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Letter to the Editor

IL-7 serum levels and lymphopenia in hemodialysis patients, non-responders to recombinant human erythropoietin therapy

There is a marked variability in the sensitivity to recombinant human erythropoietin (rhEPO) therapy in hemodialysis patients, with up to 10-fold variability in dose requirements to achieve correction of anemia [1]. Approximately 5 to 10% of patients show a marked resistance to rhEPO therapy [2]. This variability however remains poorly clarified. We showed that hemodialysis patients have lymphopenia [3], which results at least in part from a decrease in total circulating $CD3^+$ T-lymphocytes and affects both the $CD4^+$ and the $CD8^+$ T-cell subsets. We also observed that non-responders to rhEPO therapy patients present with a lower number of total lymphocyte and $CD4^+$ T-cell counts, when compared with responder patients. The lymphocyte depletion found in hemodialysis patients, particularly in non-responders to rhEPO therapy, could be related to an increased turnover of lymphocytes, to a disturbance in lymphocyte homeostasis due to uraemia, and/or to increased peripheral lymphocyte apoptosis associated with an activation stimulus.

Interleukin (IL)-7 has emerged as a key cytokine involved in controlling the homeostatic turnover and the survival of resting memory $CD4^+$ T cells [4]. We hypothesized that the serum levels of this interleukin could be related to the decreased number of total lymphocyte and $CD4^+$ T-cell counts that we have found in hemodialysis patients, especially in non-responders to rhEPO therapy. In order to test this hypothesis we selected 63 hemodialysis patients (36 males, 27 females; mean age 62.1 ± 15.7) under rhEPO treatment, for a median time period of 36 months. The hemodialysis patients included 32 responders and 31 non-responders to rhEPO therapy. Classification of hemodialysis patients, as responders or non-responders, was performed in accordance with the European Best Practice Guidelines [5]. The rhEPO maintenance dose for responder patients was 90 ± 58 U/kg per week and for non-responders was 573 ± 194 U/kg per week. The two groups of patients were matched for age, gender, weight, body mass index, mean time on hemodialysis, urea reduction ratio, urea Ktv, and serum parathyroid hormone levels. Patients with autoimmune disease, malignancy, hematological disorders, and acute or chronic infection were excluded from the study. Healthy volunteers (n=26), with normal hematological and biochemical values, without any history of renal or inflammatory disease, were used as normal controls. They were matched as far as possible for age and gender with hemodialysis patients.

Serum levels of IL-7 were determined by the Quantikine high sensitivity immunoassay (R & D Systems, Minneapolic, Minnesota, USA) according to the manufacturer's recommendations.

No statistically difference was found between patients and controls in total white blood cell count; however, hemodialysis patients were lymphopenic [1.5 ± 0.6 *vs* 2.2 ± 0.7 × 10^9/L, $p<0.05$], which was the result, at least in part, of a decrease in total circulating $CD3^+$ T-lymphocytes [1.0 (0.7–1.3 × 10^9/L) *vs* 1.6 (1.0–2.0 × 10^9/L), $p<0.05$] and both the $CD4^+$ [0.7 (0.4–0.9 × 10^9/L) *vs* 1.0 (0.8–1.6 × 10^9/L), $p<0.05$] and the $CD8^+$ [0.3 (0.1–0.4 × 10^9/L) *vs* 0.5 (0.3–0.7 × 10^9/L), $p<0.05$] T-cell subsets. When comparing responders and non-responders to rhEPO therapy, statistically significant differences were found for total lymphocyte [responders: 1.6 ± 0.5 × 10^9/L *vs* non-responders: 1.4 × 0.7 × 10^9/L, $p<0.05$] and $CD4^+$ T-cell counts [responders: 0.8 (0.5–0.9 × 10^9/L) *vs* non-responders: 0.5 (0.4–0.9 × 10^9/L), $p<0.05$].

No significant difference was found in serum IL-7 levels ($p>0.05$) between hemodialysis patients [10.5 (7.4–13.5 pg/mL)] and healthy controls [11.2 (7.2–16.0 pg/mL)], suggesting that the lymphopenia found in these patients is not associated with increased serum levels of IL-7. Moreover, no correlation between IL-7 serum levels and total lymphocyte count ($r=-0.21$; $p=0.11$) was found. However, among the two groups of patients, non-responders showed significantly higher IL-7 serum levels [non-responders: 12.0 (7.6–17.8 pg/mL) *vs* responders: 9.6 (6.1–11.5 pg/mL), $p<0.05$] (Fig. 1), suggesting a relationship between the increased levels of this cytokine and decreased number of total lymphocytes and $CD4^+$ T-cell count in the non-responder patients.

Increased IL-7 serum levels have also been described in other clinical settings associated with lymphopenia, namely marrow transplantation, HIV infection, chemotherapy treatment for cancer,

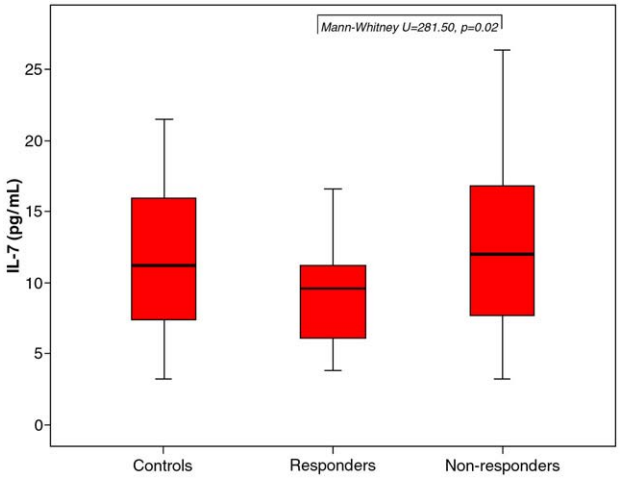

Fig. 1. Serum IL-7 levels among controls and hemodialysis patients according to the response to rhEPO therapy. Boxplot shows median value (horizontal line in box) and first and third quartiles (inferior and superior line of the box, respectively).

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and idiopathic $CD4^+$ lymphopenia [6]. The increased IL-7 serum levels found in our lymphopenic patients could be related to T-cell depletion [6]. Elevated serum IL-7 concentration may predict a lessened response to rhEPO therapy.

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