Safety and Efficiency of Recombinant Human Erythropoietin Treatment in Anemic Pregnant Women with a Kidney Transplant

M.		Szurkowski
A.		Więcek
F.		Kokot
K.		Daniel

Department of Nephrology, Silesian School of Medicine, Katowice, Poland

Prof. Dr. hab. med. F. Kokot, Department of Nephrology, Silesian School of Medicine, Francuska Street 20, 40-027 Katowice (Poland)

Dear Sir,

Severe anemia due to erythropoietin (EPO) deficiency is one of the main symptoms of chronic renal failure. Successful kidney transplantation is followed by normalization of uremic anemia or even transient polycythemia. There is some evidence that this last phenomenon is due to EPO production by the transplant and native kidneys. Successful kidney transplantation is usually followed by normalization of function of the pituitary-gonadal axis and an improvement in fertility [1]. In dialysis patients the conception rate is less than 1 among 200 females and increases to 1 in 50 women after successful kidney transplantation [2]. In pregnant kidney transplant women immunosuppressive therapy may be a potential factor for severe anemia. We report the results of recombinant human EPO (rHuEPO) therapy in 2 pregnant kidney transplant patients with severe anemia of unknown origin.

Two women, 19 and 21 years old, with end-stage renal failure caused by chronic pyelonephritis had been hemodialyzed for 69 and 9 months, respectively, when they underwent renal cadaveric transplantation. Immediately after kidney transplantation both patients were treated by prednisone and azathioprine, and later 1 of them was converted to prednisone and cyclosporin A. Graft function was excellent in both patients, and plasma creatinine levels oscillated between 106-162 and 126-141 $\mu\text{mol/l}$, respectively.

In 1 patient moderate anemia developed in spite of a normal plasma iron level (23.4 $\mu\text{mol/l}$) and ferritin (210 ng/ml). The Hct value ranged from 25 to 32%, and the Hb level from 7.1 to 9.0 g/dl. In spite of normal plasma

iron and ferritin concentrations, oral iron therapy was started together with folic acid. This treatment was only partially successful (increase in the Hct value to 32%). Six months after transplantation early pregnancy was diagnosed. Since that moment the patient was carefully monitored by a nephrologist and also an obstetrician. Immunosuppressive therapy consisted of prednisone (7.5 mg/day) and azathioprine (2 mg/kg body mass/day). During the whole gestation period graft function was normal. Ultrasound examinations of the fetus at 22, 24, 30 and 35 weeks of gestation revealed normal development. In spite of iron and folic acid supplementation aggravation of the already diagnosed anemia was observed. At the 10th week of gestation the Hb level was 7.1 g/dl and the Hct value 24%, while the ferritin level was 180 ng/ml. This was the

reason why treatment with rHuEPO (EPREX, Cilag AG) was started from the 10th week of gestation of a dose of 2,000 U s.c. twice a week. After 8 weeks of rHuEPO treatment the Hct value was 37% and the Hb level 11.2 g/dl. EPO treatment was continued at the same dose to the end of pregnancy. During that time the Hct value was always 35-37%. During EPO therapy the mean arterial blood pressure did not change. Before gestation the mean arterial blood pressure was 93.3 mm Hg and was of the same magnitude at the end of gestation. At the 39th week of gestation, a healthy female newborn with an Apgar score of 8 and a body weight of 2,180 g was delivered by cesarean section.

In the 2nd patient pregnancy was diagnosed 26 months after kidney transplantation. In this woman immunosuppression con-

sisted of prednisone (15 mg/day) and cyclosporin A (160-240 mg/day). At the 10th week of gestation the Hct value was 28% and the Hb 9.1 g/dl, and serum iron and ferritin levels were 21.5 $\mu\text{mol/l}$ and 180 ng/ml, respectively. As iron and folic acid supplementation did not influence anemia, treatment with rHuEPO was started at a dose of 4,000 U s.c. twice a week. After 12 weeks of rHuEPO treatment the Hct value increased to 35% and the Hb level to 11.6 g/dl. The dose of rHuEPO was reduced to 2,000 U s.c. twice a week up to the 32nd week of pregnancy. No influence of rHuEPO therapy on kidney graft function was observed. At the 32nd week of gestation an increase in blood pressure to 180/120 mm Hg was noticed. After hypotensive treatment with methyldopa and discontinuation of EPO therapy, arterial blood pressure decreased to 130/80 mm Hg. At the 38th week of pregnancy in spite of hypotensive therapy, blood pressure rose again to 150/125 mm Hg accompanied by an increase in serum creatinine from 126 to 186.7 $\mu\text{mol/l}$. This was the reason why a cesarean section was performed. The female newborn had an Apgar score of 9 and a body weight of 3,450 g. After delivery arterial blood pressure and serum creatinine normalized. Pregnancy in renal transplant patients is presumed to be a 'high-risk' factor for the kidney transplant [2]. In addition severe anemia in kidney transplant women may negatively influence the course of pregnancy. Among the potential factors involved in the pathogenesis of anemia in kidney transplant women immunosuppressive drugs are to be mentioned. In the 2 reported cases anemia developed at an early stage of gestation. The origin of this anemia was unclear. Taking into

account ineffectiveness of iron and folic acid supplementation, rHuEPO therapy was started. In both pregnant women a rapid improvement in hematologic parameters (Hct, Hb) was noticed. In 1 woman no side effects of EPO therapy was observed, while in the other a significant rise in blood pressure and a moderate deterioration of the kidney transplant function was observed after 22 weeks of EPO therapy. As the above-mentioned side effects did not appear before the 22nd week of EPO administration, the importance of EPO in their pathogenesis seems barely likely [3,4]. From our observations it seems that EPO is a safe and effective drug to correct anemia in pregnant women with functioning kidney grafts. In these patients monitoring of blood pressure and excretory graft function is mandatory.

References

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