Long-Term Trials of Deferiprone in Cooley's Anemia[a]

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ABSTRACT: Deferoxamine is the currently available agent for the iron-chelation therapy required by Cooley's anemia patients. The difficulties associated with parenteral administration have mandated a search for alternative therapies, especially orally active iron chelators, to remove excess iron that results in damage to the liver, endocrine organs, and heart. Four orally active agents have reached clinical trials in the last decade. The agent under consideration in this paper, deferiprone (1,2-dimethyl-3-hydroxypyridin-4-one), has shown some promise, but, according to the studies discussed here, may not provide adequate sustained control of body iron in a substantial proportion of Cooley's anemia patients.

In patients with Cooley's anemia and hereditary hemochromatosis, excess iron acquired through transfusions or absorption results in damage to the liver, endocrine organs and heart.[1] Several studies have highlighted the importance of sustained reduction of body iron burden as the principal determinant of clinical outcome in these disorders.[2–5] While venesection can effectively and safely reduce body iron in individuals homozygous for hereditary hemochromatosis,[2] patients with Cooley's anemia require life-long chelating therapy to promote the excretion of iron accumulated from transfusions.[6] The only iron-chelating agent available for clinical use is deferoxamine, long-term compliance which with prevents the complications of iron overload, and improves survival, in Cooley's anemia.[4,7] The difficulties associated with parenteral administration of deferoxamine have mandated a search for safe and effective therapeutic alternatives, including orally active iron chelators,[1] four of which have reached clinical teals in the past decade. The compounds N,N'-bis (2-hydroxybenzoyl) ethylenediamine N,N'-diacetic acid (HBED), the aryl hydrazone pyridoxal isonicotinoyl hydrazone (PIH), and the diethyl hydroxypyridinone CP94, have all been evaluated in short-term trials over the last five years, but are not under clinical development at this time.[6] The orally active iron-chelating agent most extensively evaluated to date is 1,2-dimethyl-3-hydroxypyridin-4-one (deferiprone; L1),

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one of the 3-hydroxypyridin-4-one iron chelators patented in 1982 as an potential alternative to deferoxamine for the treatment of chronic iron overload.[8]

Animal studies of deferiprone have reported variable efficacy in rodents and rabbits, and insufficient efficacy for maintenance of negative iron balance in iron-loaded primates.[6] In transfused patients with Cooley's anemia, 75 milligrams of deferiprone per kilogram body weight induces urinary iron excretion approximately equivalent to that achieved with 30–40 milligrams of deferoxamine per kilogram.[1,9,10] Because fecal iron excretion induced by deferiprone is much less than that by deferoxamine,[9,10] the short-term efficacy of deferiprone is acknowledged to be inferior to that of deferoxamine.

Effectiveness of Deferiprone as Estimated by Serum Ferritin Concentration

While the earliest studies reported no sustained decrease in serum ferritin concentration over one to 15 months of deferiprone therapy,[11,12] two short-term trials subsequently reported statistically significant reductions in mean serum ferritin concentration in patients with Cooley's anemia, with the most substantial declines observed in patients whose pre-study ferritin concentrations exceeded 5000 μg/L.[13,14] As previously noted, reliance on changes in the concentration of serum ferritin alone may lead to inaccurate assessment of body iron burden in individual patients; direct assessment of tissue iron is crucial in the evaluation of any new potential iron-chelating agent.[6] Such studies therefore could not establish convincingly the efficacy of deferiprone in the reduction of body iron burden.

Effectiveness of Deferiprone as Estimated by Hepatic Iron Concentration

Reduction in hepatic iron stores during deferiprone therapy was first demonstrated in a patient with thalassemia "intermedia."[15] In a subsequent study in patients with Cooley's anemia unable or unwilling to use deferoxamine, short-term deferiprone treatment was shown to reduce hepatic storage iron in many patients over three years.[16] As emphasized at the time of that report, the long-term effectiveness of this agent remained undetermined.[17]

To assess the effectiveness of deferiprone in the long-term control of body iron in Cooley's anemia we have continued to determine hepatic iron concentration in these patients, in whom results through June 1994 were reported previously.[16] As of June 1996, 18 of 21 patients remain evaluable; one patient interrupted deferiprone for 0.7 years, and two patients stopped deferiprone after one year. These 18 patients constitute the only group worldwide to receive long-term deferiprone in conjunction with serial measurements of hepatic iron concentration to accurately determine body iron. As in our previously reported analysis,[16] hepatic iron concentration, determined in tissue obtained at biopsy or by magnetic susceptometry,[4] was the primary endpoint of effectiveness. The criteria used are those derived from long-term studies of morbidity and mortality associated with increasing concentrations of hepatic storage iron *in vivo*.[2–5,18] These will be briefly reviewed.

Information about the risks associated with lower levels of body iron arises from experience in patients heterozygous for the iron-loading disorder hereditary hemochromatosis, in a proportion of whom maintenance of modestly elevated concentrations of hepatic iron (approximately 3.2 to 7 milligrams iron per gram liver, dry weight) is associated with normal life expectancy and no evidence of iron-induced toxicity.[18] Individuals with body iron burdens above this range, and up to about 15 milligrams iron per gram liver, dry weight, are at an increased risk of hepatic fibrosis and other complications of iron overload.[2,3,5]

Patients who sustain hepatic storage iron concentrations exceeding 15 milligrams iron per gram liver, dry weight have a greatly heightened risk of cardiac disease and early death.[4] Accordingly, patients who reduce and maintain hepatic storage iron concentrations within the range of 3.2 to 7 milligrams iron per gram liver, dry weight are considered to have maintained body storage iron within optimal range while receiving deferiprone. Patients in whom long-term chelating therapy fails to maintain hepatic storage iron in this range are considered to be at risk for iron-induced complications of iron overload. Finally, those patients in whom therapy fails to maintain hepatic storage iron below 15 milligrams iron per gram liver, dry weight, are considered to be at risk of cardiac disease and early death.[4]

Although support for Toronto's long-term trial was terminated prematurely in 1996 by the corporate sponsor, continued follow-up of hepatic storage iron concentrations has provided information regarding the long-term effectiveness of deferiprone in Cooley's anemia. Our most recent analysis of this cohort shows that, in one-third of patients, hepatic iron concentrations presently exceed the threshold associated with increased risk of heart disease and early death in Cooley's anemia.[4] Of the 16 patients with a hepatic iron concentration below this threshold when previously reported,[16] the hepatic iron concentration now exceeds the threshold in four patients ($p = 0.05$); in the two other patients, the hepatic iron concentration has continued to exceed the threshold during 2.3 and 3.9 years of deferiprone, respectively. In these six patients. mean compliance with deferiprone exceeding 90% drug taken of that prescribed.[19] Another interpretation of these data has recently been presented.[20,21]

In parallel, investigators in the United Kingdom reported the results of deferiprone therapy over 42.5 months (range, 8 to 56 months) in 42 patients with Cooley's anemia aged 29.9 years (range, 20 to 58 years).[22,23] No significant declines in serum ferritin concentration were reported in these patients over this period of therapy. In the 17 patients in whom hepatic iron concentrations were determined after therapy, concentrations exceeded the threshold for cardiac disease and early death[4] in ten patients. The conclusion of this analysis is similar to those in the Canadian study:[19] the U.K. investigators have now concluded that "long-term therapy with deferiprone may not provide adequate control of body iron in a substantial proportion of patients with thalassemia major."[22,23]

In summary, two interpretation of the results obtained from the only centers to quantitatively determine body iron burden in patients receiving long-term deferiprone therapy raise concerns that long-term deferiprone may not provide adequate sustained control of body iron in a substantial proportion of patients with Cooley's anemia.[19,22,23]

Toxicity Studies

As detailed previously,[6] deferiprone did not receive full formal toxicologic evaluation before being given to humans; permission to administer the drug in early studies in the United Kingdom, India, Europe and Canada was granted on the basis of limited toxicity studies in rodents. Adrenal hypertrophy, gonadal and thymic atrophy, bone marrow atrophy and pancytopenia, growth retardation, and embryotoxicity have also been reported in animals. In humans, the most common adverse effect associated with administration of deferiprone has been arthralgias, primarily of the large joints, the etiology of which remains elusive.[6] The most serious adverse effect associated with the administration of deferiprone has been severe neutropenia or agranulocytosis, first reported in 1989.[24] To date, this complication has been reported in several patients, most with Cooley's anemia, as early as six weeks and up to 21 months after the initiation of deferiprone. The mechanism of

deferiprone-induced neutropenia is unknown; this adverse effect appears not to be dose-dependent, but idiosyncratic and unpredictable.[6]

No study of long-term toxicity of deferiprone has been conducted. Monitoring of the safety of deferiprone in most prospective studies continues to be directed to abnormalities reported in animal studies.[23–29] Treatment of iron-loaded Mongolian gerbils with a hydroxypyridinone closely related to deferiprone (1,2-di*ethyl*-3-hydroxypyridin-4-one) has been associated with the acceleration of hepatic fibrosis and the development of cardiac fibrosis in these animals, the only species which develops hemochromatosis of the liver and heart in the same manner as patients with Cooley's anemia.[29] While hepatic iron accumulation was inhibited during co-administration of 1,2-diethyl-3-hydroxypyridin-4-one over the short-term in the gerbils, hepatic iron increased significantly during extended drug administration.[29] Of further concern, accelerated fibrosis was noted in both the livers and hearts of animals in which 1,2-diethyl-3-hydroxypyridin-4-one was co-administered with iron, compared to animals treated with iron alone. These observations, and the theoretical concerns with respect to the toxicity of a bidentate ligand, discussed elsewhere in this volume, have raised concerns as to whether long-term deferiprone therapy may be associated with worsening of hepatic fibrosis, and cardiac iron loading and fibrosis, in humans.

By oversight, in this and all other trials of deferiprone worldwide, hepatic histology has never been evaluated prospectively in patients receiving long-term therapy. As well, the effect of deferiprone on cardiac iron loading and fibrosis has not been been the primary endpoint of any prospective trial. Nevertheless, the studies by the group in the United Kingdom have provided indirect information regarding cardiac disease in patients with Cooley's anemia treated with long-term deferiprone. In this long-term treatment cohort,[23] 18 of 42 patients left the study, a dropout rate of 43 percent. Review of these 18 patients shows that five dropouts had died, four of cardiac disease, while on deferiprone therapy, while another patient withdrew from treatment because of tachycardia. In all the study dropouts, mean initial serum ferritin concentration, which exceeded 4,500 μg/L, reportedly did not change significantly during deferiprone therapy.[23] These data underscore the concerns that long-term deferiprone may not adequately reduce body iron burden below concentrations that are associated with an increased risk of cardiac disease and early death in Cooley's anemia,[4] confirming the findings summarized above.[19,22,23]

In summary, data from two centers conducting long-term trials of deferiprone support our previous conclusion that "long-term therapy with deferiprone may not provide adequate control of body iron in a substantial proportion of patients with thalassemia major."[19] Further prospective trials may be indicated to address these potential toxicities of deferiprone.

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