To the Editor:

Patients with thalassemia major are considered to have high erythropoietin (Epo) activity. However, Hammond et al reported that thalassemic patients had much less serum Epo activity compared with patients with hypoplastic anemia. Determination of serum Epo levels in 32 patients from our clinic with homozygous β-thalassemia major and intermedia showed that Epo activity was not significantly higher than in normal controls except for the groups of minimally transfused infants who had higher levels, similar to those found in patients with severe aplastic anemia. A low serum Epo level for the degree of the anemia was also found in patients with sickle cell anemia.

Recombinant human Epo (rhuEpo) has been shown to significantly increase red blood cells (RBCs), hemoglobin (Hb), and hematocrit (Hct) in patients with chronic renal failure, both in those who were maintained on hemodialysis and in those not requiring dialysis.

These observations may suggest that rhuEpo could be effective in patients with β-thalassemia intermedia and may result in an increase of 1 to 3 g of Hb, thus improving the quality of life without causing symptoms due to accelerated hematopoiesis. It is also possible that rhuEpo may specifically stimulate synthesis of fetal Hb (HbF).

Three patients with β-thalassemia intermedia were studied (two Arabs and a Kurdish Jew, Table 1). rhuEpo (EPREX) kindly supplied by Cilag AG International (Schaffhausen, Switzerland) was administered in an initial dose of 1,000 U/kg intravenously twice daily, 1 day a week for 2 weeks. One hundred and ten days later, a second course of rhuEpo in a dose of 500 U/kg was administered twice a week for 6 weeks and 1,000 U/kg were administered twice a week for 3 more weeks (Fig 1). Globin chain
synthesis was performed by the method described by Cividalli et al., and the percentage of F reticulocytes and F cells was determined by the method of Dover et al. The samples, together with shipment controls, were sent directly to Dr. G. Dover at Johns Hopkins University Medical School, Baltimore, MD. Serum ferritin levels were determined by the method of Konijn et al. Serum Epo levels were determined in vitro by the method of Manor et al.

In all three patients there was a distinct elevation of all three parameters (Hb, Hct, and RBC) when 1,000 U/kg were administered twice daily, 1 day a week for 2 weeks as illustrated for Hb values in Fig 1. These changes were not very obvious during the first period of the second course of rhuEpo. However, when the dose was increased to 1,000 U/kg once a day twice a week, there was a distinct increase in the parameters, particularly in patient Z.A. (Fig. 1). In the other two patients, the changes noted were less significant. Following the discontinuation of rhuEpo, the erythroid parameters decreased in all three patients. There were no significant changes in the percentage of F cells, F reticulocytes, or HbF or in the synthetic ratio of the globin chains. Therefore, one may conclude that rhuEpo administration did not change significantly (Table 2). Moreover, there were no significant changes in the percentage of both Hbs F and A2 determined several times throughout a 1-year period before, during, and after rhuEpo administration did not change significantly (Table 2). Moreover, there were no consistent changes in the percentage of F cells and F reticulocytes (Table 2). Globin chain synthetic ratios showed no significant changes except for a mild increase in βα synthetic ratio in patient V.A. from 0.24 to 0.44. There were no statistically significant changes in serum Epo and in lactic dehydrogenase (LDH) and uric acid levels determined more than 10 times before, during, and after the trial period.

Serum ferritin ranged without any specific pattern between 400 and 1,200 µg/L in patients Z.A. and V.A. In patient H.M., the pretreatment ferritin levels gradually increased from 585 µg/L to 1,335 µg/L, while serum iron levels decreased from 130 to 70 µg/L with corresponding increases in the serum iron binding capacity. In the other two patients, the variations in serum iron levels were inconsistent. Liver and kidney function tests remained unchanged throughout the trial period.

Patient H.M. had no side effects throughout the trial period. Between the end of July and the beginning of August he had aviral infection that most probably resulted in a temporary decrease in the erythroid parameters. Patient Z.A. had frontal and skull headaches and pain in the ankles and feet that started a few hours after injection of rhuEpo and lasted for periods from a few hours to several days. All these signs and symptoms subsided during the last four injections of rhuEpo (1,000 U/kg). Patient V.A. had similar complaints that lasted up to 36 hours after rhuEpo administration and that aggravated until August 1, 1990. After August 15, 1990, the pain subsided and disappeared towards the end of the trial. It was very difficult to judge from the individuals remarks whether the patients felt better during the trial period.

The results of the preliminary trial of rhuEpo administration to three patients with β-thalassemia intermedia indicate that all patients, particularly Z.A., had released more thalassemic RBC into the peripheral circulation, without any changes in their indices and without evidence for increased RBC turnover and/or hemolysis. Moreover, there were no significant changes in the percentage of F cells, F reticulocytes, or HbF or in the synthetic ratio of the globin chains. Therefore, one may conclude that rhuEpo administration at this dose schedule did not cause increased production of young thalassemic RBC similar to that observed in baboons and in patients with sickle cell anemia after administration of hydroxyurea. Many questions are still unanswered in regards to, primarily, what is the most effective dose, schedule, and mode of administration to achieve a maximal sustained effect. It has been suggested that rhuEpo is helpful only in patients in whom the endogenous serum Epo is less than 500 mU/mL, but a recent report documented a very impressive response to rhuEpo in a patient with human immunodeficiency virus (HIV)-associated anemia when the initial serum EPO levels were 1,340 mU/mL. It is of interest that patient Z.A., who had the lowest endogenous Epo levels (less than 50 mU/mL), seemed to respond better than the other two patients, who had mean values of 150 mU/mL (H.M.) and 160 mU/mL (V.A.).

The question of Epo's effect on iron balance in these iron-overloaded patients remains to be answered. Tissue-bound storage iron may not be used for RBC production, and iron supplementation may be necessary. Another point of concern is what could be the potential long-term side effects on the bone structure due to the possible increase in bone marrow expansion following rhuEpo. These questions as well as the question of a possible synergistic effect of rhuEpo and hydroxyurea will have to be answered by future controlled double blind trials in a large number of carefully selected patients.
REFERENCES


Administration of erythropoietin to patients with beta-thalassemia intermedia: a preliminary trial [letter]

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