Guidelines for Anemia Treatment in CKD

In this month’s issue, ASN Kidney News editorial board member Edgar Lerma interviewed Allen Nissenson, MD, about the new guidelines for treating anemia in chronic kidney disease. Nissenson is currently chief medical officer of DaVita, Inc. He is also emeritus professor of medicine with the David Geffen School of Medicine at UCLA, where he served as associate dean for special projects during the previous three years.

Nissenson has been active in the American Society of Nephrology, National Kidney Foundation, Renal Physicians Association, and American Heart Association. He was founding member, then president, of the National Anemia Action Council from 2001 to 2007, and he continues to be involved with policies and implications of recent changes in the management of anemia and the role of erythropoiesis-stimulating agents on outcomes, morbidity, and mortality.

The decision regarding the optimal hemoglobin target for a particular patient should be made jointly between the nephrologist and patient.

It appears that the studies confirm observational trials showing that patients who achieve a higher hemoglobin level have the best outcomes, while those who don’t achieve higher hemoglobin have a poorer outcome.

On the other hand, targeting a higher hemoglobin in a large population will uncover a group of patients who are poor responders to ESAs, have lower achieved hemoglobin, and receive large doses of ESAs and usually parenteral iron as part of the study protocol. It is this latter group of patients, probably with chronic inflammation, who have the adverse outcomes. Still unclear is whether the underlying inflammation, the high ESA dose, the large amount of iron, or some combination of these drives the increased morbidity and mortality.

Are there any other ongoing trials that might settle this ongoing dilemma—for example, TREAT, STIMULATE (which looks at the ESA Hematide™’s ability to stimulate production of red blood cells), and NEPHRODIAB2?

More data will be helpful, but it is questionable whether these large clinical trials will resolve the dilemma regarding targeted vs. achieved hemoglobin and mortality and morbidity. These trials are likely, however, to help resolve the controversy over patient-reported outcomes and quality of life because they are carefully assessing quality of life at various hemoglobin levels.

What about the new recommendations—such as monitoring of response—regarding administration of ESAs?

Current package insert recommendations for maintaining hemoglobin at 10–12 g/dL and avoiding dose escalation in patients seemingly resistant to ESAs seem prudent. Similarly, current CMS reimbursement policies created to incentivize maintaining this same level of hemoglobin are largely reasonable.

Recent policy to have a cutoff of ≥400,000 units per month is more problematic. First, there is an overrepresentation of patients in this category with malnutrition/inflammation and hemoglobinopathies who may need high ESA doses or will receive multiple transfusions. Decisions regarding ESA administration involve tradeoffs and should be made by the nephrologist and the patient, not the payer. Second, if the ESA dose is exceeded, CMS now denies the entire claim for the month including all erythropoietin (EPO), dialysis treatments, and other medications. This sort of administrative approach is overly punitive and clearly not patient-centered.

What are the new CMS guidelines regarding coverage for ESAs that came about as a result of the ongoing debate over their use? Aside from the obvious cost benefits, do you think the CMS guidelines will have a positive or negative impact on patients’ overall care, in terms of morbidity and mortality?

Clearly, the CMS guidelines were developed following the concern about safety at higher hemoglobin levels and charges by some that ESAs were being overused for profit. Unfortunately, the new policy has already resulted in a movement of the hemoglobin distribution curve to the left, resulting in fewer patients treated with ESAs with achieved hemoglobin >13 g/dL and more patients with hemoglobin ≥400,000 ng/mL should not routinely receive iron. The last recommendation was based on a lack of evidence from RCTs on the beneficial effects of iron above this level of ferritin, although no evidence of harm was apparent from the literature.

Tell us more about the dilemma regarding target hemoglobin levels and how the CHOIR and CREATE trials played significant roles in this conundrum.

The debate is about the importance of achieved versus targeted hemoglobin. CHOIR, CREATE, and the Normal Hematocrit Cardiac Trial (NHCT) are the key studies that contributed to the debate, but investigations are now beginning to help unravel the science.

The guidelines panel met again in the spring of 2007 to consider all of the new evidence, including several new randomized controlled trials (RCTs). After extensive evaluation, analysis, and discussion, the panel’s key recommendations included: 1) a clear articulation about the difference between target and achieved hemoglobin and the implications for interpreting the literature; 2) a clinical practice recommendation (insufficient evidence existed for a clinical practice guideline) that target hemoglobin should be 11–12 g/dL; 3) a clinical practice guideline with moderately strong evidence that hemoglobin should not be targeted to ≥13 g/dL; and 4) a clinical practice recommendation that patients with ferritin ≥500 ng/mL should not routinely target hemoglobin and the implications for in-
<10 g/dL. Time will tell if this change results in better or worse outcomes.

**What do you think about Medicare coverage of ESAs only for patients at stage 3 or higher chronic kidney disease (CKD)?**

This would clearly be an inappropriate policy. The indication for ESAs should be anemia caused by CKD. Although it is not common for anemia of CKD to be present when GFR is >60, it occasionally occurs. This is one of the only situations in which determining the serum EPO level may be useful and appropriate.

**Could you comment on how the updated changes in iron parameters might affect management of concomitant iron deficiency?**

The recommendation for use of serum ferritin as a guide to iron administration has been widely misinterpreted. Most people believe the guideline group recommends holding iron if the ferritin is >500 ng/mL. That is not the recommendation, which states that routine administration is not recommended at that level. In addition, clinicians should consider the results of the DRIVE (Dialysis Patients’ Response to Intravenous Iron with Elevated Ferritin) studies, which may modify their approach to this recommendation.

**How will these new guidelines and updates affect nephrologists’ practice? What are the pros and cons?**

Unfortunately, the guidelines have rapidly become considered standards of care and do drive clinical practice and publically reported data. They are used as the basis for pay for performance. It is still the obligation of every practitioner to do what is best for each individual patient and take guidelines as just that—tools to assist in decision making.

**What does the future of anemia in CKD hold? What new ESA products are on the horizon, e.g., CERA (continuous erythropoietin receptor activator) or HIF (hypoxia-inducible factor)? Are there new pharmacologic adjuvant drugs on the horizon, e.g., L-carnitine or Vitamin C? How far are they from being ready for prime time?**

We are about to see an explosion of new products and approaches to anemia management. In addition to enabling us to better understand the pathogenesis and management of anemia, these products may permit achieving whatever target hemoglobin we choose more safely and efficiently. Bio-similar (generic) ESAs, HIF- prolyl hydroxylase inhibitors, EPO-mimetics, and gene therapy are all approaches that are currently undergoing phase II and III clinical trials. Agents such as these are likely to be on the market in the next several years.

**When is the ideal time to start ESAs and iron replacement or supplementation therapy?**

I believe that the bulk of the evidence shows that no patient should have a hemoglobin <10 g/dL. I start an ESA as this figure is approached. Iron should be administered if transferrin saturation is <20 percent or ferritin <100 ng/mL.

**In this age of evidence-based medicine, please give us your advice regarding the appropriate management of anemia of CKD in light of all of the published RCTS and guidelines.**

The key is to maximize benefits while minimizing risks and individualizing care. For the vast majority of patients, maintaining the hemoglobin at 10–12 g/dL will achieve this balance. For some patients, however, the ability to function and quality of life are not optimized until the hemoglobin is higher. The decision regarding the optimal hemoglobin target for a particular patient should be made jointly between the nephrologist and patient. Finally, nephrologists need to focus greater attention on the ESA-resistant patient and not continue to escalate ESA doses if there is not hemoglobin response in these individuals.