Treatment of Chronic Renal Failure Anemia by Recombinant Erythropoietin and Polycythemia following Kidney Transplantation

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Dear Sir,

The major mechanism of chronic renal failure hyporegenerative anemia is due to a reduction in medullary stimulation linked to erythropoietin (EPO) deficiency. Recent work into recombinant human erythropoietin (rHu EPO) has shown that efficient treatment now exists. As a result of endogenous EPO production by the graft, kidney transplantation enables uremic anemia to be corrected. In most cases, feedback regulation of EPO secretion permits the hemoglobin (Hb) level to be stabilized at values depending on the kidney function.

Polycythemia may occur following renal transplantation, the frequency of which varies according to the criteria used. The frequency of absolute erythrocytosis defined by an increase in red blood cell (RBC) mass has been estimated at 3-11.8% [1, 2] and is responsible for an increase in morbidity and mortality due to thromboembolic accidents [3].

The results provided here come from a retrospective study of 191 patients who received transplantation in our department from October 1, 1985 to November 30, 1990, and with a well-functioning graft on June 1, 1991. The aim of the study was to establish the frequency of polycythemia and the characteristics of the polycythemic patients at the time of transplantation. Isotopic measurement of the RBC mass using ⁵¹Cr-labelled RBC was carried out on all patients with an Hb level of over 17 g/dl for males and 15 g/dl for females or a hematocrit of over 50% for males and 45% for females. A diagnosis of erythrocytosis was admitted when the measured RBC mass was over 125% of the theoretical value as calculated according to the Wennesland formulae, taking sex, height and weight into account.

27 patients (14.1%) developed erythrocytosis on average 8.5 months (1.6-31.5) after transplantation. At diagnosis, the mean Hb level was 17.3 ± 1.2 g/dl; hematocrit: 53.7 ± 5.3 vol%; measured/theoretical RBC mass: $161 \pm 3.8\%$, and plasma volume (PV) normal (measured/theoretical PV: $102.8 \pm 3.2\%$).

The etiological assessment carried out in 21 patients found no supporting evidence for polycythemia vera, reduction in arterial oxygen saturation, or kidney or hepatic tumors. One patient had severe hypertension due to renal artery stenosis.

The plasma EPO level as measured in 16 patients by immunoradiometrical dosage (I. EPO COATRIA Pasteur) was normal for 15 (9.2 ± 1.7 vs. 8.5 ± 1.1 mU/ml, the standard value within the normocytic control population). The only increased value (31 mU/ml) was found in the patient with renal artery stenosis.

When the 27 polycythemic patients were compared with 164 nonpolycythemic patients (table 1), no difference was found in terms of age, duration of dialysis treatment or past history of uni- or bilateral nephrectomy. The only difference detected concerned sex with a male predominance usually observed in polycythemia vera and causal nephropathy with an under-representation of congenital malformation in polycythemic patients [3]. Polycystic kidney disease was found with the same frequency in both groups. The time-lag for correction of anemia with respect to both the transplantation and stabilization of renal function was significantly shorter among polycythemic patients.

None of the 24 patients treated with rHu EPO at the time of transplantation with an Hb level significantly higher than the nontreated patients (11 ± 1.9 vs. 9.65 ± 1.9 g/dl, $p < 0.001$) developed polycythemia during the mean follow-up period of 15.1 ± 4.5 months.

As far as we are aware, this is the first time this has been reported. Despite the fact that the results are not statistically significant because of the small sample number and short time period covered, they do nevertheless suggest that treating uremic anemia with rHu EPO prior to transplantation may ward off the appearance of erythrocytosis following renal transplantation. The majority of polycythemic transplantation patients have normal plasma EPO levels which suggests stimulation of EPO independent of EPO secretion. This stimulation is rapid with anemia correction arising earlier in polycythemic subjects than in nonpolycythemic subjects. This could be the result of erythroblast precursor hypersensitivity at normal EPO levels by modification of receptor number or affinity. Higher levels of circulating Hb and EPO obtained by the pretransplant rHu EPO treatment may well be a factor limiting these changes, but this remains to be confirmed.

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0028-2766/92/

0623-0370\$2.75/0

Table 1. Characteristics of patients with and without polycythemia after renal transplantation

Figures in parentheses are percentages.

APKD = Adult polycystic kidney disease; rHu EPO+ = treated patients; rHu EPO- = non-treated patients.

References

- Obermiller LE, Tzamaloukas AH, Avasthi PS, Halpern JA, Sterling WA: Decrease of plasma volume in post-transplant erythrocytosis. *Clin Nephrol* 1985;23:213-217. Davis HP: Polycythemia following renal transplantation. *J R Soc Med* 1987;80:475-476. Wickre CG, Norman DJ, Bennison A, Barry JM, Bennet WH: Post-renal transplant erythrocytosis: A review of 53 patients. *Kidney Int* 1983;23:731-737.
- Heilmann E, Gottschalk D, Gottschalk I, Lison AE: Studies in polycythemia after kidney transplantation. *Clin Nephrol* 1983;20:94-97. Stockenhuber F, Geissler K, Sunder-Plassmann G, Kurtz RW, Steininger R, Muehlbacher F, Hinterberger W, Balcke P: Erythrocytosis in renal graft recipients due to a direct effect of cyclosporine. *Transplant Proc* 1989;21:1560-1562.

Goldbert MA: Biology of erythropoietin; in Garnick MB (ed): Erythropoietin in Clinical Applications: An International Perspective. New York Dekker, 1990.
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