Recombinant human erythropoietin (rHuEPO) is used for the treatment of different types of anemia, and a great deal of evidence shows that responsiveness to rHuEPO seems to be strictly related to a low or inadequate EPO response to anemia. Only a few cases of rHuEPO administration to patients with thalassemia intermedia have been reported, and in some of them an increase in hemoglobin level, without a specific effect on Hb F, was achieved.

In one of our previous studies we reported that giving low doses of rHuEPO to untransfused subjects with β-thalassemia intermedia did not improve their anemia, but did produce a decrease in the transfusional requirement of transfused thalassemia intermedia patients. Nevertheless, the impact of rHuEPO administration on in vivo thalassemic erythropoiesis has not been well characterized yet. Since it has been reported that determination of serum soluble transferrin receptor levels (sTfR) is the best indirect method to measure erythroid marrow activity, we evaluated sTfR concentrations in eight patients with thalassemia intermedia during treatment with low doses of rHuEPO.

Patients and Methods

Eight patients, 5 males and 3 females with a mean age of 36.3 years, range 20-49, were investigated. Six of them had never been transfused, while two were being regularly transfused with a mean transfusional regimen of 85 mL/kg/year and 102 mL/kg/year, respectively.

The clinical and hematologic characteristics and the thalassemic genotypes of the patients, as well as the procedure for delivering rHuEPO have already been published. Briefly, rHuEPO (EPREX-CILAG) was administered subcutaneously three times a week at low doses (50 U/kg) over a period of three months to the six untransfused patients, and over a period of six
months to the two transfused subjects.

During the rHuEPO treatment the erythropoietic activity of all patients was assessed by monthly determinations of sEPO, sTfR and reticulocyte index. The red cell indices were obtained with a Coulter Counter JS, and reticulocyte count was performed by microscopic observation after staining with brilliant cresyl blue and corrected for the anemia level.8

Circulating EPO levels were determined in duplicate by radioimmunoassay (Diagnostic System Laboratories Inc, Webster, Tx, USA); the detection limit was ≤1 mU/mL and the precision (CV) was 8.1% intra-assay and 11.6% inter-assay. The amount of serum TfR was estimated in duplicate by an enzyme linked immunosorbent assay (Amgen Diagnostics, Oaks; Technogenetics, Italy); the precision (CV) was 8.4% intra-assay and 5.8% inter-assay. The ratio of observed to predicted (O/P) serum EPO was evaluated as previously described.9

Results

In untransfused thalassemic subjects the mean basal Hb level was 9.6±0.6 g/dL and the mean basal sEPO and sTfR levels were 242±221 mU/mL and 30.3±11.1 ug/mL, respectively. The two transfused patients had a mean basal Hb level of 8.2±0.5 g/dL and mean basal values of sEPO and sTfR of 100±17 mU/mL and 13±4.2 ug/mL, respectively. The pretreatment serum ferritin level was 315±133 ug/mL in the untransfused and 1552±116 ug/mL in the transfused thalassemic patients.

Twenty age-matched, healthy subjects showed a mean sEPO level of 12.8±2.6 mU/mL and a mean sTfR level of 3.1±1.1 ug/mL. In all the thalassemic patients the O/P value of sEPO (mean basal value 1.2±0.2; range 1.49–0.92) was consistent with an adequate EPO response to anemia.

Figure 1 shows the variation in the mean sTfR values in the untransfused thalassemic patients and the values of the two transfused patients during rHuEPO administration. In spite of the low doses of rHuEPO used and the different basal values of sTfR, the majority of the untransfused patients (five out of six) showed an increment in their sTfR level in the first month of treatment.

A higher and enduring increase in sTfR concentration, lasting until the discontinuation of rHuEPO, was observed in the two transfused patients only. At the same time a significant increment in the reticulocyte index (from 0.6 to 1.2 in one and from 1.6 to 2.3 in the other; p<0.01) was achieved in these two transfused patients. No significant change in serum ferritin levels was observed during the treatment with rHuEPO in any of the thalassemic patients.

![Figure 1](https://www.example.com/figure1.png)
**Discussion**

Even though it has recently been observed in several clinical trials\(^2\)\(^-\)\(^4\) that different doses of rHuEPO may improve the anemia of some patients with thalassemia intermedia, the modifications of thalassemic erythropoiesis related to rHuEPO therapy are still unknown.

β-thalassemia intermedia is a phenotypically and genetically heterogeneous disorder characterized by varying degrees of anemia and bone marrow expansion. The heterogeneity of erythropoietic activity in thalassemic syndromes has been confirmed in different studies, which report variable levels of sEPO and sTfR in Cooley’s disease and particularly in β-thalassemia intermedia.\(^7\)\(^-\)\(^11\) According to the data reported in these studies, our thalassemic patients presented basal sTfR levels from four times higher than normal in the transfused, to ten times higher than normal levels in the untransfused group.

In the present study we assessed how low doses of rHuEPO were able to produce different increases of sTfR levels in the transfused and untransfused patients with thalassemia intermedia. The untransfused subjects showed a transitory mean increase in basal sTfR concentration (more than 30%) for the first month only but without a significant increase in the overall Hb levels. The two transfused patients, on the other hand, not only demonstrated a major and lasting increment in sTfR level, but also experienced a reduction of the transfusional requirement until rHuEPO was discontinued.

The significant increase in the reticulocyte index, together with sTfR increment observed in the two transfused patients only, suggests the presence of residual effective erythropoiesis that was probably inhibited by transfusion therapy. These data indicate that low doses of rHuEPO are able to increase erythroid marrow activity, particularly in transfused patients, who are characterized by lower sTfR levels, and that basal erythropoietic activity could be one of the main causes for the differences in responsiveness to low doses of rHuEPO given in thalassemia intermedia.

Recently, Cazzola et al.\(^7\) demonstrated that the sTfR level is a very reliable indicator of bone marrow erythroid suppression in polytransfused Cooley’s anemia patients, who should therefore be transfused on the basis of individual sTfR values.

We think that serum TfR evaluation should be regularly performed, even in transfused patients with thalassemia intermedia, for whom an optimal transfusional regimen should take into account the variable degree of bone marrow expansion as well as the variable amount of effective erythropoiesis.

Extensive clinical trials could determine whether low doses of rHuEPO\(^12\) might reduce the transfusional requirement of thalassemia intermedia patients, providing they have been selected according to low basal sTfR levels.

**References**