Effectiveness of Subcutaneous Low-Dose Erythropoietin in Patients with Chronic Renal Failure despite Functional Iron Deficiency

P.L.	Pier Luigi	Bedani
E.	Eugenio	Cecchetti
P.	Paolo	Gilli

Division of Nephrology, S. Anna Hospital, Ferrara, Italy

Dr. Pier Luigi Bedani, Division of Nephrology, S. Anna Hospital, I-44 100 Ferrara (Italy)

Dear Sir,

There are many causes of decreased responsiveness to erythropoietin (EPO) in patients with chronic renal failure. The commonest is insufficient iron to meet the demands of increased erythrocyte production

[1].

However, there are patients who respond to EPO with a rapid increment of haemoglobin despite the lowest ferritin levels [2].

We report on 4 patients with anaemia due to chronic renal failure, who responded favourably to weekly subcutaneous low-dose EPO despite functional iron deficiency.

The patients (4 females; mean age: 47 ± 21 years; serum basal creatinine ranged between 476 and $724 \mu\text{mol/l}$) participated in a study made in various hospitals assessing the effect of EPO on anaemia due to progressive renal failure. Inclusion criteria for the study were a minimum age of 18 years irrespective of sex, a serum creatinine level between 200 and $800 \mu\text{mol/l}$ and serum haemoglobin concentration of less than 90 g/l. After 2 weeks of prophylactic oral iron supplementation (40 mg/day of elemental iron), all patients were treated with EPO (Eprex, Cilag) 100 U/kg/week by the subcutaneous route. The target haemoglobin concentration for this study was set at 110 g/l, and after having arrived at this level the EPO dose was adjusted to maintain it at a stable value. Before treatment, all but 1 patient had normal serum ferritin concentrations (54, 61, 55 and 8 ng/ml , respectively; normal range 15-300 ng/ml), while calculated percentage saturation of

Transferrin saturation

Ferritin

Haemoglobin

Fig. 1. Behaviour of serum ferritin levels, percentage of transferrin saturation and haemoglobin concentrations in 4 patients treated over 24 weeks with EPO.

transferrin was $> 20\%$ only in 1 case (i.e. 3 patients showed a functional iron deficiency).

During all the phases of EPO treatment, each patient received oral iron supplementation (80-120 mg/day of elemental iron) besides other drugs and a hypoproteic diet. Despite a slight fall in serum ferritin levels and constant values of transferrin saturation of less than 20% over the

first 12 weeks of EPO treatment, the increase in haemoglobin concentration ranged between 27 and 36% (fig. 1). During this phase, the target haemoglobin level was reached by 3 patients; in the fourth patient, who in the last year had received numerous blood transfusions, the increase in haemoglobin was less significant. After 24 weeks of therapy, 2 patients needed to start regular dialytic treatment, and so their follow-up was stopped. One patient maintained the target for a long time (over a further 30 weeks) using a very low dose of EPO (34 U/kg/week).

In renal patients, serum ferritin concentrations of < 50 ng/ml and transferrin saturation below values of 15-20% indicate functional iron deficiency [3-5]. It is a widespread opinion that oral iron supplements are less efficacious than parenteral iron administration in increasing haemoglobin in

uraemic patients treated with EPO [6, 7]. In addition, Bainton and Finch [8] showed that once the transferrin saturation fell below 16%, the iron supply for EPO therapy may be inadequate. On the contrary, our data suggest that an excellent response may be obtained by oral iron supplements (80-120 mg/day of elemental iron) when low doses of EPO are administered once a week by the subcutaneous route. Because the lower threshold of serum ferritin and transferrin saturation is quite variable among uraemic patients on EPO therapy [9], it is possible that those patients who are able to reduce their serum ferritin concentrations to low values have a better bio-availability of iron from deposits. Therefore, the regular availability of small amounts of iron, in patients with constant low serum concentrations of EPO, could allow an effective stimulation of erythropoiesis.

In conclusion, in patients with chronic renal failure, it seems possible to correct anaemia irrespective of ferritin and transferrin saturation values, provided that iron is present in sufficient amounts to balance functional iron deficiency and EPO is given by the subcutaneous route.

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