Association of phlebotomy and subcutaneous bolus injection of deferoxamine for the treatment of anemic patients with iron overload

We studied the efficacy of the association of bimonthly phlebotomy and twice daily subcutaneous bolus injection of deferoxamine (DFO) in 5 anemic patients with iron overload. This protocol was well tolerated and serum ferritin levels normalized in all patients after a median of 14 months of treatment.

Phlebotomy is the most rapid and effective technique to remove iron from the body and is the mainstay treatment in patients with disorders of iron overload, such as hereditary hemochromatosis (HH). However, anemic patients with concomitant iron overload are not able to tolerate frequent phlebotomies.[1] In such patients, chelation therapy with deferoxamine mesylate (DFO), alone or associated with phlebotomy, can be used in order to deplete excess body iron.[2,3] Unfortunately, since DFO has a short half-life and is poorly absorbed by the gastrointestinal tract, it must be administered parenterally, usually by daily subcutaneous continuous infusion over 8 to 12 hours using a battery-operated portable pump. As DFO infusion therapy is very demanding for the patients and requires high patient compliance, in the last few years the search for new chelators or improved methods of administering old ones has been underway.[1,4,5]

In this study we tested the association of phlebotomy and twice-daily subcutaneous bolus injection of deferoxamine in 5 anemic patients (4 patients with β-thalassemia trait and 1 patient with hereditary spherocytosis) with histologically proven iron overload and heterozygosity for mutations in the HFE-1

Table 1. Patients' characteristics at diagnosis.

	Patients				
	#1	#2	#3	#4	#5
Sex	M	F	M	M	M
Age	47	64	62	54	42
Anemia	β-thal	β-thal	β-thal	β-thal	Spher
Hb (g/dL)	10.3	12.2	11.3	12.4	13.1
RBC ($\times 10^{12}$/L)	4.12	5.76	5.53	4.93	3.97
MCV (fL)	76	71	73	75	85
Transferrin saturation (%)	98	87	64	61	78
Ferritin (μg/mL)	4398	692	1412	1600	2360
β-globin genotype mutations	CD 39	IVSI:110	IVS1:110	IVS1:110	–
HFE genotype					
C282Y	-/-	-/-	-/-	-/-	+/-
H63D	+/-	+/-	+/-	+/-	-/-
Liver biopsy	C, 4	F, 3	F, 4	F, 3	F, 4
ALT (U/L)	87	29	37	62	83
UIE after DFO bolus (μg/48 h)	24280	2325	4860	3600	6200
UIE after DFO infusion (μg/48 h)	22570	2625	4540	3830	6700

β-thal, heterozygous β-thalassemia; Spher, hereditary spherocytosis; Hb, hemoglobin; C, cirrhosis; F, fibrosis; 3-4, grade of hepatic siderosis; ALT, alanine aminotransferase; UIE, urinary iron excretion; DFO, deferoxamine. Normal values: ALT 15-45 U/L; transferrin saturation < 45%; ferritin 30-250 μg/L.

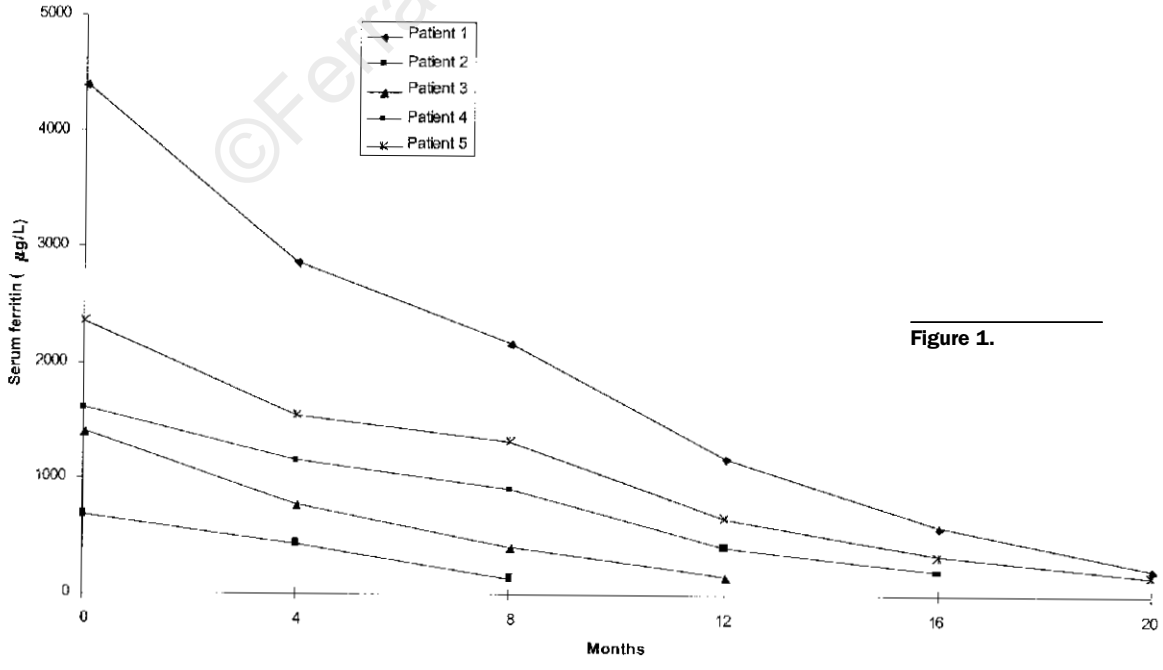

Figure 1.

gene. All the patients were seen at our city hospital between November 1998 and December 2000 and all were negative for antibodies to hepatitis C virus and for hepatitis B virus surface antigen. None of them was on chelation therapy before starting the protocol. The patients underwent bimonthly phlebotomy (each of 350 mL of whole blood) and received oral folic acid supplementation (5 mg/die). They also received 30 mg/kg of body weight per day of DFO administered by subcutaneous bolus injection in 2 separate doses given 12 hours apart 5 days a week. Before starting the DFO administration, a 48-hour DFO-induced urinary iron excretion after DFO subcutaneous bolus injection and after DFO subcutaneous continuous infusion for 12 hours with a battery-powered syringe pump was recorded in order to be able to compare and evaluate the short term efficacy of the bolus method versus the conventional continuous infusion method. When serum ferritin levels returned within normal range (30 - 250 μg/L), the patients underwent maintenance therapy only with phlebotomy and its frequency was established on the basis of serum ferritin levels. The patient's characteristics at diagnosis and their urinary iron excretion after the subcutaneous bolus or infusion test of deferoxamine are shown in Table 1. The mean 48-h DFO-induced urinary iron excretion after bolus injection of DFO and after continuous infusion was similar (8253 μg/48 h vs. 8053 μg/48 h, p = NS). Patient #1, a male aged 47 with β thalassemia trait and heterozygous for the His63Asp mutation in the HFE-1 gene, had, at diagnosis, skin pigmentation, clinically manifested pituitary hypogonadism and increased serum alanine aminotransferase (ALT) levels. Liver biopsy showed liver cirrhosis due to iron overload with marked deposition of hemosiderin granules within hepatocytes and Kuppfer cells (grade 4 siderosis). The return of serum ferritin levels within normal range, after 20 months of treatment, was associated with an improvement of endocrine function and ALT normalization. Liver function tests normalized also in patients #4 and 5, the former with β thalassemia trait and heterozygous for His63Asp mutation and the latter with hereditary spherocytosis and heterozygous for Cys282Tyr mutation, respectively after 14 and 16 months of combination therapy. Patient #3 complained of mild redness and pain at the injection site during the bolus test. These symptoms disappeared rapidly after the injection and did not reappear with further injections. Figure 1 reports the serum ferritin decrease during the combined treatment of phlebotomy and DFO. The association of bimonthly phlebotomies and twice daily subcutaneous injections of deferoxamine was well tolerated and rapidly reduced excess iron in our patients after a median of 14 months (range 6-16 months) of treatment. The return of serum ferritin levels within normal range was also accompanied with ALT normalization in patients with abnormal liver function tests at diagnosis. From our experience, we think that bimonthly phlebotomy and subcutaneous bolus injection of deferoxamine could be a valid therapeutic procedure for those iron overloaded patients with coexistent anemia who are unable to tolerate an aggressive phlebotomy program.

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