Combination therapy of deferasirox and deferoxamine shows significant improvements in markers of iron overload in a patient with β-thalassemia major and severe iron burden

Ersi Voskaridou, Veroniki Komninaka, Antonis Karavas, Evangelos Terpos, Vasilis Akianidis, and Dimitrios Christoulas

BACKGROUND: Iron overload is a common complication of patients with β-thalassemia major (TM). Despite the availability of three iron chelators, deferoxamine (DFO), deferiprone (DFP), and deferasirox (DFX), some patients fail to respond adequately to monotherapy with any of them. We report a case of TM who had refractory severe iron overload and was successfully and safely chelated with the combination of DFX with DFO.

CASE REPORT: A 40-year-old male with β-TM, who had been regularly transfused from the age of 2, had been administered in the past iron chelation with DFO, DFP, and DFX monotherapy, without major improvement on his iron overload status. Liver and cardiac magnetic resonance imaging (MRI) revealed severe iron overload, while serum ferritin was persistently greater than 2500 μg/L. After the patient gave informed consent, he was administered combination therapy of DFX at 30 mg/kg/day for 7 days per week and DFO at 2500 mg/day for 4 days every week and routinely followed up for compliance.

RESULTS: Eighteen months later, serum ferritin was reduced to 680 μg/L, while both liver and cardiac MRI T2* values improved, reflecting lower iron overload. The combination regimen was well tolerated and no adverse events were documented.

CONCLUSION: This is the first official report of simultaneous daily administration of the two iron chelators DFX and DFO that demonstrates the beneficial effect of the combination on heart and liver hemosiderosis. If our observation is confirmed in more patients, this combination could constitute a useful option in tailoring individual chelation therapy for β-TM patients with iron overload.

Iron overload is a common complication of patients with β-thalassemia major (β-TM) mainly resulting from frequent blood transfusions. Without adequate iron chelation therapy, the majority of β-TM patients will eventually accumulate potentially fatal iron levels leading to cardiac disease, liver disease (cirrhosis, hepatocellular carcinoma) and endocrine abnormalities. Deferoxamine (DFO) has been the standard of care for more than 40 years doubling the average life span of patients, although the administration through subcutaneous infusions negatively affects patients' compliance.[1] The available oral iron chelators deferiprone (DFP) and deferasirox (DFX) have shown to be effective in reducing iron burden, simultaneously improving compliance and patients' quality of life.[2,3] The combination of DFP with DFO has been used to increase the efficacy and induce negative iron balance in some patients with severe iron overload.[4] However, there are very limited data reported in the literature regarding combination therapy of DFX with DFO. We report a case of β-TM who had refractory severe iron

ABBREVIATIONS: DFO = deferoxamine; DFP = deferiprone; DFX = deferasirox; LIC = liver iron concentration; MRI = magnetic resonance imaging; TM = thalassemia major.

From the Thalassaemia and Sickle Cell Disease Reference Centre, Laikon General Hospital; the Thalassaemia Unit, Korgialeneio Benakeio Hospital; the Department of Clinical Therapeutics, University of Athens School of Medicine; Medical Advisor of Novartis Hellas SACI; and the Department of Hematology, 251 General Air Force Hospital, Athens, Greece.

Address reprint requests to: Ersi Voskaridou, MD, Thalassaemia and Sickle Cell Disease Reference Centre, Laikon General Hospital, 16, Sevastoupoleos Street, Ampelokipoi, 11526 Athens, Greece; e-mail: ersi.voskaridou@gmail.com.

Received for publication April 18, 2013; and accepted June 2, 2013.

doi: 10.1111/trf.12335

TRANSFUSION 2014;54:646-649.

overload and was successfully and safely chelated with this combination.

CASE REPORT

A 40-year-old male with β-TM (IVSI-110/IVSI-110) had been regularly transfused with 2 units of red blood cells (RBCs), every 30 days, from the age of 2 until the age of 20 years. The transfusion rate was then increased due to massive splenomegaly to 3 units of RBCs every 20 days until the age of 25 years, when the patient had splenectomy. Thereafter, he has been placed on a transfusion scheme consisting of 2 units of RBCs, every 20 days. The patient had been administered in the past iron chelation monotherapy with DFO or DFP but with poor compliance due to administration issues for DFO and gastric discomfort for DFP. He was then started on DFX monotherapy, at a dose of 20 mg/kg/day, without major improvement on his iron overload status, even when DFX dose was escalated to 30 mg/kg/day, although there were concerns about his compliance. Liver and cardiac magnetic resonance imaging (MRI) revealed T2* values of 0.55 and 5.8 msec, respectively (both indicative of severe iron overload; normal values of heart T2* are >20 msec). The estimated liver iron concentration (LIC) by MRI was 46.4 mg Fe/g dry weight, while serum ferritin was persistently greater than 2500 µg/L. MRI was performed as previously described.[5] It has been reported that serum ferritin values greater than 2500 µg/L are associated with increased cardiac complications[6] while LIC values greater than 15 mg Fe/g dry weight with increased risk of liver fibrosis, liver dysfunction, and premature death.[7,8] The severity of iron overload necessitated the administration of an intensive iron chelation regimen to which the patient could adhere. After informed consent and approval from the Hospital Ethics Committee was received, the patient was administered combination therapy of DFX at 30 mg/kg/day for 7 days per week and DFO at 2500 mg/day for 4 days every week. The patient was routinely followed up for compliance. Eighteen months later, serum ferritin was reduced to 680 µg/L, while both liver and cardiac MRI T2* values improved (2.5 and 10.2 msec, respectively; the estimated LIC was 12.3 mg Fe/g dry weight), reflecting lower iron overload (Fig 1). DFO was then discontinued due to patient's will. He continued on DFX monotherapy with further improvement of iron overload status after 6 months. (The liver and cardiac MRI T2* were 2.4 and 12.6 msec, respectively; the estimated LIC was 10.4 mg Fe/g dry weight.) The combination regimen was well tolerated and no adverse events were documented. Full blood count was monitored every 15 days, while serum cystatin-C and serum creatinine along with proteinuria and creatinine clearance were monitored monthly, to early identify any renal toxicity. No differences from baseline values were detected (Table 1). There was no gastrointestinal discomfort, decrease in creatinine clearance, elevation of serum creatinine, or skin reactions during combined therapy.

DISCUSSION

Despite the availability of three iron chelators, some patients fail to respond adequately to monotherapy with any of them. Combination therapy, consisting of the use of any two chelators on the same day, has been introduced to increase the efficacy and to induce negative iron balance in patients with severe toxic iron levels. Extensive long-term experience has shown that combined chelation with DFP and DFO rapidly reduces liver iron, serum ferritin, and myocardial siderosis; improves cardiac function; reverses and prevents endocrine complications; reduces cardiac mortality; and improves survival.[9,10] The combination of DFX and DFO has also been used both in the preclinical and in the clinical setting.[11-13] The clinical studies have demonstrated that the combination of DFX and DFO induces negative iron balance and a decrease in serum ferritin but there is no information about the effect in iron concentration in the liver or the heart. To the best of our knowledge this is the first official report of simultaneous daily administration of the two iron chelators DFX and DFO that demonstrates the beneficial effect of the combination on heart and liver hemosiderosis, as documented by both MRI and serum ferritin levels. Our patient was treated with the two drugs simultaneously and this combination was shown to be efficacious and very safe for this patient.

In a recent study by Grady and colleagues[13] infusing DFO daily was more effective than using DFX in most patients, despite patient-to-patient variability. Nevertheless, the adherence to the use of DFO is a major issue in the management of TM patients. The reduction of chelation to 3 or 4 days each week could sound attractive to many patients, but this approach would allow non–transferrin-bound iron to accumulate in the plasma when no iron chelator is present. To avoid this situation (increased deleterious effects of non–transferrin-bound iron and LPI), DFX could be taken daily, supplemented with DFO four times a week, like in our patient, preferably on alternate days to minimize injection-related side effects, still providing continuous chelation (almost 24 hr each day). It is difficult to establish from a single case the possible mechanism for the efficacy of this combined regimen. It is suggested that daily use of both drugs might have a synergistic (like the "shuttle" effect of the DFX-DFP combination) or additive effect,[13] but this could only be determined by a randomized clinical trial. If our observation is confirmed in more patients, the combination of DFO and DFX could constitute a useful option in tailoring individual chelation therapy for β-TM patients with iron overload.

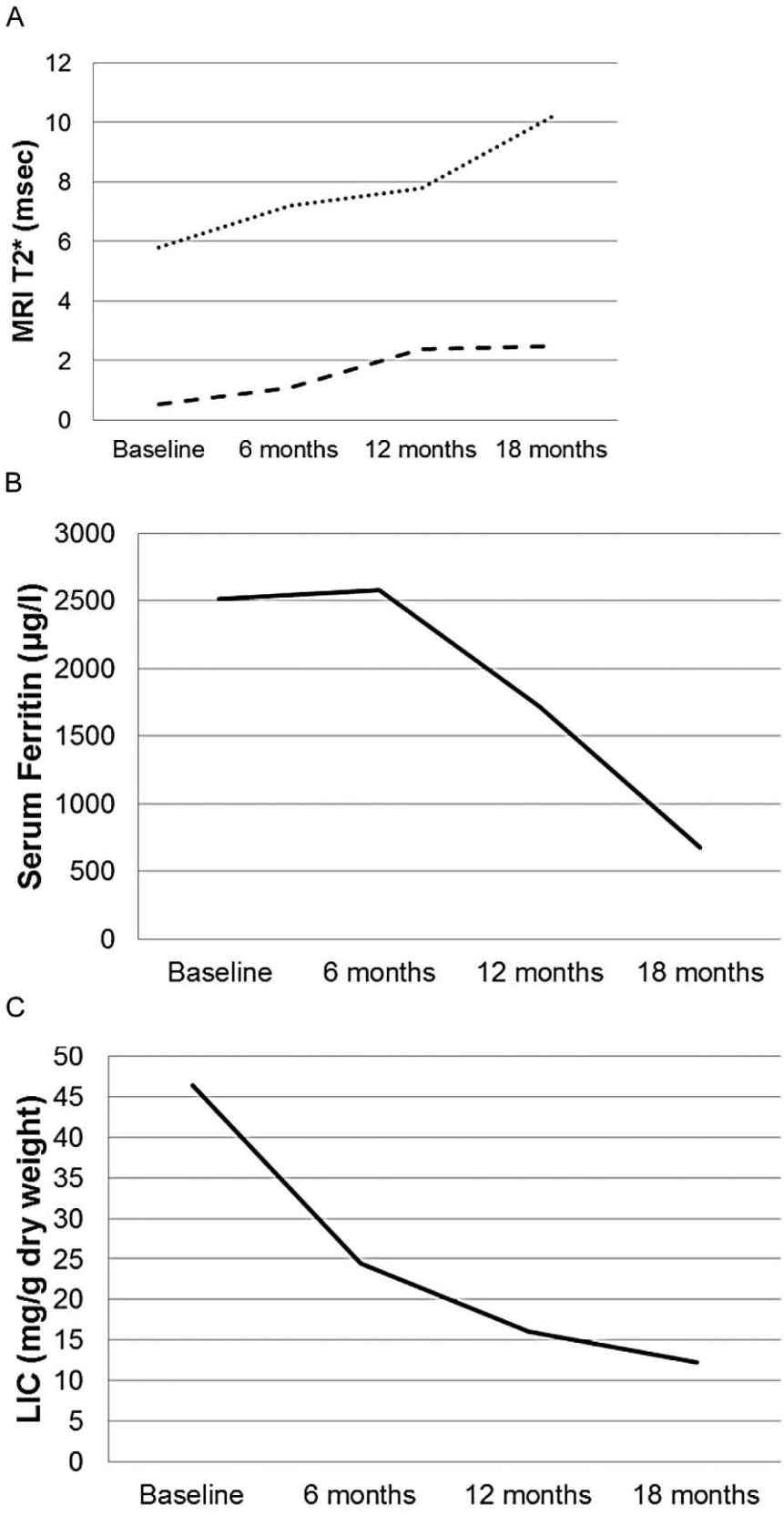

Fig. 1. MRI, ferritin levels, and LIC during treatment. The figure shows the rapid increase of both liver (– –) and heart (·····) MRI T2* (A) and the dramatic reduction of ferritin levels (B) and LIC (C) after 18 months of combined (DFX and DFO) therapy.

TABLE 1. The patient's characteristics at baseline and after 18 months of combined (DFX and DFO) therapy

Characteristics	Baseline	After 18 months
Hb (g/dL)	9.5	11.6
Ferritin (μg/L)	2515	681
Serum creatinine (mg/dL)	0.8	0.9
Serum cystatin (mg/L)	0.7	0.8
Proteinurea (mg/24 hr)	100	40
Creatinine clearance (mL/min/1.73 m^2)	118	101
Aspartate transaminase (u/L)	20	16
Alanine transaminase (u/L)	16	12
Gammaglutamyl transferase (u/L)	46	46
Bilirubin (mg/dL)	2.25	2.53
Alkaline phosphatase (u/L)	210	86
MRI T2* liver (msec)	0.55	2.5
MRI T2* heart (msec)	5.8	12.6
Estimated LIC (mg/g dry weight)	46.4	10.2

ACKNOWLEDGMENTS

The authors thank Maria Tsalkani and Vasiliki Grigoriou for checking the patient's compliance and collecting data.

CONFLICT OF INTEREST

The authors have no conflicts to declare.

REFERENCES

1. Delea TE, Edelsberg J, Sofrygin O, Thomas SK, Baladi JF, Phatak PD, Coates TD. Consequences and costs of noncompliance with iron chelation therapy in patients with transfusion-dependent thalassemia: a literature review. Transfusion 2007;47:1919-29.
2. Meerpohl JJ, Antes G, Rücker G, Fleeman N, Motschall E, Niemeyer CM, Bassler D. Deferasirox for managing iron overload in people with thalassaemia. Cochrane Database Syst Rev 2012;(2):CD007476.
3. Roberts DJ, Brunskill SJ, Doree C, Williams S, Howard J, Hyde CJ. Oral deferiprone for iron chelation in people with thalassaemia. Cochrane Database Syst Rev 2007;(3): CD004839.
4. Galanello R, Agus A, Campus S, Danjou F, Giardina PJ, Grady RW. Combined iron chelation therapy. Ann N Y Acad Sci 2010;1202:79-86.
5. Voskaridou E, Douskou M, Terpos E, Papassotiriou I, Stamoulakatou A, Ourailidis A, Loutradi A, Loukopoulos D. Magnetic resonance imaging in the evaluation of iron overload in patients with beta thalassaemia and sickle cell disease. Br J Haematol 2004;126:736-42.
6. Olivieri NF, Brittenham GM. Iron chelating therapy and the treatment of thalassaemia. Blood 1997;89:739-61.
7. Olivieri NF. The β-thalassemias. N Eng J Med 1999;341:99-109.
8. Jensen PD, Jensen FT, Christensen T, Nielsen JL, Ellegaard J. Relationship between hepatocellular injury and transfusional iron overload prior to and during iron chelation with desferrioxamine: a study in adult patients with acquired anemias. Blood 2003;101:91-6.
9. Farmaki K, Tzoumari I, Pappa C, Chouliaras G, Berdoukas V. Normalisation of total body iron load with very intensive combined chelation reverses cardiac and endocrine complications of thalassaemia major. Br J Haematol 2010;148: 466-75.
10. Tanner MA, Galanello R, Dessi C, Smith GC, Westwood MA, Agus A, Pibiri M, Nair SV, Walker JM, Pennell DJ. Combined chelation therapy in thalassemia major for the treatment of severe myocardial siderosis with left ventricular dysfunction. J Cardiovasc Magn Reson 2008;10:12.
11. Otto-Duessel M, Brewer C, Gonzalez I, Nick H, Wood JC. Safety and efficacy of combined chelation therapy with deferasirox and deferoxamine in a gerbil model of iron overload. Acta Haematol 2008;120:123-8.
12. Jetsrisuparb A, Komvilaisak P, Wiangnon S, Jetsrisuparb C. Retrospective study on the combination of desferrioxamine and deferasirox for treatment of iron-overloaded thalassemic patients: first evidence of more than 2 years. J Pediatr Hematol Oncol 2010;32:400-3.
13. Grady RW, Galanello R, Randolph RE, Kleinert DA, Dessi C, Giardina PJ. Toward optimizing the use of deferasirox: potential benefits of combined use with deferoxamine. Haematologica 2013;98:129-35.