Possible Mechanisms Underlying Potentiating Effects of Iron Chelators in Hematopoietic Response to Erythropoietin

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Sir,

In a recent issue of this journal, Roger et al. [1] reported their interesting experiences with the iron chelator desferrioxamine (DFO) and recombinant human erythropoietin (r-Hu-Epo) in the treatment of anemia of chronic renal failure (ACRF). The enhancing effects of DFO on Epo treatment of ACRF in their study were explained by a combination of reducing aluminum toxicity and overcoming Epo deficiency. It is likely, however, that other mechanisms may be involved that could explain their observations. Although the anemia of chronic disease (ACD), occurring in many chronic conditions such as rheumatoid arthritis (RA), has a multifactorial pathogenesis [2] different from ACRF, we believe there are some similarities.

Impaired Epo Responsiveness to Anemia. Serum Epo levels in RA patients with ACD are considerably lower than in RA patients with simple iron deficiency anemia [3,4], and Epo levels in ACD may be comparable to levels found in ACRF [5]. Indeed, it was shown that r-Hu-Epo may be of value in the treatment of anemia of RA [6], although in this study, the majority of patients had concomitant iron deficiency and were treated with iron supplementation simultaneously.

Increased Iron Stores. Increased iron stores as indicated by elevated ferritin levels [1, 2] are present if anemia is not complicated by iron deficiency. In both types of anemia, this is at least in part explained by decreased erythroblast iron utilization. Based on the concept of serum Epo levels being lower in ACD as compared to iron deficiency, we treated RA patients with ACD with the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L1). In this preliminary study, we demonstrated that L1 was able to chelate iron from iron stores and to cause a rise in Hb and serum Epo [7]. The Hb rise correlated positively with the rise in serum Epo and inversely with ferritin change. The Epo rise correlated positively with the ferritin decrease. Apparently, there is a relationship of Epo responsiveness to anemia with the dependence on iron stores, although it is unclear

through what mechanism. In ACRF, the rise in Epo responsiveness following iron chelation probably is less pronounced because the site of its production is affected although it could be argued that Epo production occurs at other sites like the liver. Rich et al. [8] have shown Epo can be produced by bone marrow macrophages. In RA patients with ACD as well as in controls, we were unable to demonstrate bone marrow Epo production [9]. These findings do not support compensatory bone marrow Epo production in ACD but it cannot be ruled out that in ACRF, a shift from renal towards bone marrow Epo production takes place. The adverse events Roger et al. [1] reported, like ocular disturbances, also occurred in a group of RA patients treated with DFO [10]. In our study, we did not observe such

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effects but the patients were treated for a short period only. In trials using iron chelators in a non-iron overload state, one should be very careful; dosages must be in relation to ferritin values; serum levels of other ions like copper and zinc must be monitored accurately. Decreased Erythroblast Iron Availability. In ACD in RA, bone marrow iron availability is reduced because of increased iron retention by the mononuclear phagocyte system [2] and impaired iron transport through the erythroblast membrane [11]. In ACRF, aluminium may block transferrin-bound iron release within the erythroid cells [12]. Iron chelators can act as iron transporters like transferrin. For LI, it has been shown that it can diffuse through the erythroblast membrane [13] and, hence, increase iron availability for Hb synthesis. LI-bound iron may also be partially transferred to transferrin [14], and iron chelators may increase the transferrin receptor expression on erythroblasts [15] and, thus, facilitate erythroblast iron transport in both ACD and ACRF. Ferritin levels decrease during treatment with r-Hu-Epo in both ACD in RA and ACRF [2, 6] suggesting iron mobilization from iron stores being utilized by proliferating erythroblasts. Like DFO, Epo is able to increase transferrin receptor expression on cells [16], whereas it also causes a rise in cellular transferrin uptake. Apparently, there are similarities in the effects of DFO and Epo on iron metabolism, and it may thus be postulated that these drugs indeed can potentiate each other. The iron released from iron stores by iron chelators may be preferentially transported to the bone marrow because of increased demands induced by r-Hu-Epo rather than being excreted in the urine. In this way, DFO treatment may reduce the amounts of Epo necessary for correcting ACRF (and possibly ACD in RA).

In conclusion, the observations made by Roger et al. [1] showing enhancing effects of DFO on Epo treatment of ACRF deserve great attention. It may be assumed that other mechanisms than aluminum chelation by DFO and increased erythroid growth by Epo are involved. Since DFO and Epo apparently possess similarities in their effects on iron mobilization from iron stores and its handling by erythroblasts, it is not unlikely that these drugs potentiate the increase in erythroblast iron availability and, hence, erythropoiesis. The toxicity of DFO shown by Roger et al. [1] demands proper patient selection, dose modifications and careful monitoring of the patients.

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