Does Erythropoietin Production after Renal Transplantation Depend on the Type of Immunosuppression?

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Dear Sir,

After successful renal transplantation the kidney resumes its endocrine and exocrine functions that result in the correction of anemia associated with uremia [1]. There is a general agreement that a major factor contributing to the correction of anemia is the production of erythropoietin (EPO) by the donor kidney. After kidney transplantation, red-cell production is related to the ability of the graft to release EPO and the potential of bone marrow progenitor cells to respond to the circulating hormone. Immunosuppressive drugs used in renal transplantation may affect both processes: azathioprine (Aza) possesses a well-known suppressive effect on the bone marrow and in a recently published paper, Jensen et al. [2] suggested that this might cause a compensatory increase in EPO production. Clinical observations as well as in vivo and in vitro experimental studies showed that cyclosporine (CsA) impaired EPO response to hypoxia [3-5]. On the other side, CsA increased the proliferative potential of myeloid progenitors in vitro [6]. We studied 159 long-term (> 6 months) renal-allograft recipients with stable graft function to assess if the serum EPO level differs depending on immunosuppressive therapy. Thirty-two recipients were treated with prednisolone (Pred) and Aza as the only immunosuppressive agents since transplantation, 31 received only Pred + CsA and 96 were on triple immunosuppression (Pred + Aza + CsA). Also, sera obtained from 63 healthy blood donors were used as a control. Patient data are presented in table 1. Each patient underwent a thorough examination (including measurement of saturation of hemoglobin with oxygen, determination of carboxyhemoglobin level, pulmonary function tests, liver function tests, ultrasound examination of transplanted and native kidneys) to exclude possible causes that might affect EPO production. None of the patients had had phlebotomy or blood transfusion for at least 4 weeks before obtaining samples for EPO determination. Serum EPO and ferritin levels were measured using commercially available radioimmunoassays (BioMérieux, Marcy-l'Etoile, France). As shown in table 1, there were no differences in hematocrit values between patients receiving Pred + CsA, Pred + Aza or Pred + Aza + CsA. Iron stores, as estimated by serum ferritin levels were highly variable but not significantly different among the groups (table 1).

The serum EPO levels were similar in all studied groups. Recipients treated with Pred + CsA presented the same serum EPO concentrations (13.0 ± 2.4 mIU/ml) as patients receiving Pred + Aza or Pred + Aza + CsA (13.8 ± 1.9 and 13.2 ± 1.0 mIU/ml, respectively). Those levels differed significantly from serum EPO concentrations in healthy volunteers (7.5 ± 1.5 mIU/ml), despite similar hematocrit values ($47 \pm 1.0\%$). Higher serum EPO levels in renal allograft recipients were also found by other authors [7]. They may result from increased release of the hormone due to diffuse vascular lesions induced by clinically undetectable rejection and/or CsA toxicity. Damage to the renal vascular bed may cause tissue hypoperfusion

which in turn stimulates EPO release. The role of CsA in stimulating the red-cell production was supported by observations of increased frequency of erythrocytosis in renal-graft recipients treated with this drug [8,9].

In healthy people and in nonrenal anemias there is a reciprocal correlation between serum EPO and hematocrit [10]. In our patients however, EPO levels failed to display the characteristic inverse relationship to hematocrit (fig. 1). Therefore, our data suggest that even successful renal transplantation did not resume the normal feedback loop of EPO secretion.

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Fig. 1. Individual EPO concentration in renal-allograft recipients related to the hematocrit. · = Pred + Aza; ▼ = Pred + CsA; Δ = Pred + Aza + CsA.

30 40 50 60
Hematocrit (%)
70

Table 1. Patient characteristics

Immunosuppressive regimen

Age	Gender	Hematocrit	EPO	Ferritin	Creatinine
years	M/F	%	mIU/ml	ng/ml	μmol/l

Data are presented as means $\pm$ SEM.

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