

Successful recovery of acute hemosiderotic heart failure in beta-thalassemia major treated with a combined regimen of desferrioxamine and deferiprone

We report the case of a 25-years-old male with beta-thalassemia major who developed acute heart failure, with severe systolic dysfunction, resulting from iron overload. Combined iron chelation with desferrioxamine and deferiprone together with standard cardiological treatment induced prompt and complete restoration of the cardiac function.

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Patients affected by beta-thalassemia major need transfusions of concentrated red blood cells (RBC) every 2-4 weeks throughout their lifetimes. This treatment leads to progressive iron overload in all tissues and subsequent cardiac, hepatic and endocrine damage. Cardiac disease occurs in the first decade of life in thalassemic patients undergoing transfusion therapy without chelation treatments. Thus, these patients must be treated with iron chelating agents from the first years of life. For decades the only chelating drug utilized was desferrioxamine (DFO) by subcutaneous infusion lasting almost 10 hours/day. During the last decades, improvement of either transfusional and chelation schemes or management of disease complications drastically improved beta-TM life expectancy.^{1,2} Nevertheless, heart failure (HF) and fatal arrhythmias due to iron overload are still the main cause of death.^{3,4}

Continuous intravenous DFO treatment is reported to revert cardiac damage by uninterrupted chelation of circulating non-transferrin bound iron, which is very toxic.^{5,6,7} More recently the new oral chelating agent deferiprone (L1) has become available for patients for whom DFO therapy is contraindicated or inadequate.

It has recently been suggested that L1 achieves superior penetration of myocardial cells^{8,9} and that a synergistic effect of the two drugs exists.^{10,11,25}

Little is known about the role of the combined therapy with the two chelators in patients with symptomatic heart failure.

We describe a case of prompt and complete restoration of the cardiac function in a young patient with beta-thalassemia major who developed severe heart failure treated with combined iron chelation.

Case Report. A 25 year-old male with transfusion-dependent beta-TM was admitted to the Cardiological Semintensive Unit for the abrupt onset of NYHA class IV HF in September 2003. The patient was regularly transfused with RBC since the age of 12 months (mean Hb value = 10 g/dL). Chelation treatment with subcutaneous (s.c.) DFO 20 to 50 mg/kg over 10 hours daily was started when he was 3 years old. By the age of 14, however, a poor compliance to DFO resulted in steadily increased serum ferritin levels (median: 2500 µg/L, range: 1043-3970 µg/L, normal: 30-400 µg/L). Indeed, in March 2001 Superconducting Quantum Interference Device (SQUID) demonstrated a severe hepatic iron overload (2032 µg iron/g liver wet weight; normal < 400 µg iron/g liver wet weight; severe > 2000 µg iron/g liver wet weight). During the last year before admission, after the abrupt onset of diabetes mellitus, the patient's compliance to DFO improved, resulting in ferritin levels decrease (median: 1124 µg/L, range 803-1263 µg/L) and hepatic iron overload reduction, as detected by SQUID (1383 µg iron/g

liver wet weight = moderate overload). Serial cardiological evaluations before admission displayed only unspecific S-T alterations at electrocardiography (ECG), and mild increase of left ventricular (LV) telediastolic diameter indexed to body surface with a borderline LV ejection fraction (EF) (55%) at echocardiogram (ECHO).

At entry, the patient complained dyspnea on minimum exertion. Physical exam showed peripheral edema, pulmonary congestion, mild hepatomegaly, and 11% weight gain.

ECG showed sinus tachycardia, negative T waves in V2 to V6 and in D1-aVL. ECHO displayed increased LV telediastolic diameter, diffuse LV hypokinesia and severe systolic function reduction with 15% LVEF, severe mitral regurgitation and a restrictive diastolic pattern. Cardiac magnetic resonance imaging (MRI) performed with SIR method (Signal Intensity Ratio heart/muscle) Figura 1 and SQUID showed a severe cardiac iron overload with low hepatic burden.

Viral myocarditis, thyroid disorders, autoimmune diseases or exposure to cardiotoxic agents were reasonably excluded as causative factors: the patient was afebrile, without signs or symptoms of current or recent infection; he did not report chest pain. All hematochemical parameters were normal, in particular markers of inflammation were negative and he had no lymphocytosis or neutropenia; he was euthyroid and not significantly anaemic; creatine phosphokinase MB-isoform levels were not elevated; the patient was questioned carefully about recent cardiotoxic medication or illicit drug use.

Considering the severe conditions and prognosis the patient was considered for heart transplantation.

The patient was treated according to the guidelines for HF with ACE-inhibitors and diuretics; low-dose carvedilol was added from the third day. Intravenous chelation with continuous infusion of DFO 40 mg/kg/day was promptly initiated. Six days after the first i.v. DFO administration, L1 75 mg/kg/day p.o. was added. Figure 2.

During hospitalization, the patient was transfused with RBC to keep hemoglobin levels > 9 g/dL.

Progressive normalization of pulmonary findings and significant weight loss were progressively recorded. At discharge, 20 days after admission, clinical conditions were steadily improved and LVEF was 34%. Cardiological therapy with oral furosemide 75 mg/day, carvedilol 12.5 mg/day, captopril 75 mg/day, digoxin 0.25 mg/day, spironolactone 25 mg/day, L1 75 mg/kg/day and continuous s.c. infusion of DFO 50 mg/kg/day were continued Figure 2.

During follow-up a dramatic clinical improvement was observed and ferritin levels rapidly declined finally reaching a plateau (<300 µg/L) in March 2004 (month +7), when a peak in urine iron excretion was observed (52688 µg/24 h, normal: 3-98 µg/24 h). fig 2 At that time, diuretics and digoxin were withdrawn for further cardiological improvement. Steadily low ferritin levels and gradual urine iron excretion reduction allowed progressive DFO tapering. In October 2004 (month +13), DFO was suspended and L1 alone was continued. At that time ECHO was further ameliorated (LVEF 67%), and cardiac MRI showed significant cardiac iron burden reduction as compared to diagnosis. Figure 1,2 In February 2006, 29 months after the occurrence of acute HF, the patient is doing well with moderate physical activity under ramipril 5 mg/day, carvedilol 12.5 mg/day (no further increase was accomplished for detection of 1° AV block at Holter monitoring) and L1 75 mg/kg/day Figure 2.

Discussion. Cardiac disease due to iron overload is still the most common cause of death in beta-thalassemic

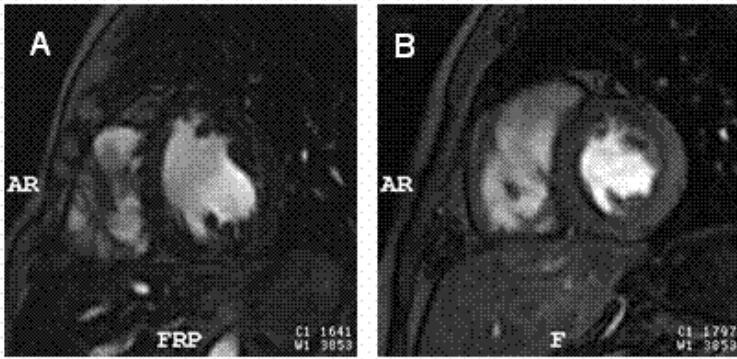


Figure 1. Cardiac MRI at onset of heart failure **A** and one year later **B** recovery of signal intensity of myocardium indicates a marked reduction in cardiac iron overload.

major patients. The drug currently used in these cases is intravenous DFO which can reverse some cases of hemosiderotic HF.^{5,6,16-18,23} Oral L1 is reported to be more effective than DFO in removal of myocardial iron^{5,8,9} and it is suggested that the two chelators have a synergistic effect through iron shuttling (L1 easily enters cells, including myocytes, and is subsequently able to transfer the intracellularly chelated iron to the stronger iron chelator, DFO, in the plasma).^{5,19} In two recent wide studies, L1 therapy is associated with a significantly greater cardiac protection than DFO in patients with thalassemia major.²⁴⁻²⁶

Considering that cardiac MRI of our patient was consistent with severe cardiac iron overload and HF developed despite optimal compliance to the DFO based chelation strategy, the off-label combination (following patient's consent) of L1 appeared justified. The treatment induced a drastic iron depletion and a rapid recovery of the severe HF in few weeks, with a persistent excellent clinical situation after more than two years.

After discharge we opted for the 24 h/24 subcutaneous route of infusion of DFO which has an efficacy equivalent to 80% of the intravenous one. This has avoided the positioning of a CVC which has an high incidence of infective and thrombotic complications.²⁰ The intermediate doses of both chelators used in the schedule maintained the drug's capacity to decrease cardiac iron excess, avoiding dose-related toxicity. The chelating therapy did not cause significant side effects (two episodes of mild

neutropenia, rapidly reversed by a brief interruption of L1).

In beta-thalassemia the HF generally occurs more frequently and at a younger age in patients with poor compliance to DFO and consequent high values of ferritin, but, like in this case, it can occur also with moderate levels of ferritin because some patients have predisposition to amass higher iron amounts in the heart than in other organs and/or because an ameliorated compliance to DFO reduces the iron in the heart more slowly than in other organs.²³ Indeed, a HF in a thalassemic must be always supposed of siderotic origin, even if a date of cardiac MRI is not available. However, it would be very useful to have diagnostic tools to quantify cardiac siderosis for therapeutic decisions, also in the periodic follow-up of thalassemic patients without evident cardiopathy.

Viral myocarditis was considered as a possible underlying condition explaining HF in this patient; however, it was excluded since inflammatory markers were negative, the patient had no chest pain and had no signs of flu-like syndrome before onset. We did not perform an endomyocardial biopsy because, in our opinion, it was not necessary to subject the patient to an invasive exam which would have not changed our therapeutic strategies; moreover, the utility of endomyocardial biopsy is controversial because of the possibility of a high false-negative result rate and because there is no proven therapy, even when a positive biopsy is obtained.

To conclude, a single case does not allow to define in a

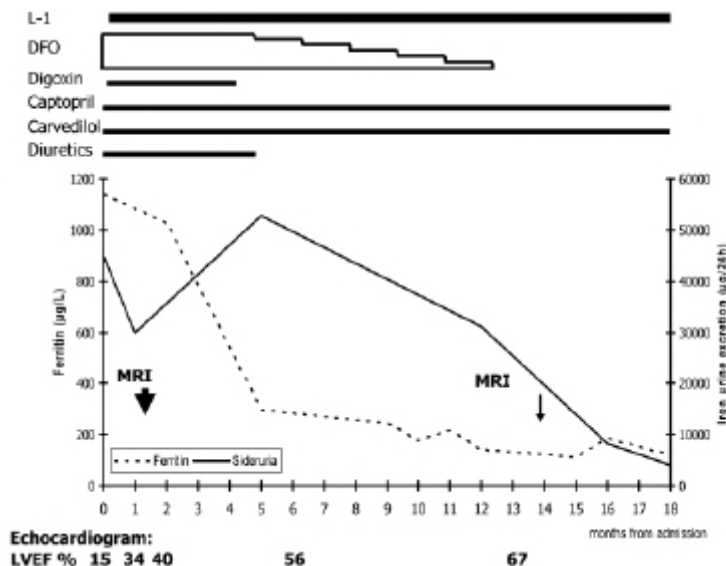


Figure 2. Cardiological findings, iron kinetics, and treatment: LVEF and cardiac iron overload measured by MRI improve concomitantly with reduction of ferritin levels and a peak of sideruria; the initially intensive cardiological and chelating therapy is progressively reduced (large arrow indicates high cardiac iron overload and small arrow low cardiac iron overload).

specific way the role of L1 in association with continuous DFO, but, in absence of controlled clinical studies, single reports of severe cardiopathy treated with combined therapy can be useful.

It is possible that L1 could represent a specifically useful addition in the treatment of cardiac complication in thalassemia, but this has not been clarified. A plurality of protocols with different schedule of associations DFO/L1 have been proposed (i.e. sequential or combined) but, up to now, there are not conclusive studies. The prospective randomized comparison of the benefit/risk profile of available preventive or therapeutic options is certainly the mandatory tool to provide a reliable answer.

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