

## Iron Chelation Therapy for Treatment of Cardiac Hemochromatosis

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### Editorial

Hemochromatosis is a clinical syndrome caused by abnormal accumulation of iron in parenchymal organs leading to organ toxicity and dysfunction. Cardiac hemochromatosis is a cardiomyopathy due to primary iron-overload cardiomyopathy which causes congestive heart failure. Patients with cardiac hemochromatosis may be asymptomatic early in the disease. Once heart failure develops, there is rapid deterioration. Cardiac hemochromatosis is characterized by a dilated cardiomyopathy with dilated ventricles, reduced ejection fraction, and reduced fractional shortening. Deposition of iron may occur in the entire cardiac conduction system, especially the atrioventricular node [1]. Cardiac hemochromatosis should be ruled out in patients with unexplained congestive heart failure.

Myocardial iron load can be quantitatively assessed by cardiac magnetic resonance imaging. Myocardial iron content is accurately predicted by the T2\* relaxation time [2]. Aa T2\* relaxation time greater than 20 milliseconds predicts a low risk for development of congestive heart failure. Aa T2\* relaxation time between 10 and 20 milliseconds predicts an intermediate risk for development of congestive heart failure. These patients probably have myocardial iron deposition. A T2\* relaxation time below 10 milliseconds predicts a high risk for development of congestive heart failure, and these patients need iron chelation therapy [3]. In a 662 patients with thalassemia major, congestive heart failure developed within 1 year in 47% of patients with a T2\* relaxation time below 6 milliseconds, in 21% of patients with a T2\* relaxation time of 6 to 10 milliseconds, and in 0.2% of patients with a T2\* relaxation time more than 10 milliseconds [4]. Cardiac arrhythmias occurred within 1 year in 19% of patients with a T2\* relaxation time below 6 milliseconds, in 18% of patients with a T2\* relaxation time of 6 to 10 milliseconds, and in 4% of patients with a T2\* relaxation time more than 10 milliseconds [4]. When the T2\* relaxation time is below 20 milliseconds, left ventricular systolic function progressively worsens accompanied by increased left ventricular end-systolic volume and left ventricular mass [5].

Phlebotomy is not an option for treatment of patients with cardiac hemochromatosis who have anemia (secondary iron-overload disorders) or severe congestive heart failure [6]. The therapy of choice for these patients is iron chelation therapy [7]. The iron excretion rate is increased by iron chelating agents through their binding to the iron in plasma and tissues, thereby depleting the body of excess iron [8]. Serum ferritin levels must be monitored periodically. When the serum ferritin level reaches less than 1000 ng/mL, iron chelation therapy should be avoided because the adverse effects of nephrotoxicity, neurotoxicity, and hepatic toxicity from iron chelation therapy outweigh the beneficial effects of further lowering serum ferritin levels [9]. The 3 iron-chelating drugs approved by the United States Food and Drug administration for treatment of chronic secondary iron overload are deferoxamine, deferiprone, and deferasirox.

Deferoxamine is a hexadentate molecule which can bind directly to labile iron in plasma and in tissues including the heart [10]. Deferoxamine has a poor oral bioavailability and a short half-life. This drug is used as a subcutaneous or intravenous infusion. The recommended dose in adults is 40 to 50 mg/kg/day infused over 8 to 12 hours for 5 to 7 days per week. Therapy with use of deferoxamine therapy lowers myocardial iron content approximately 24%, delays onset of cardiac hemochromatosis, reverses early cardiac hemochromatosis, improves left ventricular function, and increases survival in transfusion-dependent patients who have thalassemia [11-14]. However, long-term compliance with use of deferoxamine is poor [15].

Deferiprone is an orally active bidentate iron chelator approved for treating iron overload in transfusion-dependent patients with thalassemia when current chelation therapy is inadequate. The initial dose of deferiprone is 75 mg/kg/day administered in 3 divided doses. The maximum dose of deferiprone is 99 mg/kg/day. Some studies have found that deferiprone is better than deferoxamine in lowering myocardial iron content [16,17]. Combination therapy with deferiprone plus deferoxamine has been found to rapidly lower iron overload and improve cardiac function in iron overload patients with congestive heart failure and unstable hemodynamics [18-20]. Compared to deferoxamine plus placebo, deferoxamine plus deferiprone reduced serum ferritin more (976 ng/mL from deferoxamine plus deferiprone to 233 ng/mL from deferoxamine plus placebo,  $p < 0.001$ ) [20]. The combination of deferoxamine plus deferiprone also improved left ventricular ejection fraction and endothelial function more than deferoxamine plus placebo ( $p < 0.001$ ) [20].

Deferasirox is a tridentate iron chelating drug with good oral bioavailability approved for treatment of iron overload resulting from recurrent blood transfusions. The initial oral dose of deferasirox given once daily is 20 mg/kg/day which can be increased to a maximum dose of 40 mg/kg/day [21]. Deferasirox lowers the serum ferritin level and lowers iron overload of the heart and liver [22-26]. Data from the thalassemia participants' enrolled in the Myocardial Iron Overload in Thalassemia network showed that the cohort of patients treated with oral deferiprone developed less myocardial iron burden and better global systolic ventricular function than the patients treated with oral desferasirox or subcutaneous desferrioxamine [17]. Treatment of cardiac hemochromatosis with phlebotomy plus desferasirox reversed congestive heart failure with severe left ventricular and right ventricular systolic dysfunction [27].

Newer iron-chelating agents that are being investigated for treatment of chronic iron overload disorders include silybin [28], DE ferritin [29], and starch conjugated deferoxamine [30]. The goal is to design an iron chelating agent that is 1) orally active, 2) can cross cell membranes, and 3) can remove iron from specific areas of the body

such as the heart, liver, endocrine organs, and brain, sparing the bulk of physiologically essential iron [31].

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