treated patients and in 15 (20%) of 75 deferoxamine-treated patients \((P = .007).\) None of the patients treated with deferiprone died, while 3 of the deferoxamine-treated patients died, all of cardiac failure.\textsuperscript{91}

References


