ADMINISTRATION OF ERYTHROPOIETIN TO PATIENTS WITH β-THALASSEMIA INTERMEDIA:  
A PRELIMINARY TRIAL

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

Table 1. RBC Parameters and Hb Analysis in Three Patients With β-Thalassemia Intermedia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Hb Mean</th>
<th>Hct Mean</th>
<th>Rct Mean</th>
<th>HbA2 Mean</th>
<th>Supplementary Ratio</th>
<th>β/α</th>
<th>γ/δ</th>
<th>Mutation</th>
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<tbody>
<tr>
<td>Z.A.</td>
<td>M</td>
<td>33</td>
<td>8.2</td>
<td>26.5</td>
<td>3.0</td>
<td>5.0</td>
<td>0.24</td>
<td>0.12</td>
<td>TATA/PolyA</td>
<td></td>
</tr>
<tr>
<td>H.M.</td>
<td>F</td>
<td>24</td>
<td>7.1</td>
<td>22.7</td>
<td>2.0</td>
<td>4.3</td>
<td>0.23</td>
<td>0.3</td>
<td>IVS1-6/?</td>
<td></td>
</tr>
<tr>
<td>V.A.</td>
<td>M</td>
<td>25</td>
<td>7.3</td>
<td>25.5</td>
<td>11.6</td>
<td>5.0</td>
<td>0.24</td>
<td>0.05</td>
<td>IVS1-6/IVS1-6</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Spx, splenectomy; Rct, reticulocyte.

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Fig 1. Hb levels before, during, and after rhuEpo administration. The three patients are referred to by (○, ●), (△, △), and (□, ■). Empty symbols denote values obtained before and after rhuEpo; solid symbols are values obtained during therapy.
The results of the preliminary trial of rhuEpo administration to three patients with θ-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.

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Table 2. Percentage of F Reticulocytes, F Cells, and HbF Before, During, and After rhuEpo Administration

<table>
<thead>
<tr>
<th></th>
<th>V.A.</th>
<th>Z.A.</th>
<th>M.H.</th>
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<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
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<tr>
<td></td>
<td>Rct</td>
<td>Cells</td>
<td>Hb</td>
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<td>56</td>
<td>16</td>
<td>30</td>
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</tbody>
</table>

Abbreviation: Rct, reticulocyte.
*Before/after treatment.
†Delayed shipment.
REFERENCES


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

EA Rachmilewitz, A Goldfarb and G Dover