Renal failure, anaemia, cytokines and inflammation

Sir,

We have read with interest the editorial comment by Bárány [1] on the negative effects of inflammation on erythropoiesis, and the importance of this condition as cause of resistance to erythropoietin (Epo) in dialysis patients. In this context, we would like to highlight the relevance of inflammation as a potential factor contributing to anaemia in patients with advanced renal failure in predialysis stage.

Among the compounds capable of exerting a suppressive action on erythropoiesis, a prominent role must be attributed to cytokines, including tumour necrosis factor alpha (TNF-α). Cytokines have been related, among other actions, to shortened red cell survival, abnormal mobilization of reticuloendothelial iron stores, blunted Epo response and impaired erythroid colony formation in response to Epo [2–5]. Moreover, a relevant effect of TNF-α on anaemia of chronic renal disease has been suggested [6].

In 1996 we performed a study to analyse the effects of pentoxifylline administration, a pharmacologic agent with anti-TNF-α properties, on haematologic parameters and the serum levels of this cytokine in anaemic patients with advanced renal failure [7]. We studied 12 diabetic patients with a creatinine clearance below 30 ml/min. There was no clinical evidence of blood loss, infection or neoplastic disease. The iron status was normal in all cases, defined as a serum ferritin and a transferrin saturation higher than 50 ng/ml and 20%, respectively. None were under treatment with angiotensin-converting enzyme inhibitors, androgens, Epo or theophylline preparations. Seven patients received pentoxifylline (400 mg orally daily) for 6 months, and the evolution was compared with those observed in five control patients. During the study, haemoglobin and haematocrit progressively increased in subjects receiving pentoxifylline, from
9.9 ± 0.5 g/dl and 27.9 ± 1.6% at baseline to 10.6 ± 0.6 g/dl and 31.3 ± 1.9% after 6 months, respectively (P < 0.01).
Conversely, no significant variations were observed in these parameters in the control group. Serum TNF-α levels exhibited a significant decrease with respect to basal values in patients treated with pentoxifylline (562 ± 358 vs 623 ± 366 pg/ml, P < 0.01), but not in controls.

In spite of the small number of patients, the results of this study are in agreement with the editorial comments by Bárány. Although in our work the serum levels of C-reactive protein were not measured, the elevated concentrations of TNF-α in patients with advanced renal failure, were similar to previous findings by other authors [8,9] and suggested the existence of an underlying inflammatory condition in these subjects.

Recent work has suggested that peripheral mononuclear cells from patients with chronic renal failure generate greater amounts of TNF-α than normal mononuclear cells [10]. Furthermore, both in vitro and in vivo studies show that treatment with TNF-α results in the generation of anaemia [11,12]. In our study, patients treated with pentoxifylline experienced a significant improvement of haematologic parameters, which was associated with a significant reduction of serum TNF-α concentrations. In contrast, serum Epo levels remained unchanged in patients treated with pentoxifylline, suggesting that the potential effect of this drug is not mediated by an action on Epo production.

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