Anemia Management in Chronic Kidney Disease: Role of Factors Affecting Epoetin Responsiveness

JOSEPH W. ESCHBACH

The article by Coladonato et al., “Trends in Anemia Management among US Hemodialysis Patients,” (1) notes an encouraging increase in mean hematocrit levels from 31.1% to 34.1% between 1994 and 1998, an increase into the target range (33 to 36%) recommended by the 1997 and 2000 DOQI Anemia Work Groups of the National Kidney Foundation (2,3). On the other hand, the authors claim in this analysis of up to 7660 hemodialysis patients that this rise in hematocrit was associated with a disproportionate increase in recombinant erythropoietin (epoetin) dosing, suggesting that there were factors blunting the response to epoetin. The implication of the authors is that American nephrologists are not using epoetin in an effective and optimal manner.

Part of their analysis is based on an imprecise understanding of the action of epoetin, and part of their analysis is relevant, but their translation of this information into improved therapy is less clear.

In the thirteen years since the US Food and Drug Administration approved epoetin for clinical use, the mean hematocrit of ESRD patients has gradually increased from <30% to >34%. The achievement of these favorable results has required increasing amounts of epoetin (1,4). On the one hand, there is a biologic need for more hormone to attain higher hematocrit levels; on the other hand, there are factors that can blunt the response to epoetin and therefore increase epoetin usage.

Coladonato et al. (1) noted that a 17.2% increase in epoetin dose was needed to increase the hematocrit 9.7% from 31.1% to 34.1%. The authors consider this a disproportionate increase in epoetin and attempt to verify this by using a nonphysiologic term, “EPO Resistant Index”. The ERI is defined as the average weekly dose of epoetin divided by the mean hematocrit. Because the ERI increased in association with the increased hematocrit, the authors assume that there are nonbiologic factors to explain the increased epoetin requirements. The reason this is not a physiologic term is that at least three studies have shown that it requires approximately two times the dose of epoetin to increase the hematocrit of 30 to 33% to 40 to 42% (5–7). If the ERI were physiologic, doubling the epoetin dose should result in a hematocrit of 60%!

There is a broad range of response to epoetin, both in ESRD and normal subjects (8). Although there is a dose response “curve” with epoetin (9), there is also a wide individual range of response to a fixed dose of epoetin (10). In the first US multicenter study of iron-replete hemodialysis patients, 15 U/kg to ≥150 U/kg of intravenous epoetin three times a week were needed to maintain a hematocrit of 32 to 38%. This variable response was also noted in clinical trials with epoetin in which the percent of patients reaching target hematocrit was a function of the starting dose of epoetin (11).

Only 25% of patients reached target with 25 U/kg three times a week versus 96% treated with ≥150 U/kg three times a week. The increase in epoetin dosage was logarithmic, not linear, to achieve these results.

Nevertheless, despite the nonlinear and biologically variable responses to either native or exogenous erythropoietin, Coladonato et al. (1) have defined variable factors that influence epoetin responsiveness and its associated hematocrit response. Male gender, more years on dialysis, older age, higher urea reduction ratio (URR) and transferrin saturation, use of intravenous iron, and lower serum ferritin were noted to be favorably associated with higher hematocrit levels. It was also noted that those patients achieving higher hematocrit values tended to require less epoetin. In addition, increasing weight, URR, and transferrin saturation, male gender, diabetes mellitus, and older age were associated with significantly lower epoetin doses. Although some of these variables may be biologic, others can influence the management of anemia in ESRD patients, such as iron deficiency.

Patients with hematocrit levels >33% required less epoetin. However, the data depict only the converse: higher doses of epoetin were required below a hematocrit of 33%, with no further decrease in epoetin requirements at hematocrit levels >33%. There may be several explanations for this observation. Patients with lower hematocrit levels often have been infected or have had surgery, leading to an inflammatory block and therefore epoetin hyporesponsiveness. Nephrologists are evidently using more epoetin to try to improve the hematocrit in this setting. On the other hand, absolute or functional iron deficiency may also be contributing to this “extra” use of epoetin. In Coladonato et al. (1), <60% of patients were getting intravenous iron if their transferrin saturation (Tsat) was <20%. As a result, 6 to 8.5% of patients had absolute iron deficiency (Tsat, <20%; serum ferritin, <100 ng/m); 40 to 50% of those with hematocrit values <33% had either functional iron deficiency and/or inflammation, because they had Tsat values of <20% in association with normal serum ferritin levels. Unfortunately, the authors neither discuss functional iron deficiency, a condition that will occur in every epoetin-treated patient unless adequate iron reserves are maintained and/or replenished with intravenous iron, nor do they attempt to separate inflammatory block from functional iron deficiency. This is important because intravenous iron is needed for the latter and is not effective in the former condition.

More of the patients with hematocrit values >33% were receiving intravenous iron than patients with lower values. Unfor-
fortunately, the use of intravenous iron continues to be controversial; therefore, many patients are denied adequate iron stores to meet the need for optimal epoetin-induced erythropoiesis. When the only intravenous iron preparation available for use in the United States was iron dextran, the 1:150 occurrence of anaphylaxis restricted its use. There are now two safer forms of intravenous iron available: iron gluconate and iron sucrose, which are not associated with dextran-induced anaphylaxis and which should increase the use of intravenous iron. Like any intravenous product, iron must be given for specific indications and iron status must be monitored regularly. In Seattle, the DOQI guidelines for intravenous iron administration have been followed for the past 5 yr (2). Tsat and serum ferritin are measured every 3 mo, and intravenous iron is not given if the Tsat or the serum ferritin exceed 50% or 800 ng/ml, respectively. Five percent of patients transiently exceed these limits. The mean Tsat and serum ferritin levels were 30 ± 13% and 389 ± 307 ng/ml, respectively, in June 2001, associated with a hematocrit of 35.9 ± 3.7% and an epoetin dose of 193 ± 245 U/kg per wk for 988 patients (12). This indicated that by maintaining adequate iron stores by weekly intravenous iron doses of 15 to 125 mg of iron gluconate the mean hematocrit was greater and was achieved with less epoetin than that reported by Coladonato et al. (1) for 1998. Higher hematocrits can only be achieved without inappropriately higher epoetin doses if iron replacement is given on a regular basis (i.e., weekly or biweekly) to replace the repetitive dialyzer blood losses and to prevent functional iron deficiency. The observation by Coladonato et al. (1) that the use of intravenous iron was inversely proportional to the hematocrit and directly proportional to the epoetin dose conflicts with their later statement that intravenous iron use is associated with higher epoetin doses and higher hematocrit levels. More epoetin is needed to achieve higher hematocrit levels, and more iron will also be needed, but it is unlikely that the extra iron will prevent the need for more epoetin. More iron will be needed to maintain a higher hematocrit because iron losses from whole blood dialyzer residual increases as a function of more red blood cells in that residual.

The observation that heavier patients require less epoetin to achieve similar hematocrit levels as occurs with less heavy patients is intriguing. This also applies to Seattle dialysis patients (12). Either more epoetin is given to less heavy patients to attain the target hematocrit or heavier patients are more sensitive to the effect of epoetin. However, improving nutrition and increasing the weight of obviously undernourished patients should help reduce epoetin requirements. It is unfortunate that the authors purposely did not analyze serum albumin levels and its relationship to the other variables analyzed. They correctly note that a low serum albumin has a strong association with higher epoetin doses. However, the relationship among weight, gender, albumin levels, nutrition, and epoetin responsiveness is not clear. In Seattle, as also reported by Coladonato et al. (1), men required less epoetin than women, but men also had significantly higher serum albumin (bcp method) levels. Serum albumin levels also decreased in both genders as epoetin doses increased (12). The decrease in albumin levels as a function of increasing epoetin doses could be the result of inflammation/malnutrition, or it could be biological, but the lower albumin levels observed in women compared with men is unlikely to be solely the result of inflammation or malnutrition.

Older age and longer duration of dialysis were noted to be associated with higher hematocrit and/or better epoetin responsiveness. Before the availability of epoetin, it had been observed that patients over time had a tendency to increase their hematocrit (13). Whether this was the result of more native erythropoietin secretion from the liver and/or remnant kidneys or the result of the presence of other erythroid growth factors, such as insulin-like growth factor-1 (14), is not known. Epoetin-treated ESRD patients occasionally develop normal hematocrit levels and no longer require epoetin therapy, confirming that native erythropoiesis may improve with time in some patients.

Only 12% of patients received their epoetin subcutaneously. Those patients required 11% less epoetin to maintain the same hematocrit as achieved with intravenous dosing. It has been known for over 12 yr that epoetin given subcutaneously is more effective for the majority of patients than if given intravenously. The cost implications of this are significant. If an additional 12%

---

**Figure 1.** Distribution of normal hemoglobin values for healthy men and women with superimposed recommended target hemoglobin level for patients with chronic kidney disease. Adapted by A. Besarab with permission from reference 21.
of patients were to use epoetin subcutaneously, this would amount to a savings of $110,000,000 on the basis of the one billion dollar expenditure for epoetin in 1999 (15). Unfortunately, there is a negative cost incentive to reduce the amount of epoetin administered because dialysis centers rely on the “profits” achieved from Medicare-reimbursed payments. Ideally, every patient receiving an erythropoietin preparation before beginning dialysis should continue with subcutaneous injections.

One encouraging observation from Coladonato et al. (1) is that the percent of patients achieving hematocrit levels >36% has increased from <10% to >30% between 1994 and 1998. Nephrologists are realizing that patients not only feel better at these closer-to-normal levels, but there have been no significant side effects with this improved hematologic state. In view of the increasing number of studies now showing even superior functional, survival, and quality-of-life status at a normal hematocrit, (16–20), the day will come when governmental reimbursement mechanisms will allow our patients with chronic kidney disease to enjoy the same hematocrit/hemoglobin values as normal subjects, adjusted for gender, as seen in Figure 1. It is inevitable that more epoetin will be needed to achieve this goal, but it is imperative that every effort be made to optimize the effectiveness of epoetin to minimize its cost burden. Maintaining optimal iron balance, improving nutrition, which includes optimal dialysis, minimizing the chances for infection (e.g., avoiding central catheters), and administering the hormone subcutaneously will all help to achieve this goal.

References