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EDITORIAL

Evaluating iron sufficiency: A clearer view

Anemia is a frequent and serious complication of end-stage renal disease (ESRD). Since the introduction of recombinant human erythropoietin (EPO) into clinical practice in the 1980s, our understanding of the importance of iron supply for optical erythropoiesis with EPO has increased. In the past decade we have clearly learned that anemia management can be optimized only if *functional iron deficiency* can be avoided [1, 2]. During functional iron deficiency, erythropoietic capacity of the bone marrow to respond to epoetin is limited by iron release from storage sites and/or by a limited capacity to transport iron via transferrin [3]. The National Kidney Foundation–Dialysis Outcomes Quality Initiative (NKF-DOQI) guidelines advocate aggressive detection and management of functinoal iron deficiency [4]. The presence of functional iron deficiency is confirmed by the response to a course of parenteral iron that produces either a decrease in dose of EPO needed to maintain the terget hematocrit level or an increase in hemoglobin at the same dose of epoetin. Analysis of these "iron restoration" protocols, the most common of which administer 1000 mg of parenteral iron over five to ten consecutive dialysis treatments, indicates that ferritin increases from a pre-treatment mean of 209 ng/mL to a post treatment mean of 447 ng/mL [3]. The latter is higher than the upper limits for a normal population and is of concern to many physicians.

These experiences underscore the limits of the currently used iron indices to accurately indicate the iron supply needs in EPO-treated dialysis patients. Avoidance of iron-limited erythropoiesis anemia depends on its detection. Under normal conditions, plasma transferrin is 30 to 40% saturated with iron. Overall serum ferritin levels reflect iron stores but levels are well known to increase in inflammatory conditions [5]. Recently, uremia, per se, has been described as an inflammatory state, perhaps explaining the poor correlation between ferritin levels and marrow iron stores in patients on dialysis. What is frequently forgotten is that transferrin, the iron transport protein commonly measured as total iron binding capacity, is a negative acute phase reactant and is thus decreased in ESRD by an average of one third compared to subjects without kidney disease [6]. As a result, the total iron transport capacity of plasma is decreased. Transferrin saturation values of 20 to 30% in ESRD patients are comparable to values of 13 to 20% in normal patients. Yet, because of increased blood losses and shortened red cell survival associated with ESRD, production of red cells has to be normal to slightly increased to maintain hemoglobin levels higher than 11 g/dL. The low total iron-binding capacity may one of the key mechanisms leading to functional iron deficiency in ESRD patients since a low capaicty would automatically limit uptake from tissue stores.

It is therefore not surprising that functional iron deficiency does develop and that a transferrin saturation level higher than 20% or a serum ferritin level higher than 100 ng/mL, levels recommended by NKF-DOQI [4], cannot exclude the presence of functional iron deficiency. Marrow iron deficiency can develop in ESRD patients at transferrin saturation values approaching 30% or ferritin levels in excess of 500 ng/mL. The only definitive way to show that functional iron deficiency is not present is to demonstrate no change in erythroid response to *additional* iron administration. Our studies demonstrated that increasing transferrin saturation from 20 to 30% to 30 to 50% with intravenous iron dextran in "iron-replete" hemodialysis patients resulted in a decreased need for EPO to maintain hemoglobin of 10 to 12 g/dL, that is, a higher epoetin response index (hematocrit or hemaglobin/weekly EPO dose). However, mean ferritin rose progressively to values approaching the upper limits of those recommended by NKF-DOQI [1].

The dilemma arising is how to provide sufficient iron to achieve and maintain the target hemoglobin level of $\geq$11 without incurring an excessive accumulation of body iron [8]. The key question in the optimal use of iron to manage anemia in patients with ESRD is whether there are readily available hematopoietic parameters that can detect functional iron deficiency that is superior to the traditional measures, can be measured sequentially to guide iron and indirectly EPO therapy, and yet is inexpensive. I believe the answer is yes. In our study, content of hemoglobin in reticulocytes (CHr) increased in the patients maintained at the higher level transferrin saturation range of 30 to 50% and the epoetin response index increased, indicating more efficient erythropoiesis. In this issue of *Kidney Internationa*, Fishbane et al extend their previous work [9] and report findings on the use of CHr compared to the traditional iron indices in guiding iron therapy in EPO-treated hemodialysis patients

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[10]. In this study, Group 1 patients received a "pulse" of 1000 mg over ten treatments if they met the traditional criteria of transferrin saturation less than 20% or ferritin less than 100 ng/mL compared to Group 2 patients in whom the CHr criteria of less than 29 pg hemoglobin. The average amount of iron administered was less than half in the group assessed with CHr and this resulted in lower ferritin levels but no difference in transferrin saturation or CHr levels at study end compared to Group 1. Importantly, neither the hematocrit level nor the epoetin response index differed at study end. Because hemoglobin varies independently of therapy within subjects over time and the standard deviation of this variation is large, 0.4 to 1.4 g/dL among patients (unpublished observation), it is difficult to use criteria of a 1 g/dL increase in hemoglobin or a 15% decrease on weekly EPO dose within 8 weeks of the pulse dose of intravenous iron as "absolute" in diagnosing functional iron deficiency. However, I do believe that the nearly twofold difference in positive predictive value of diagnosing "functional iron deficiency," CHr versus the traditional iron indices will stand up over the course of time.

Why should CHr be a better measure than other indicators of iron in our patients? Assessment of iron-limited erythropoietic activity can be done with repeated bone marrow tests (too invasive) or sophisticated ferrokinetic studies (too expensive and time consuming). The cells actively utilizing iron for the synthesis of hemoglobin are in the bone marrow, not in the peripheral circulation. Reticulocytes are the immature red blood cells closest to this process that we can easily assess and identify in adequate qualities from the peripheral blood. When red blood cell production is normal, they exist in the circulation for only 1 to 2 days but reflect the iron-status that existed 3 to 4 days before when iron incorporation into hemoglobin was at its maximum. Thus, the amount of iron available during red blood cell development is reflected in the hemoglobin content of the reticulocytes. Studies have shown that CHr is a more accurate measure of the iron supply to the developing red blood supply progenitors during the EPO therapy than are serum ferritin and transferrin saturation in both normal patients [11] as well as in patients with ESRD [12]. The CHr is a relatively fast responsive marker of iron status. A single dose infusion of intravenous iron results in correction of iron deficiency at the level of the reticulocyte within 48 hours [13]. Some markers that measure hemoglobin levels in more mature red blood cells (% hypochromic red blood cells in the peripheral blood) are not as likely to pick up changes in iron delivery as quickly, since it takes time for the change to be seen in a larger older population of cells.

The CHr values used to define iron deficiency have evolved as the technology has improved. Iron-limited erythropoiesis is defined as a Chr value less than 29 pg using third-generation analyzers. Our own observations indicate that CHr can be used during maintenance iron therapy to adjust the parenteral iron doses (unpublished observation). It is particularly useful in those cases in which ferritin exceed 500 ng/ml but TSAT is less than 15%. In many cases, the CHr indicates abundant iron delivery permitting downward adjustment of iron dose. We also use Chr measurements in conjunction with C-reactive protein, a sensitive marker of inflammation. If the C-reactive protein is normal (less than 10 mg/L), we attempt to find the lowest maintenance iron dose that maintains Chr higher than 31 pg and will maintain that dose even if the transferrin saturation decreases to less than 20% so long as ferritin is greater than 100 ng/mL. If the patient has a low CHr and a high C-reactive protein (higher than 15 mg/L), then we believe that providing additional iron might be problematic because the patient is either inflamed or has an infection. In this situation, we look for reversible causes of inflammation, treat them and cut back on the iron therapy. Much of our experience is still evolving as we search for means of optimizing iron delivery yet avoiding excess iron. The cost of the test is significantly lower than that of the conventional iron indices and does not require any additional blood besides that which is routinely sent for Coulter counter hemotology. In this era of cost-effectiveness, further studies with CHr will no doubt define optimal iron management.

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