Haematologica 2000; 85:865-867
case of the month

Red Cells & Iron

Juvenile hemochromatosis associated with β-thalassemia treated by phlebotomy and recombinant human erythropoietin

MARCO DE GOBBI, PAOLO PASQUERO, FRANCO BRUNELLO,* PIERO PACCOTTI, UMBERTO MAZZA, CLARA CAMASCHELLA

*Dipartimento di Scienze Cliniche e Biologiche, Università di Torino, Azienda Ospedaliera S. Luigi, Orbassano, Turin; * U.O.A. Gastroenterologia, Azienda Ospedaliera S. Giovanni Battista, Turin, Italy*

ABSTRACT

Juvenile hemochromatosis is a rare genetic disorder that causes iron overload. Clinical complications, which include liver cirrhosis, heart failure, hypogonadotropic hypogonadism and diabetes, appear earlier and are more severe than in HFE-related hemochromatosis. This disorder, therefore, requires an aggressive therapeutic approach to achieve iron depletion. We report here the case of a young Italian female with juvenile hemochromatosis who was unable to tolerate frequent phlebotomy because of coexistent β-thalassemia trait. The patient was successfully iron-depleted by combining phlebotomy with recombinant human erythropoietin.
©2000, Ferrata Storti Foundation

Key words: hemochromatosis, thalassemia, phlebotomy, rHuEPO

Regular phlebotomy is the treatment of choice for primary iron overload, since it is safe, cost-effective and easy to perform.[1] However, a minority of patients cannot undergo the desired phlebotomy program because of low hemoglobin levels. Iron chelation by desferrioxamine is usually the treatment of choice in these patients. Recombinant human erythropoietin (rHuEPO) has been used in selected patients with secondary iron overload induced by administration of excessive doses of iron[2,3] or complicated by coexistent anemia.[4,5] The aim of this treatment was to increase erythropoiesis in order to allow phlebotomy treatment.

Here we describe a patient affected by a severe form of juvenile hemochromatosis (JH) and heterozygous β-thalassemia who was unable to tolerate regular phlebotomy, but was successfully iron-depleted by combined treatment with phlebotomy and rHuEPO.

Case report

A 25-year old female was admitted to our Department because of weakness, fatigue, secondary amenorrhea and liver dysfunction. A partial description of this case has been reported elsewhere.[6] Physical examination revealed skin pigmentation, frequent premature heart beats and enlarged liver and spleen. Blood tests showed hypochromic microcytic anemia: Hb was 105 g/L, RBC 5.45x10^{12}/L, MCV 64.7 fL and MCH 19.7 pg. Hemoglobin A_2 was 6%. Iron parameters and liver function tests are reported in Table 1. The biopsy showed a cirrhotic liver with heavy iron deposition both in hepatocytes and in Kupffer cells.

Holter electrocardiogram recording revealed atrial and ventricular premature beats; at echocardiography ejection fraction was normal and the heart was not enlarged. Endocrine evaluation revealed hypogonadotropic hypogonadism (undetectable FSH and LH levels and lack of response to the GnRH test) and subclinical adrenal insufficiency (low basal urine free cortisol, low levels of dehydroepiandrosterone, ACTH and absence of ACTH response to insulin-induced hypoglycemia). An oral glucose tolerance test revealed impaired carbohydrate tolerance. Free thyroid hormones and TSH were normal.

Analysis of C282Y and H63D mutations of the HFE gene gave negative results and genetic studies excluded a linkage to chromosome 6p, where the HFE gene resides.[6] On this basis JH was diagnosed.

Replacement corticosteroid and estro-progesterone therapy was given. A therapeutic program based on 200 mL weekly phlebotomy was planned, associated with desferrioxamine (1 g i.m. daily). However, due to concomitant β-thalassemia, the scheduled program was not completed. Phlebotomy was stopped when the patient's Hb dropped to less than 100 g/L; in addition, the patient's compliance with iron chelation treatment was unsatisfactory. Fourteen months later, after 30 phlebotomies (200 mL volume), the total volume of blood removed was 6,150 mL and the total iron removed (corrected for the degree of anemia) was 2,084.15 mg. To accelerate iron depletion, after informed consent, rHuEPO (150 U/kg subcutaneously twice per week) was added. During the following twenty-four months 88 phlebotomies (350 mL each) were performed. A further 10,755.55 mg of iron were removed. Overall, the total volume of blood removed was 35,850 mL and the total iron removed was 12,839.7 mg. The course of the levels of Hb serum ferritin and iron removed are illustrated in Figure 1. No adverse effects due to rHuEPO were observed.

Iron parameters and liver function tests at the end of treatment are reported in Table 1. After treatment glucose intolerance improved, but hypogonadism

Correspondence: Clara Camaschella, M.D., Dipartimento di Scienze Cliniche e Biologiche, Azienda Ospedaliera S. Luigi,10043 Orbassano, Turin, Italy. Phone: international +39-011-9026610 – Fax: international +39-011-9038636 – E-mail: camaschella@ope.net

Table 1. Iron parameters and hepatic evaluation before and after treatment.

	At diagnosis	*After treatment*
Serum iron (μmol/L)	40.1	24.9
Serum transferrin saturation	100%	40%
Serum ferritin (μg/L)	3768	51
AST (U/L)	130	32
ALT (U/L)	94	26
γGT (U/L)	51	22
AlPh (U/L)	147	66
HIC (μmoL/g/liver dry weight)	55.8	3.13
HII (HIC/age)	2.7	0.11
Histology	cirrhosis	cirrhosis
Perls' Prussian staining	4+	-

HIC = hepatic iron concentration; HII = hepatic iron index.

continued to require specific therapy. A repeat liver biopsy confirmed liver cirrhosis but showed disappearance of iron deposition.

Discussion

Criteria for the diagnosis of JH are based on the age at presentation (before 30 years) and evidence of severe iron overload in the absence of mutations in the HFE gene. The clinical complications of iron overload include endocrine failure, especially hypogonadotropic hypogonadism and diabetes, cardiac disease, as defined by heart failure and/or left ventricular dilatation with low ejection fraction or arrhythmias requiring medical treatment and liver involvement.[7] Genetic evidence indicates that JH is a disorder distinct from HFE 6 and mapping to chromosome 1q.[8]

The earlier development of severe complications in JH, as compared to hemochromatosis,[9] reflects greater tissue iron deposition.[10] As a consequence this disorder requires aggressive therapy which was hindered in our patient by coexistent β-thalassemia. We may speculate that the ineffective erythropoiesis associated with β-thalassemia contributes to a further increase in intestinal iron absorption, although the clinical manifestations in JH patients of comparable ages, not carriers of β-thalassemia, are equally severe.[6,11,12]

Traditional treatment by phlebotomy was unfeasible in our patient. As an alternative to iron chelation we evaluated treatment by rHuEPO associated with phlebotomy.

rHuEpo in patients with β-thalassemia intermedia at doses up to 500-1000 U/Kg x 3 weekly has been shown to increase total Hb in a proportion of cases.[13,14] The only experience available in β-thalassemia trait concerns a few cases with concomitant chronic renal insufficiency. Usually these patients require a higher dosage of rHuEPO to achieve the same Hb levels as non-thalassemic controls.[15]

Treatment with rHuEpo had multiple positive effects in our patient. First, this therapy allowed both the frequency and the volume of venesections to be

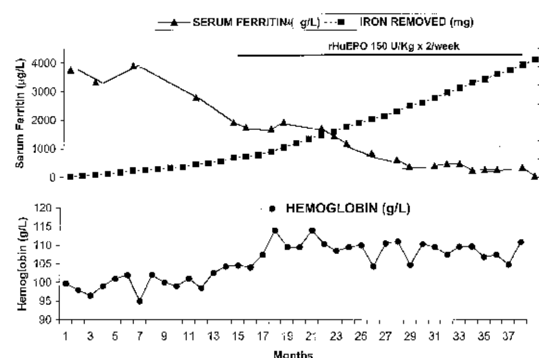

Figure 1. Level course of serum ferritin, hemoglobin and iron removed before and during treatment with rHuEPO.

increased without exacerbating the anemia. In addition, the patient's clinical course indicated that the persistent stimulus to erythroid production provided by the rHuEPO was able to mobilize consistent amounts of iron from parenchymal tissues. To our knowledge this is the first time that this combined treatment has been used to treat severe iron overload associated with heterozygous β-thalassemia; this approach could be of use in other severely iron-loaded anemic patients.

Contribution and Acknowledgments

CC and UM were responsible for the design of the study and writing the paper. MDG was responsible for data collection and analysis. PP, PP and FB followed the patient clinically. All the authors gave their critical contribution to the manuscript. The name order was a joint decision considering the different contributions to the work.

Funding

This work was partially supported by MURST (Ministry of University and Scientific and Technologic Research) 1998.

Disclosures

Conflict of interest: none.

Redundant publications: molecular characterization of this case and a partial description of the clinical phenotype is reported in Camaschella et al., Eur J Hum Genet 1997; 5:371-5. The present paper deals with the patients' treatment. There is only overlap in the description of clinical phenotype. This is clearly stated in the paper.

Manuscript processing

Manuscript received February 21, 2000; accepted May 22, 2000.

References

1. Barton JC, McDonnel SM, Adams PC, et al. Management of hemochromatosis. Ann Intern Med 1998; 129:932-9.
2. Hotta T, Inoue C, Tsushita K, Miura Y, Saito H. Successful treatment of hemosiderosis with regular phlebotomy and recombinant human erythropoietin. Case

report and ferrokinetic studies. Acta Haematol 1991; 86:214-6.
3. Inoue Y, Nakanishi K, Hiraga T, et al. Recovery of pancreatic B-cell function in hemochromatosis: combined treatment with recombinant human erythropoietin and phlebotomy. Am J Med Sci 1997; 314:401-2.
4. Bilgrami S, Bartolomeo A, Synnott V, Rickles FR. Management of hemosiderosis complicated by coexistent anemia with recombinant human erythropoietin and phlebotomy. Acta Haematol 1993; 89:141-3.
5. de la Serna J, Bornstein R, Garcia-Bueno MJ, Lahuerta-Palacios JJ. Iron depletion by phlebotomy with recombinant erythropoietin prior to allogenic transplantation to prevent liver toxicity. Bone Marrow Transplant 1999; 23:95-7.
6. Camaschella C, Roetto A, Cicilano M, et al. Juvenile and adult hemochromatosis are distinct genetic disorders. Eur J Hum Genet 1997; 5:371-5.
7. Camaschella C. Juvenile hemochromatosis. In: Powell LW, ed. Hereditary disease of the liver. Baillière's Clinical Gastroenterology. London: Baillière Tindall; 1998; 12:227-35.
8. Roetto A, Totaro A, Cazzola M, et al. The juvenile hemochromatosis locus maps to chromosome 1q. Am J Hum Genet 1999; 64:1388-93.
9. Camaschella C, Piperno A. Hereditary hemochromatosis: recent advances in molecular genetics and clinical management. Haematologica 1997; 82:77-84.
10. Cazzola M, Cerani P, Rovati A, Iannone A, Claudiani G, Bergamaschi G. Juvenile genetic hemochromatosis is clinically and genetically distinct from the classical HLA-related disorder. Blood 1998; 92:2979-81.
11. Lamon JM, Marynick SP, Roseblatt R, Donnelly S. Idiopathic hemochromatosis in a young female. A case study and review of the syndrome in young people. Gastroenterology 1979; 76:178-83.
12. Cazzola M, Ascari E, Barosi G, et al. Juvenile idiopathic haemochromatosis: a life threatening disorder presenting as hypogonadotropic hypogonadism. Hum Genet 1983; 65:149-54.
13. Nisli G, Kavakli K, Vergin C, Oztop S, Cetingul N. Recombinant human erythropoietin trial in thalassemia intermedia. J Trop Pediatr 1996; 42:330-4.
14. Rachmilewitz EA, Aker M. The role of recombinant human erythropoietin in the treatment of thalassemia. Ann NY Acad Sci 1998;850:129-38.
15. Cheng IK, Lu HB, Wei DC, Cheng SW, Chan CY, Lee FC. Influence of thalassemia on the response to recombinant human erythropoietin in dialysis patients. Am J Nephrol 1993; 13:142-8.

©Ferrata Storti Foundation