Influence of the Treatment with Recombinant Human Erythropoietin on Plasma Concentration of Interleukin-1-Alpha and Tumour Necrosis Factor-Alpha in Hemodialyzed Subjects

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Dear Sir,

Erythropoietin is the most important regulatory factor in the erythropoiesis process, but almost all cytokines can inhibit or stimulate erythropoiesis [1]. Within the substances able to perform a suppressive activity on erythropoiesis, a prominent role must be recognized to interleukin-1 (IL-1) and to tumour necrosis factor-alpha (TNF- α) [1-7].

Therefore, we decided to evaluate the plasmatic levels of IL-1 α and TNF in hemodialyzed patients undergoing treatment with recombinant human erythropoietin (rHuEPO). This study was performed to test the possible role of such cytokines in the response of the hemodialyzed patients to the treatment with rHuEPO. The variations of the plasmatic levels of IL-1 α and TNF determined by the treatment with rHuEPO were also evaluated.

Ten patients were studied (7 male 3 female, mean age 51 ± 6 years) affected by chronic renal failure, undergoing dialytic treatment 3 times a week for about 4 h. These patients had been on dialytic treatment for 8 ± 3 months, using a Gambro AK 10 system, filter 5H Cuprophan, liquid with bicarbonate Sifra SRsO SBs8. Ten normal individuals were considered as the control group.

All the hemodialyzed subjects showed an important anemic status (normochromic type); the mean predialysis levels of creatinine were 12.1 ± 2 mg/dl. No patient was on a corticosteroid therapy or on therapy with immunosuppressors and none of them had infectious or inflammatory pathologies able

to determine an important activation of the immune system. Nephrectomized patients were also not admitted in the study in order to avoid that a different response from such patients to the treatment with rHuEPO could interfere with the evaluation of the results [8].

The administration of rHuEPO was of 50 U/kg intravenously 3 times weekly immediately after the hemodialysis session. The dosage of rHuEPO was increased every 4 weeks by 25 U/kg till hematocrit values reached 30%. Before starting the treatment, plasma samples were

frozen (-20 °C) for the radioimmuno-munological dosages of IL-1 α (IL-1 α ¹²⁵I assay system, Amersham International plc, Amersham, UK).

Before measurement, plasma samples were extracted twice with chloroform.

Such dosages were also carried out in the control groups and were repeated monthly in the hemodialyzed patients during the treatment with rHuEPO until a prearranged end-point was reached (hematocrit 30%).

Plasma levels of IL-1 α in hemodialyzed subjects before they were treated with rHuEPO were 16.1 ± 7 pg/ml and did not show significant changes when compared to the control group (14.5 ± 3.2 ; $p = \text{NS}$; fig. 1). Even TNF- α plasma concentrations in the hemodialyzed and in the control group seemed superimposable (6.01 ± 1.24 pg/ml vs. 5.47 ± 1.68 ; $p = \text{NS}$). The treatment with rHuEPO for a period of 4 months was able to determine a significant increase in the plasma concentration of IL-1 α (22.1 ± 3 , $p < 0.05$;

Fig. 1. Plasma IL-1 α levels (pg/ml). * $p < 0.05$ versus hemodialyzed patients. fig. 1). No change of the plasma levels of TNF- α after the treatment with rHuEPO was found (5.70 ± 1.5 ; $p = \text{NS}$). High variability of the two cytokines within the uraemic group was observed (range 11.38-25.7 for IL-1 α and 3.6-7.9 for TNF- α). For this reason, we decided to evaluate if the patients with the highest levels of cytokines needed higher dosage of rHuEPO to reach the prearranged end-point.

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By using the correlation Pearson test, we did not find any correlation among the levels of IL-1 α or TNF- α and the need of rHuEPO.

In conclusion, our data confirm the presence of normal plasma levels of IL-1 α and TNF- α in the patients submitted to a hemodialytic treatment, as already shown by other authors [9, 10]. The results seem moreover contrasting with other studies where an increase in alpha IL-1 α and TNF- α from hemodialyzed patients was reported [11, 12]. A possible explanation for such a disagreement

may be the period of hemodialytic treatment. Our patients had been under dialysis treatment for only 8 months, whereas the patients reported by the other authors were long-term hemodialysis patients. It is well known that per se dialytic treatment is able to determine a rise in the cytokine plasma level [13]. Chronic stimulation exerted by the dialysis treatment on the cells of the monocyte-macrophage system, is likely to bring about on the long run a progressive increase in the synthesis of cytokines.

In our study, we did not find any negative action of cytokines on the efficacy of the treatment with rHuEPO.

We think that a similar investigation carried out on patients treated for a long time with dialysis and with highest plasma concentrations of IL-1 α and TNF- α may give different results. The present study shows that the treatment with rHuEPO determines an increase in plasmatic levels of IL-1 α , probably achieved modifying the activity of the cells of the monocyte-macrophage system.

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