Immunological Effects of Recombinant Human Erythropoietin on End-Stage Renal Disease Pediatric and Adult Patients

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Dear Sir,

Many immunological abnormalities, especially depression of the cellular immune system, have been described in patients with end-stage renal disease (ESRD) [1,2]. Recently, recombinant human erythropoietin (rHu-EPO) has been introduced in the treatment of anemia of ESRD patients [3]. Many reports showed that treatment with rHu-EPO in ESRD patients may have immunological effects.

Some authors reported immunosuppressive action of rHu-EPO with decrease of CD4 (T-helper lymphocytes) and CD3 (total T lymphocytes) and increase in CD8 (T-suppressor lymphocytes) [4,5]. Other researchers demonstrated increase of helper/suppressor (CD4/CD8) ratio, decrease of T cells, and increase of B cells [6]. About the effect of rHu-EPO on humoral immune response in ESRD patients, proof of increased IgA and IgG production by B lymphocytes was described [6,7] but no statistically significant difference was seen by other authors [8].

rHu-EPO caused a transient enhancement of lowered T- and B-lymphoproliferative responses in ESRD patients [9]. Immunologic changes in uremic patients induced by rHu-EPO seem to be modulated by calcitriol, with stimulation of monocytic proliferation and inhibition of the natural killer cells' activity [10].

The use of rHu-EPO avoiding iterative transfusions in hemodialysis patients may theoretically suppress the mean factor of immunization and decrease anti-HLA antibodies improving graft function in renal transplantation [11]. Some immunological effects of rHu-EPO (increased secretion of interleukin-2, gamma-interferon, tumor necrosis factor, colony-stimulating factor by peripheral blood mononuclear cells) seem to be mediated by the rise in red blood cells [12].

There is no report about immunological effects of rHu-EPO treatment on a pediatric population. To evaluate the influence of rHu-EPO on the immune system we studied an adult (20 patients) and a pediatric (8 patients) population of ESRD dialysis patients. Lymphocyte subsets were investigated before and after rHu-EPO treatment with flow cytometry and monoclonal antibodies (Biorad, Italy). Serum concentration of immunoglobulins (IgG, IgA, IgM) was measured at the beginning and at the end of the study. In the first group (adult population) of patients, therapy with rHu-EPO determined increase of CD8 values and reduction of CD4/CD8 ratio. Baseline values: CD3=76.72; CD4=41.44; CD8= 28.55; CD4/ CD8 ratio = 1.510. Values after rHu-EPO: CD3=74.83; CD4 = 41.27; CD8 = 38.72 ($p < 0.0005$); CD4/CD8 ratio = 1.098 ($p < 0.005$). In the pediatric group of patients there was a decrease of CD8 values with a not statistically significant increase of CD4/CD8 ratio. Baseline values: CD3= 68.40; CD4 = 42.10; CD8=23.50; CD4/CD8 ratio = 1.880.

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Values after rHu-EPO: CD3 = 64.60; CD4 = 41.60; CD8 = 21.00 ($p < 0.025$); CD4/CD8 ratio = 2.040. No statistically significant difference in B lymphocytes, IgG, IgM, immunoglobulin production was seen in both groups, but IgA values decreased from 197 to 183.8 mg% ($p < 0.05$) in pediatric patients. In conclusion, according to reported data from literature, treatment with rHu-EPO in adult ESRD subjects seems to have minimal immunosuppressive effects on T-cell function, but with no apparent consequences on the susceptibility to infections. These changes in lymphocyte subpopulations might have an impact on the outcome of a subsequent allogenic renal transplantation. In pediatric patients rHu-EPO therapy seems to have mild immunostimulating effects, secondary to the probable different immunopathogenic backgrounds of the adult and pediatric uremic populations. The clinical impact of these data deserves further studies.

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