Red Cell Folate: An Appropriate Index of Folate Body Stores

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Dear Sir,

We have read with interest the paper recently published by Pronai et al. [1]. They reported an uncontrolled open study in 13 patients with anemia resistant to rHu-EPO; 8 of them received folinic acid (FA) orally (10 mg/day), and the response to rHu-EPO treatment was improved. The authors recognized no significant changes in plasma FA levels, which were clearly within the normal range during the whole study. Finally, they concluded that: 'for first time the study presents data showing that rHu-EPO affects the metabolism of FA' [1].

While not wanting to detract many virtues of this paper, concerning the controversial matter of the FA supplements, there are several methodological and interpretational issues which need further discussion. From a physiological point of view, EPO induces the activation of bone marrow cell metabolism, enhancing the consumption of FA as other substances. However, the authors did not demonstrate changes in FA metabolism since the FA stores were not evaluated all over the study.

Only serum levels were measured, which remained unchanged. The plasma folate levels are small compared to total body stores (3-18 µg/l vs. 7.5-50 mg) [2]. Red cell FA (RCFA) is the most reliable parameter to evaluate total FA stores; plasma levels reflect only recent changes in FA balance [3]. We and other groups have measured both (RCFA and SFA) in hemodialysis (HD) patients and found levels within the normal range without supplementation, and above the normal range in patients treated with supplementary FA [4, 5].

Dietetic studies clearly state that the non-severe restrictive diets used nowadays supply sufficient FA to dialysis patients [2], Normal mean intake of FA in the USA is 0.5 mg/day, and patients under very restrictive diets with a content of FA as low as 5 µg/l take 4 months in developing meg-aloblastic anemia [6]. Hence, other groups do not recommend FA supplements in adequately nourished HD patients with [5] or without EPO treatment [7].

On the other hand, this treatment could bear some risks, and there are reports of secondary effects following vitamin supplementation [8, 9]. In our experience, adequately nourished patients without FA supplements present RCFA and SFA values in normal ranges, and higher values when FA supplements are given. One HD patient with anemia resistant to high doses of rHu-EPO needed multiple blood transfusions and was treated with 10 mg/day FA during 8

months. Anemia did not improve and we found pre-dialysis values of RCFA of 11,782 µg/l (normal range 175-700 µg/l) and SFA of 853 µg/l (normal range 3-18 µg/l). These data are in agreement with other authors that found increased levels in patients receiving FA at doses under those of Pronai [4, 9].

Another question is the improvement of the response to rHu-EPO following FA treatment. The authors labeled 13 patients as EPO resistant after a period as short as 1 month in some cases (range 1-27 months). No information is available about urea kinetics, an important factor in rHu-EPO resistance [10], and about the EPO dose protocol, only the mean doses that seem not excessive (75 U/kg × 3/week). Other authors failed to demonstrate a better response of rHu-EPO patients receiving FA supplementation [5].

The authors recommended a close observation of MCV for the decision whether FA is necessary or not. However, this is difficult to assume since it is generally accepted that rHu-EPO causes an increment in the reticu-locyte count that raises MCV values [10].

Finally, we believe that this article suggests a 'possible role' for FA in patients with rHu-EPO-resistant anemia, but failed to follow up FA stores. Red cell folate is the best marker of folate deficiency, and supplementation may be restricted to malnourished patients or patients with proven FA deficiency. Hence, we avoid an unnecessary treatment that may carry some risks.

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