Parathyroidectomy and response to erythropoietin therapy in anemic patients with chronic renal failure

Sir,

Secondary hyperparathyroidism (HPT) is one of the factors potentially involved in the pathogenesis of anemia in uraemic patients and is considered a cause of resistance to recombinant human erythropoietin (rHuEpo) therapy [1,2]. Replacement of the cellular components of the marrow by fibrous tissue and inhibitory effect of parathyroid hormone (PTH) on erythropoiesis are the two main mechanisms suggested [3–5]. Parathyroidectomy (PTX) seems to improve anaemia and allow the lowering of the rHuEpo dose. However, these results have been observed in studies performed on small numbers of patients [6–8]. We retrospectively investigated 39 uraemic patients on dialysis (dialysis duration 14.8 ± 5.1 years) with severe HPT in order to evaluate the effect of PTX on anaemia and rHuEpo response.

Criteria for parathyroidectomy were severe HPT associated with hypercalcaemia, progressive increases in PTH concentrations despite vitamin D therapy, calciphylaxis, or bone fractures. Patients were divided into two groups according to rHuEpo therapy at the time of PTX (group A, n = 20, not treated with rHuEpo; group B, n = 19, on rHuEpo therapy in order to maintain haematocrit between 25 and 32%). Haemoglobin, haematocrit, serum iron, serum ferritin, transferrin saturation, and PTH were measured before and 2, 6, and 12 months after PTX. The PTH levels of the two groups of patients are reported in Table 1. Twenty patients underwent a bone biopsy before PTX: osteitis fibrosa was documented in 17 patients, signs of mild hyperparathyroidism in two, and a mixed pattern of hyperparathyroidism and osteomalacia in one patient. Bone stainable aluminium was weakly positive (5 and 12% of trabecular bone surface) in two patients. Peritrabecular fibrosis was >50% in five patients.

A significant (P < 0.005) increase in haemoglobin (from 8.6 ± 1.0 to 10.4 ± 1.2 g/dl) and haematocrit (from 26.3 ± 3.2 to 31.3 ± 4.8%) levels had been observed 2 months after surgery in group B. No further increases were observed after 6 and 12 months. The improvement of anaemia following PTX was further emphasized by the concomitant reduction in the mean weekly rHuEpo dose (from 170 ± 67 to 112 ± 48 and 96 ± 78 I.U./kg after 2 and 6 months, P < 0.005). Also, group A showed a significant (P < 0.01) increase in haemoglobin (from 10.1 ± 1.3 to 11.1 ± 1.1 g/dl) and haematocrit (from 31.4 ± 4.8 to 34 ± 4.4%) 2 months after PTX. We did not find any significant correlation between the degree of fibrosis and haematocrit or haemoglobin levels before PTX or between the degree of fibrosis and the increase in haematocrit and haemoglobin levels after surgery.

Several mechanisms are reported to explain the linkage between HPT and rHuEpo hyporesponsiveness. Meytes et al. [4] demonstrated that PTH inhibited erythroid burst-forming units in human peripheral blood as well as in mouse bone marrow. Dunn and Trent [9] reported that very high concentrations of PTH inhibit both endogenous and erythropoietin-mediated haeme synthesis. Brickmann et al. [10] first hypothesized that an excess of PTH induces anaemia by marrow fibrosis due to osteitis fibrosa, which limits the availability of red marrow and reduces the number of red cell forming units. Recently Rao et al. [3] showed that hyporesponsiveness to rHuEpo was related to the degree of osteitis fibrosa in patients in hemodialysis. Myelofibrosis may be irreversible [2] or may regress slowly after PTX [1].

In our study, most of the patients showed a mild or moderate degree of marrow fibrosis (<50%) and we found no significant correlation between the degree of fibrosis and the improvement of anaemia after surgery. Moreover, we observed a rapid improvement of anaemia after PTX. Thus, we suppose that the improvement of anaemia in our patients, showing mainly a mild degree of marrow fibrosis at the time of PTX, can be related to the drastic decrease in PTH levels more than to improvement of marrow fibrosis. Unfortunately, our study cannot clarify whether an increase in endogenous erythropoietin levels after PTX, as reported by Washio et al. [11], may have played a role in the improvement of anaemia after PTX.

In summary the effect of PTX on anaemia and rHuEpo response was studied in two groups of dialysis patients with severe HPT and osteitis fibrosa. Surgery improved anaemia in patients both receiving or not receiving rHuEpo therapy before PTX. The improvement of anaemia following PTX in patients receiving rHuEpo was further emphasized by a concomitant lowering of the weekly mean rHuEpo dose by 30–45%. Greatly increased PTH levels may play a significant role in the pathogenesis of anaemia and in the hyporesponsiveness to rHuEpo in uraemic patients.

Renal Units Lodi Pavia and Desio Italy

S. Mandolfo F. Malberti M. Farina M. Villa R. Scanziani M. Surian E. Imbasciati

8. Goichhoechea M, Gomez-Campdera F, Polo JR et al. Secondary hyperparathyroidism as cause of resistance to treatment with
Serum ferritin level required for adequate response to recombinant human erythropoietin in haemodialysis patients with hepatitis C virus infection

Sir,

Iron deficiency is the major cause of a diminished response to recombinant human erythropoietin (rHuEpo) in uraemic patients [1]. Although the serum ferritin (SF) concentration is most commonly used as an indicator of iron storage, the concentrate may increase in systemic inflammation, infection and liver disease [2]. The release of intracellular ferritin from damaged hepatocytes can lead to a high level of SF, thereby overestimating iron storage. Hepatitis C virus (HCV) has become the primary cause of chronic liver disease among maintenance dialysis patients in Taiwan [3–5]. However, the minimum requisite of SF for adequate response to rHuEpo in HCV-positive haemodialysis (HD) patients has never been studied. The aim of this study was to establish a new cut-off value of SF for better association of rHuEpo responsiveness in HD patients with HCV infection.

One hundred and forty-six patients (58 M, 88 F) who had been on regular HD for at least 6 months were enrolled. Patients found to be HBsAg(-) (RIA, Abbott Labs) were excluded. The determination of anti-HCV was made using an EIA method (Abbott Labs, HCV-EIA kit, 2nd generation) and, if indeterminate, an immunoblot assay (RIBA-2, Chiron) was performed for confirmation. Factors potentially interfering with rHuEpo responsiveness, except viral hepatitis, were surveyed individually. These included marked hyperparathyroidism (intact PTH higher than 500 pg/ml), aluminium toxicity, vitamin B12, or folate deficiency, gastrointestinal blood loss, haemolysis, malignancy, red-cell enzyme defect, and haemoglobinopathies. Subjects with such factors or use of drugs such as androgens were excluded.

Finally, a total of 118 patients (43 M, 75 F) were included. The mean age was 54.8 years (range 22–79) and average time on HD was 45.2 months (range 6–122). Serum biochemistries and iron indices were analysed on a monthly basis; the mean values of each variable during the previous 4 months were used. No samples were taken for measuring the iron profile within 1 month of the patient’s last iron supplement or blood transfusion. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), commonly used in screening liver disease [5], were determined by Hitachi auto-analysers. The complete blood count was evaluated by computerized Coulter counter (STSK model). Plasma iron (Fe, µg/dl), SF (ng/ml) and total iron binding capacity (TIBC, µg/dl) were obtained using a Hitachi 736–40 autoanalyzer (Tokyo, Japan). Post-dialysis rHuEpo was administered subcutaneously three times per week. Therapy was begun with the initial dosage of 3 × 50 U/kg/week and was adjusted by ± 3 × 25 U/kg/week to achieve and maintain the target haemoglobin (Hb) level. The minimum target Hb level was no less than 10 g/dl. Adequate rHuEpo responsiveness was defined arbitrarily as achievement of the target Hb value with an average rHuEpo dosage of no more than 3 × 100 U/kg/week. The mean values of both variables during the study period were collected for analysis. Patients received no iron supplementation during the study period, since the impact of SF on rHuEpo responsiveness was our main interest.

As shown in Table 1, HCV-positive patients had higher mean AST, ALT, and SF levels than patients who were HCV-negative (unpaired t test, P < 0.05). There was no statistically significant difference in rHuEpo dosage, Hb level, and transferrin saturation (TSAT) between the two groups. By linear regression and correlation coefficient, we found a significantly positive correlation between SF and serum aminotransferases in anti-HCV(+) HD patients. However, among individuals who were anti-HCV negative, no such association was noted. For elucidating the influence of HCV on responsiveness to rHuEpo, we classified patients according to their rHuEpo response (Table 2). As shown in the table, there were no statistically significant differences in any items, except SF of those who had adequate rHuEpo response, between the two groups (anti-HCV(+) vs anti-HCV(–)). Patients with adequate response to rHuEpo, as expected, consumed a significantly lower dosage of rHuEpo than those with inadequate response. The best cut-off values of SF in anti-HCV(+) HD patients with adequate rHuEpo responsiveness were obtained from the ROC (receiver-operating characteristic) curve [5,6] (Figure 1). The calculated cut-off values of SF in anti-HCV(+) and anti-HCV(–) HD patients were 360 ng/ml (sensitivity 66.7%, specificity 57.8%) and 304 ng/ml (sensitivity 60.8%, specificity 61.2%) respectively.

Few case reports have observed an improved rHuEpo response and higher SF levels during viral hepatitis in HD patients, which phenomena reflect endogenous Epo production by regenerating hepatocytes in such population [6]. The positive relationship between SF and aminotransferases, demonstrated in this work and in other series [7], indicated that the presence of HCV infection in HD patients may lead to an overestimation of SF and their iron storage. By ROC curve analysis (Figure 1), we established a new cut-off value of SF. This higher threshold of SF resulted in a gain in sensitivity for predicting rHuEpo responsiveness and iron storage without a major decrease in specificity. Although there was no difference in SF levels between our patients with SVTs and those with rHuEpo response and higher SF levels during viral hepatitis in HD patients, which phenomena reflect endogenous Epo production by regenerating hepatocytes in such population [6]. The positive relationship between SF and aminotransferases, demonstrated in this work and in other series [7], indicated that the presence of HCV infection in HD patients may lead to an overestimation of SF and their iron storage. By ROC curve analysis (Figure 1), we established a new cut-off value of SF. This higher threshold of SF resulted in a gain in sensitivity for predicting rHuEpo responsiveness and iron storage without a major decrease in specificity. Although there was no difference in SF levels between our patients

### Table 1. Clinical characteristics in subgroups of HD patients with different viral hepatitis markers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Anti-HCV(+)</th>
<th>Anti-HCV(–)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 51)</td>
<td>(n = 67)</td>
<td></td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>17:34</td>
<td>26:41</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.7 ± 13.1</td>
<td>53.4 ± 10.4</td>
</tr>
<tr>
<td>Albumin (gm/dl)</td>
<td>4.16 ± 0.42</td>
<td>4.33 ± 0.40</td>
</tr>
<tr>
<td>AST (IU/l)*</td>
<td>28.4 ± 9.8</td>
<td>17.5 ± 5.7</td>
</tr>
<tr>
<td>ALT (IU/l)*</td>
<td>32.9 ± 21.2</td>
<td>14.5 ± 7.0</td>
</tr>
<tr>
<td>Ferritin (ng/ml)#</td>
<td>23.8 ± 11.4</td>
<td>25.3 ± 11.9</td>
</tr>
<tr>
<td>Epo-dosage (U/kg/week)</td>
<td>272.8 ± 142.3</td>
<td>316.1 ± 112.2</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>9.96 ± 1.23</td>
<td>9.39 ± 0.85</td>
</tr>
</tbody>
</table>

**Transferrin saturation (Fe divided by TIBC); *P < 0.01, anti-HCV(+) group vs anti-HCV(–) group; #P < 0.05, anti-HCV(+) group vs anti-HCV(–) group.**