REVIEW

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Getting the iron out: Preventing and treating heart failure in transfusion-dependent thalassemia

ABSTRACT

Congestive heart failure is the most common cause of death in patients with thalassemia, as chronic accumulation of iron due to regular blood transfusions leads to biventricular systolic dysfunction and death at a very young age. The quantity of iron deposited in the heart is a key determinant of outcome. Early diagnosis and intensive chelation of the cardiac iron can avert heart failure and its fatal outcome.

KEY POINTS

Conventional measures of iron, such as serum ferritin, and even measurements in myocardial biopsy samples correlate poorly with the actual amount of iron in the heart.

Two new imaging tests, myocardial T2-star magnetic resonance imaging and tissue Doppler echocardiography, can indicate the degree of myocardial iron deposition before it leads to symptomatic heart failure.

The degree of myocardial iron deposition needs to be estimated to regulate the intensity of chelation. With intensive chelation, the heart can recover nearly completely from states of very poor function.

Long-term regular chelation with deferoxamine (Desferal), a parenteral agent, prevents the complications of iron overload. Deferiprone, an oral agent not yet available in the United States, also provides a definite and marked cardioprotective effect. Deferasirox (Exjade), another oral chelating agent, has not been studied as extensively.

THALASSEMIAS are a group of chronic, inherited anemias characterized by defective hemoglobin synthesis and ineffective erythropoiesis.[1] Patients with these disorders require blood transfusions at regular intervals throughout their lives to eliminate the ensuing anemia and compensatory bone marrow expansion. However, this treatment causes a second disease: an inexorable accumulation of iron in tissues, which, without treatment, leads to congestive heart failure and is usually fatal in the second decade of life.[2]

This article reviews the emerging tests that can be used to assess myocardial iron deposition before it becomes damaging to myocardial function. We also discuss the beneficial cardiac effects of chelators currently being used and ones undergoing development.

PATIENTS ARE LIVING LONGER

In recent years the ethnicity, age distribution, and genotypes of North American patients affected by severe thalassemia have changed dramatically, as reported by Vichinsky et al[3] in an analysis of data from the Thalassemia Clinical Research Network.

Thalassemia mostly affects people of Mediterranean, African, or Asian ancestry. Overall birth rates among Greek and Italian Americans have been decreasing, but as immigration from Asia has been increasing, so have births among Asian Americans.[3,4] Asian patients now account for more than 50% of the thalassemic population, and due to this Asian influx, births of babies with thalassemia

may actually be increasing in North America, as suggested by screening studies in newborns.[3]

Thanks to improved therapies and better management of transfusion schedules, thalassemia, often considered a pediatric disease, has now become a chronic adult illness, with a median life span approaching 40 years in North America. More research is needed into the complex medical problems faced by older patients, particularly heart disease, the final common pathway leading to death in transfusion-dependent patients.

HOW IRON DAMAGES THE HEART

The human body has no mechanism for excreting excess iron, which is stored as crystalline iron oxide within ferritin and hemosiderin in the body. Iron overload can occur due to either excess gastrointestinal absorption or repeated blood transfusions; in thalassemia, it is a result of both processes.[5]

Excess iron is deposited in the reticuloendothelial cells of the spleen, liver, and bone marrow. This process appears to be relatively harmless.[6] After repeated transfusions, however, iron starts to accumulate in the parenchymal cells of the heart, pancreas, and other endocrine glands, all of which are sensitive to its toxic effects.

Thalassemia, often considered a pediatric disease, has now become a chronic adult illness

In healthy people, iron is tightly bound to the proteins transferrin and ferritin and therefore cannot catalyze the formation of oxygen-free radicals. When the body exhausts its iron-binding capacity, free iron appears as non-transferrin-bound iron. The labile component of that free iron is called labile plasma iron, which in turn within cells becomes labile cellular iron. These labile components are highly toxic, as they promote free radical formation, which results in peroxidative damage to the membrane lipids and proteins. In the heart, this damage leads to impaired function of the mitochondrial respiratory chain and is manifest clinically as heart failure.[2] The chronic anemia in thalassemia also exacerbates the heart failure.

Iron begins to have an effect on the heart when about 20 grams of it have accumulated in this organ, usually after age 10 years in children who have received transfusions regularly without adequate chelation.[7]

THE FAILING HEART IN THALASSEMIA: UNIQUE FEATURES

The most common presentation of myocardial dysfunction in thalassemic heart disease, and still the most common cause of death, is left heart failure.

Hahalis et al,[8] however, found that most patients with beta thalassemia major (a severe form) and heart failure had severe right ventricular dysfunction, independent of pulmonary arterial pressures and left ventricular systolic function. They postulated that the thin-walled right ventricle may be more prone to earlier and rapid dysfunction via iron deposition. Right heart failure may occur early and predominate, though it can also evolve secondarily after the onset of left heart failure.

The disproportionate rise in right ventricular end-diastolic pressure with minimal elevation of pulmonary arterial pressures indicates severe right ventricular chamber involvement resulting in marked right ventricular systolic dysfunction. This hemodynamic profile is strikingly similar to that in right ventricular infarction.[8]

Interesting but less-convincing arguments have been made in favor of chronic pulmonary hypertension[9] and myocarditis[10] as mechanisms in thalassemic heart disease.

Late cardiac complications also include pericarditis,[11] which may be recurrent. Widespread infiltration and fibrosis of the conduction system may lead to a myriad of atrial arrhythmias (eg, atrial flutter and fibrillation, paroxysmal supraventricular tachycardia) and ventricular arrhythmias (runs of ventricular tachycardia and frequent premature ventricular contractions).

Some patients do not have overt signs of heart failure. Aldouri et al[12] identified a group of patients with preserved left ventricular function and high myocardial tissue levels of iron who were at high risk of cardiac complications. The authors advocated intensified chelation for this group, a therapy that is known to improve cardiac outcomes.

Cardiac complications in thalassemia typically correlate directly with the amount of iron in the heart and abate with chelation therapy. Once heart failure develops and left ventricular function is reduced, the prognosis

is poor: rates of heart disease and death dramatically rise, beginning in the teenage years and leading to a 50% mortality rate before age 35 years.[7] Patients with overt heart failure (moderate to severe) and marked myocardial iron overload tend to be less responsive to intensive chelation.

In some cases, the heart can recover nearly completely from states of very poor systolic function with chelation therapy. Unfortunately, this response is not observed in the majority of patients with poor cardiac function, and therefore direct and accurate estimation of myocardial iron should be pursued to allow for earlier diagnosis and treatment.

MYOCARDIAL IRON IS HARD TO MEASURE

Until recently, the amount of myocardial iron deposition has been hard to estimate accurately. The diagnosis of myocardial iron overload is often delayed because cardiac iron deposition is unpredictable and symptoms and echocardiographic abnormalities arise late in the course of the disease.[13,14]

Serum ferritin

To indirectly estimate body iron stores in patients with thalassemia, decide whether to start chelation therapy, and titrate it, most physicians monitor the serum ferritin level. The serum ferritin level does not, however, correlate closely with myocardial iron levels.

Ferritin is an acute-phase protein, and so its levels can change independently of the body's iron burden. Factors that influence ferritin levels include fever, acute infection, ascorbate deficiency, acute and chronic hepatic damage, hemolysis, and ineffective erythropoiesis.[15,16]

Nevertheless, Olivieri et al[17] found that serial measurements of ferritin (once every 6 months) had value in predicting cardiac disease. Patients with a serum ferritin concentration of less than 2,500 µg/L had an estimated cardiac disease-free survival rate of 91% at 15 years, compared with only 20% in patients who had higher ferritin levels. Accordingly, a serum ferritin value of 2,500 µg/L can be used as a threshold to identify patients at risk of cardiac disease and early death.[2,17]

Iron in the liver does not equal iron in the heart

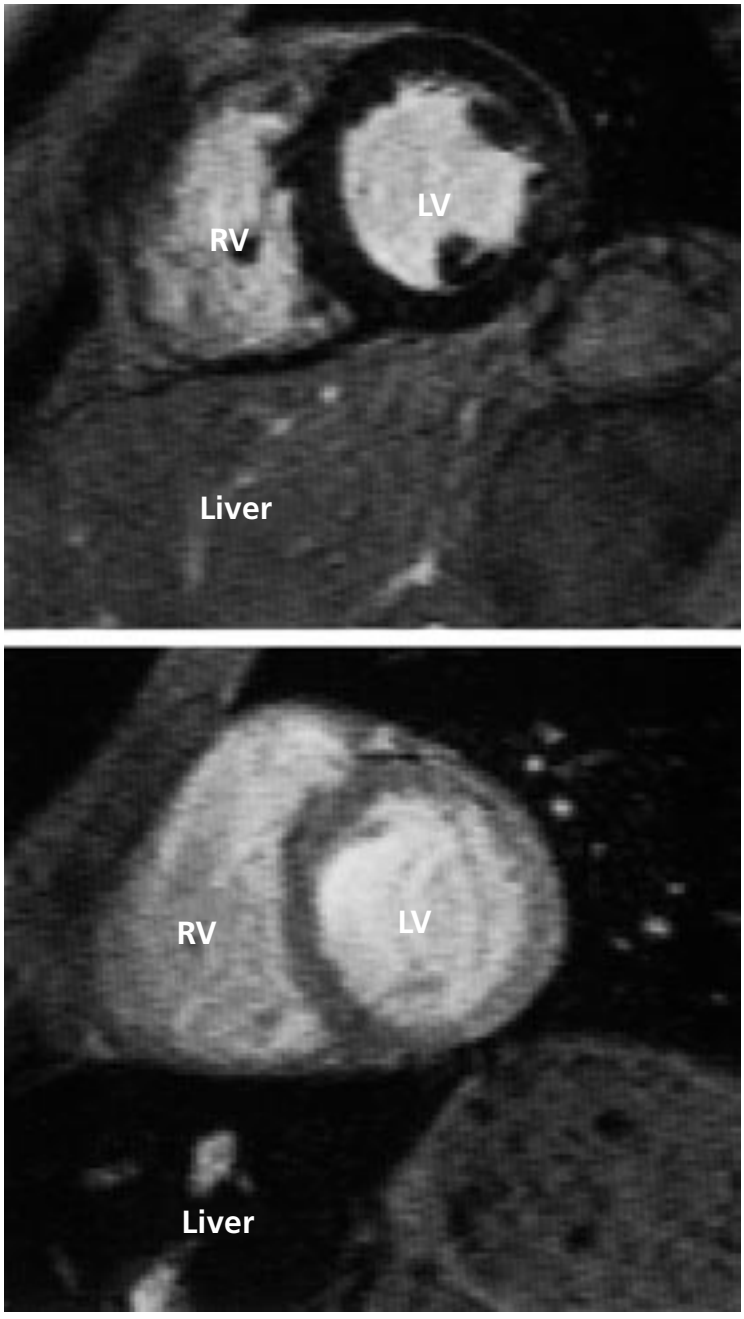

FIGURE 1. T2-star magnetic resonance images show discordance of iron deposition in the liver and in the heart. The top panel shows a patient with severe cardiac iron deposition but minimal liver iron deposition (heart darker than liver). The lower panel shows a patient with normal myocardial iron but severe liver iron overload (liver darker than heart). RV = right ventricle, LV = left ventricle

ANDERSON LJ, HOLDEN S, DAVIS B, ET AL. CARDIOVASCULAR T2-STAR (T2*) MAGNETIC RESONANCE FOR THE EARLY DIAGNOSIS OF MYOCARDIAL IRON OVERLOAD. EUR HEART J 2001; 22:2171–2179. REPRODUCED WITH THE PERMISSION OF THE OXFORD UNIVERSITY PRESS.

Liver biopsy

The liver iron concentration, measured in a biopsy sample, is the gold standard for estimating the total-body iron burden, but it shows a marked discordance with the cardiac iron concentration as assessed by T2-star magnetic resonance imaging (T2* MRI), which is currently the optimum test of myocardial iron deposition (FIGURE 1; also, see discussion below).[5]

Heart biopsy

Surprisingly, the more direct and invasive method of myocardial biopsy also has shortcomings. The iron concentration in the subendocardial layer is half that in the epicardial layers; thus, the iron concentration in an endomyocardial biopsy specimen (obtained via catheter) can lead one to underestimate the iron deposition.[18] Also, iron is deposited within the myocytes rather than in the interstitium,[19] in a nonuniform, patchy pattern.[18]

Barosi et al[19] performed endomyocardial biopsy in iron-overload patients and found no correlation between the presence of stainable iron in the myofibrils and the serum iron, transferrin, or ferritin concentrations.

Ferritin is an acute-phase protein, and its levels can change independently of the body's iron burden

Tests of cardiac function

Electrocardiography or resting echocardiography may reveal heart failure due to iron overload late in the course of the disease, but these tests are not very sensitive for early detection of cardiac dysfunction.[20–24]

Patients without clinical symptoms may show decreased left ventricular reserve on multigated exercise radio-nuclide angiography[24] or low-dose dobutamine echocardiography.[25] These tests may be useful in the early diagnosis of iron-induced cardiac disease.

NOVEL DIAGNOSTIC TESTS

Two novel imaging tests—myocardial T2* (star) MRI and tissue Doppler echocardiography—are noninvasive, sensitive, and reproducible methods of estimating cardiac iron.

Myocardial T2* MRI

T2* MRI differs from standard T2 MRI and is more sensitive for iron.

T2* is a magnetic resonance relaxation variable arising principally from local magnetic field inhomogeneities that are increased with iron deposition.[5] T2* MRI involves a gradient-echo T2* magnetic resonance sequence rather than the usual spin-echo T2 sequence. The gradient-echo sequence has greater sensitivity to iron deposition. Iron overload causes signal loss in affected tissues because iron is magnetized in the scanner, inducing local irregularities in the magnetic field that cause water protons to lose phase coherence.

Another advantage of T2* MRI is that acquisition times are shorter than in T2 MRI, minimizing motion artifact from myocardial contraction and respiratory movement, which greatly affects the accuracy and reproducibility of the usual T2 spin-echo images.

In addition to producing images, T2* MRI can also give a quantitative result. Vogel et al[26] found the normal T2* value to be between 20 and 83 ms, whereas a T2* value of less than 20 ms represented an abnormal myocardial iron load (FIGURE 2).

It is not possible to definitely predict the myocardial T2* value because no validation has been performed with cardiac tissues. This requires myocardial biopsy and would be difficult because of inhomogeneous myocardial deposition.[18]

Myocardial T2*, however, has been validated by comparing liver T2* values and tissue iron concentrations in patients undergoing liver biopsy. This study, by Anderson et al,[5] showed a definite curvilinear inverse correlation between liver T2* and liver iron content for all liver samples, as compared with fibrotic liver samples. Interestingly, the liver and heart iron concentrations sometimes differed markedly (FIGURE 1), thus proving that liver biopsy is a good measure of total body iron burden but not necessarily of myocardial iron. The study also showed a strong relationship between declining T2* and impaired ventricular function, clearly indicating the empirical value of myocardial T2* MRI.

Anderson et al[5] also showed that T2* MRI can detect myocardial iron loading even before symptoms and signs of congestive heart failure arise, and before chelation therapy is typically considered.[27]

Tissue Doppler echocardiography

Tissue Doppler echocardiography is done

Wall motion abnormalities due to myocardial iron loading

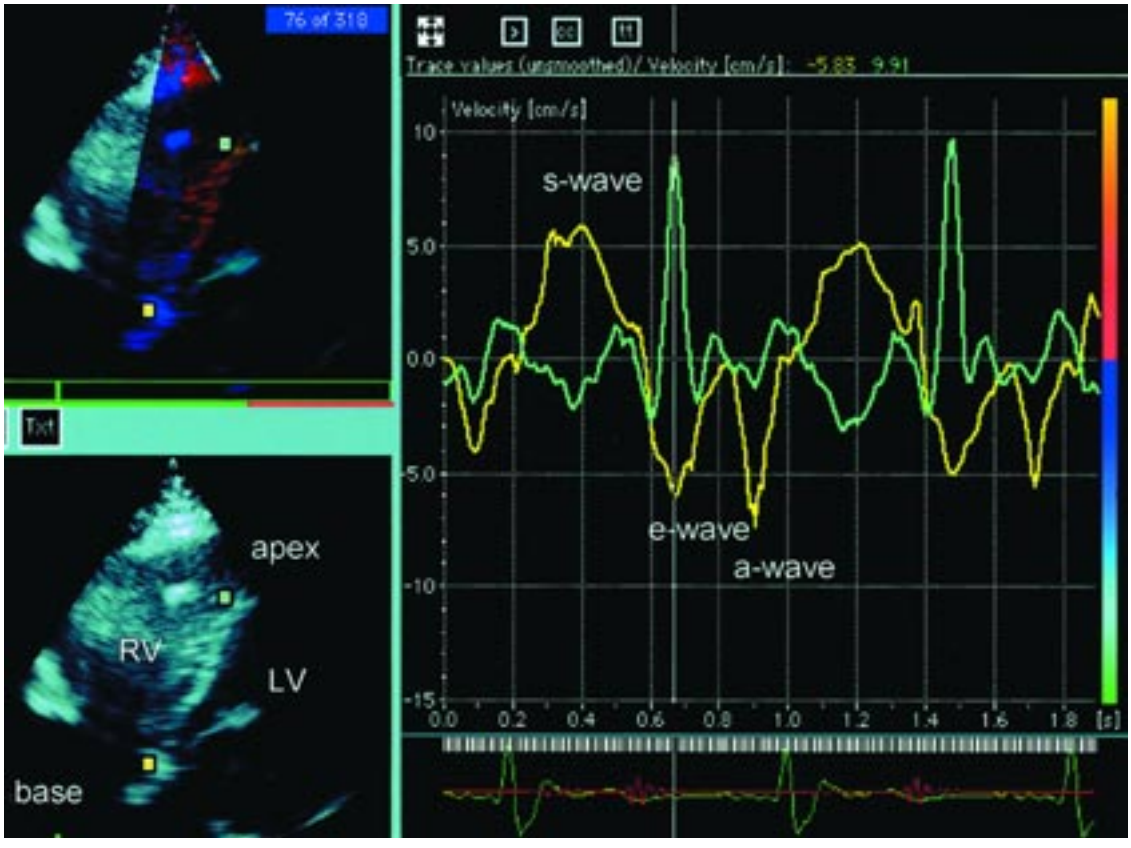

FIGURE 2. A tissue Doppler echocardiographic study shows a change of color from blue to red in the myocardial septum as evidence of iron loading. The reversals of the s and e waves at the apex denote systolic and diastolic wall motion abnormalities. This may occur even in patients with thalassemia whose ejection fractions are within the normal range.

VOGEL M, ANDERSON AJ, HOLDEN S, DEANFIELD JE, PENNELL DJ, WALKER JM. TISSUE DOPPLER ECHOCARDIOGRAPHY IN PATIENTS WITH THALASSEMIA DETECTS EARLY MYOCARDIAL DYSFUNCTION RELATED TO MYOCARDIAL IRON OVERLOAD. EUR HEART J 2003; 24:113–119. REPRODUCED WITH PERMISSION OF THE OXFORD UNIVERSITY PRESS.

T2* MRI has become the gold-standard test for iron overload in the heart

transthoracically with a frame rate between 96 and 158 Hz, using a 2.5 or 3.5 MHz transducer interfaced with a Vingmed System 5 sector scanner (GE Vingmed, Horten, Norway). Imaging is performed via the apical four-chamber acoustical window. The myocardial velocities are sampled continuously from base to apex in the free walls of the left and right ventricles and in the interventricular septum. Simultaneous electrocardiographic and phonocardiographic recordings are also made and stored for analysis.[26]

Peak myocardial velocities during systole (the s wave), early diastole (the e wave), and late diastole (the a wave) are measured at the base, mid, and apical positions of the free walls of the right and left ventricles and the interventricular septum. The myocardial velocities are color-coded, with reversal (wall motion abnormality) being indicated by a change of color from red to blue or vice versa (**FIGURE 2**).

Vogel et al[26] found that the sensitivity of tissue Doppler echocardiography for detecting abnormal iron loading was 88% and the specificity was 65%, using T2* MRI as the gold-standard test. Tissue Doppler echocardiography detected significantly more abnormalities in patients who had abnormal myocardial iron loading (T2* < 20 ms) than in patients with normal T2* findings. More importantly, it detected abnormal wall motion velocities in thalassemic patients whose MRI-derived ejection fractions (a conventional index of global systolic function) were within normal range.

Another intriguing finding in this study was that wall motion abnormalities were restricted to the interventricular septum in 88% of cases. At the same time it indicated that iron loading in the myocardium can be patchy and mainly affects the ventricles. The authors hypothesized that in early stages, iron deposition is predominantly in the septum, with other areas of the heart being affected later in the disease.

Tissue Doppler echocardiography is simple, repeatable, and noninvasive. Considering the ease and economy of the technique, it is particularly recommended for use in third-world countries, which face the greatest burden of thalassemia patients. Its use is not limited to diagnosing myocardial iron deposition disease; it can also be used to monitor the effects of chelation therapy, thus potentially improving the outcome of patients.[27]

FEWER TRANSFUSIONS, LESS IRON

To minimize iron loading, transfusions should be done more judiciously while adequately suppressing erythropoiesis. A protocol in which transfusions are not given unless the hemoglobin level is less than 9.5 g/dL has been shown to result in fewer transfusions and better control of the body iron burden. In turn, myocardial iron deposition may be less.[28]

Deferoxamine's principal drawback is the need for prolonged infusions

In patients with thalassemia who need more than 200 mL of packed cells per kilogram of body weight per year, splenectomy should significantly diminish red blood cell requirements and iron accumulation.[2,29]

CHELATION THERAPY

When chelation should be started is controversial. Reports of abnormal linear growth and metaphyseal dysplasia in children treated with deferoxamine before the age of 3 have prompted recommendations for later therapy.[30,31]

Olivieri et al[2] recommend that initiation of chelation be based on hepatic iron concentration obtained after 1 year of regular transfusions. For hepatic iron concentrations of 3.2 mg/g dry weight or greater, their recommendation is to start deferoxamine (Desferal) at 25 mg/kg per night for 5 weeks (see below).

Deferoxamine

Deferoxamine is a trihydroxamic acid produced by *Streptomyces pilosus*. It has specificity for ferric iron (iron's oxidation state in the ferritin protein complex). It is poorly absorbed orally and is rapidly metabolized; thus, its principal drawback is the need for prolonged parenteral infusion.[2]

Though most clinicians begin deferoxamine therapy after measuring serum ferritin levels, Oliveiri et al[2] suggest starting it at 1 year of age, after estimating liver iron by biopsy, at a dose not exceeding 25 to 35 mg/kg body weight/24 hours.

Adverse effects include high-frequency sensorineural hearing loss, retinal abnormalities, and metaphyseal and spinal abnormalities, which may lead to a decline in height. At very high doses (> 50 mg/kg body weight/24 hours) deferoxamine may also lead to deterioration in renal function and to pulmonary toxicity. The drug may also potentiate the growth of organisms with an affinity for iron, such as *Yersinia* and *Klebsiella* species, which may lead to life-threatening infections.

Low ascorbate (vitamin C) levels have been found in iron-loaded thalassemia patients.[32] Supplementation results in marked improvement in deferoxamine-induced iron excretion by expansion of the chelatable iron pool. This therapy should be done cautiously, as ascorbate-induced expansion of this pool may enhance free radical formation and aggravate iron toxicity.[2,33]

Though compliance with deferoxamine therapy is an ongoing problem, Wolfe et al[34] found it has a cardioprotective benefit in patients who continue with it on a regular basis. Two recent trials, both longer than 10 years in duration, have shown that effective long-term use of deferoxamine in thalassemia major is associated with long-term survival free of the complications of iron overload.[17,35]

Deferiprone

Deferiprone (1,2 dimethyl-3 hydroxypyridin-4-one; L1) was patented in 1982 but is not available in the United States. Nevertheless, it is one of the most extensively evaluated orally active chelators. Long-term trials of deferiprone in thalassemia have reported statistically significant reductions in mean serum ferritin concentra-

Chelation therapy removes myocardial iron

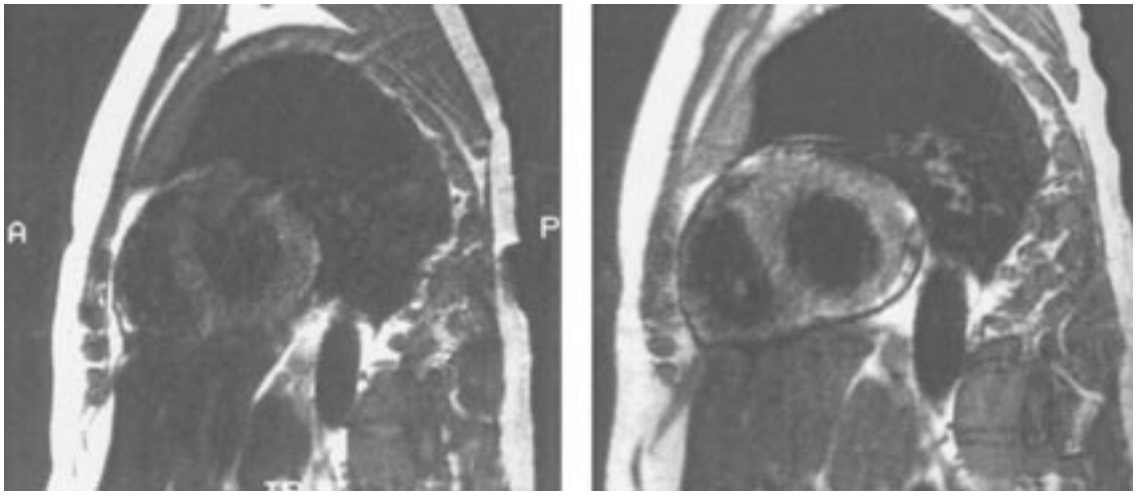

FIGURE 3. Sagittal T1-weighted spin-echo magnetic resonance image of the heart before (left) and after (right) therapy with the orally active iron chelator deferiprone. Inhomogeneity of the cardiac signal on the left is compatible with significant iron deposition, while improvements in signal intensity after 9 months of chelating therapy indicate a reduction in cardiac iron content.

OLIVEIRI NF, KOREN G, MATSUI D, ET AL. REDUCTION OF TISSUE IRON STORES AND NORMALIZATION OF SERUM FERRITIN DURING TREATMENT WITH THE ORAL IRON CHELATOR L1 IN THALASSEMIA INTERMEDIA. BLOOD 1992; 79:2741–2748.

tions, particularly in patients whose prestudy ferritin values exceeded 5,000 µg/L.[36,37]

A significant cardioprotective effect has been observed with deferiprone. In two key studies, published in May 2006, no cardiac events were noted at all in 157 patients receiving deferiprone for up to 9 years (750 patient-years of exposure).[38] Furthermore, the drug was significantly more effective than deferoxamine in removing deposited myocardial iron in asymptomatic patients (**FIGURE 3**).[39] Compared with deferoxamine, the use of deferiprone was associated with significantly greater cardiac protection.

Though this agent has been a major relief for patients (since it is taken orally), it has adverse effects as well. Arthralgias, primarily of the large joints, are common. The most serious side effect reported has been severe neutropenia or agranulocytosis. Though no deaths have been attributed to deferiprone, it requires regular monitoring of complete blood counts. A single case of fatal deferiprone-induced systemic lupus erythematosus has been reported in India.[40]

Deferasirox

The latest oral chelator, which has been approved by the US Food and Drug Administration, is deferasirox (ICL-670; Exjade). Given as a once-daily dose of one tablet dissolved in a glass of water, it is generally well tolerated; reported side effects include nausea, vomiting, diarrhea, abdominal cramps, skin rash, and a mild stable increase in serum creatinine.[41]

Deferiprone provides a significant cardioprotective effect

The chelation efficiency of deferasirox is twice that of deferoxamine: 1 mg of deferasirox will remove twice as much iron as 1 mg of deferoxamine.[42] The chelation efficiency of deferasirox is dependent on the iron intake. At iron intake levels of less than 0.3 mg/kg/day its chelation efficiency is 22%, increasing up to 34% at iron intake levels of greater than 0.5 mg/kg/day. The overall chelation efficiency of deferoxamine is 13%.

A phase III study of deferasirox,[41] carried out in more than 25 centers on three continents, showed a significant reduction in liver iron concentrations, though the reduction was not enough to reach the prespecified criteria for success.

The effect of deferasirox on the heart has yet to be evaluated on the same scale as deferoxamine or deferiprone. Further clinical trials of its efficacy in treating myocardial siderosis are pending. ■

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