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Posterboard 41-IV, THALASSEMIA AND GLOBIN GENE REGULATION II

CARDIAC FAILURE AND MYOCARDIAL FIBROSIS IN A PATIENT WITH THALASSEMIA MAJOR (TM) TREATED WITH LONG-TERM DEFERIPRONE

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We report the development of acute congestive cardiac failure in a 23-year-old man with TM after prolonged treatment with deferiprone, an orally active iron chelator. This patient had complied with deferoxamine (DFO) for 15 years until 1993, when he was randomized to deferiprone treatment in a prospective trial comparing deferiprone and DFO. Deferiprone, 75 mg/kg/day, was given for 3.6 years; hepatic iron varied between 9 and 13 milligrams per gram liver, dry weight (mg/g), and cardiac ejection fraction between 50 and 70% (normal >50%). Because of concerns about the safety of deferiprone, the patient was advised to discontinue deferiprone and resume DFO. Six months later, he presented with severe acute congestive cardiac failure. Transthoracic echocardiogram and Doppler showed an ejection fraction of <20% and markedly impaired diastolic relaxation. Myocardial and hepatic biopsies were performed: biochemical results are shown in the Table and compared with findings in the explanted heart and liver of a 20-year-old TM patient who had been non-compliant with DFO for several years, and had required combined heart and liver transplantation for end-stage iron-induced disease (N Engl M Med 1994;330:1125-7). Note that patients with TM in whom the body iron burden, as assessed by hepatic iron, is maintained below 15 mg/g have a low risk of cardiac complications (N Engl J Med 1994;331:567-73). Although the cardiac iron concentration in the patient treated with deferiprone was lower, both myocardial biopsies showed similar widespread endocardial and interstitial fibrosis with extensive muscle fiber degeneration. No other risk factors for cardiac fibrosis were present.

Patient	Hepatic iron (mg/g, dry weight)	Myocardial iron (mg/g, dry weight)
Deferiprone therapy	13.2	3.7
No iron-chelating therapy	28.1	5.8

In cultured cardiomyocytes, deferiprone fails to mobilize iron and promotes iron-induced cardiotoxicity (Blood 1997;90 (Suppl. 1):11a). Studies in an animal model of human iron overload have found that the combination of iron overload and treatment with a hydroxypyridinone structurally similar to deferiprone was associated with redistribution of iron, leading to increased cardiac iron deposition and fibrosis (BioMetals 1994;7:267-71). Long-term clinical studies suggest that deferiprone may accelerate hepatic fibrosis (N Engl J Med 1998;339:617-23). Deaths from cardiac causes have been reported in patients treated with deferiprone for up to 2 years (Blood 1998;91:295-300) but ascribed solely to the underlying iron overload; no autopsy results have been reported. Overall, these observations raise concerns that deferiprone treatment in patients with TM may be associated with (i) redistribution of body iron, leading to increased cardiac iron deposition at lower body iron burdens, and (ii) an exacerbation or acceleration of cardiac fibrosis. We conclude that the risk of cardiac disease associated with deferiprone therapy needs further evaluation.

Iron transport and kinetics
Iron overload and hemochromatosis
Thalassemias