ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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American Society of Nephrology – Comments
Centers for Medicare & Medicaid Services
Medical Evidence Development and Coverage Advisory Committee (MedCAC) meeting
Presented by Wolfgang Winkelmayer, MD, ScD, FASN
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Dear Ladies and Gentlemen:

My name is Dr. Wolfgang Winkelmayer, and I am a clinical nephrologist, Director of Clinical Research, and Associate Professor of Medicine at Stanford University School of Medicine. I am speaking today on the behalf of the American Society of Nephrology, a large not-for-profit organization of 11,000 physicians and scientists dedicated to promoting excellence in the care of patients with kidney disease.

Anemia is a common complication in patients with advanced chronic kidney disease (or CKD) and occurs in most patients even before they require chronic dialysis treatment. Prior to the availability of erythropoietin treatment, patients with advanced CKD were often anemic and blood transfusions were common. Epoetin alfa was approved by the US FDA based on studies demonstrating its efficacy in reducing the requirement for blood transfusions. Availability of the drug for clinical use in 1989 led to a demonstrable effect on reduced transfusion rates on a population level.

The effectiveness and safety of epoetin in patients with CKD not requiring dialysis, however, was not formally examined in large trials until many years later.

In 2006, results from two landmark trials of CKD patients were presented. The CREATE trial studied 603 patients with advanced CKD to respective target hemoglobin concentrations of 13-15 g/dL or 10.5-11.5 g/dL using epoetin beta. It showed no differences between the study arms in the risk of the composite cardiovascular endpoint. Higher hemoglobin targets, however, did result in improved quality of life measures.

The CHOIR trial compared hemoglobin targets of 13.5 g/dL versus 11.3 g/dL in 1432 patients with CKD. The higher hemoglobin target group experienced a 34% increased risk of the composite endpoint of death and cardiovascular events. A direct consequence of these findings, addition of a black-box warning to ESA labels was implemented in March 2007.

More recently, TREAT studied 4038 patients with CKD, diabetes, and anemia. Patients were randomized to treatment with darbepoetin to a target hemoglobin of 13 g/dL or placebo with rescue darbepoetin treatment at hemoglobin ≤9 g/dL. TREAT revealed that both study groups had similar rates of the primary and several secondary endpoints. Quality of life was significantly but not meaningfully different between the two groups. There was, however, an increased risk of stroke in the higher hemoglobin target group as well as higher mortality in patients with preexisting cancer.

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Thus, the hypothesized benefits of more aggressive hemoglobin targets and, implicitly, higher ESA dosing, did not materialize, with important safety signals from more aggressive approaches discovered in two of these three trials in CKD patients.

Where do we stand in March 2010, in our considerations of the appropriate place of ESAs in the treatment of anemia in patients with CKD? Most scientists and clinicians familiar with the evidence would agree on two things:

First, ESAs are doing exactly what they were originally approved for – they help avoid blood transfusions as most recently reaffirmed in TREAT. Twice as many patients required transfusions in the placebo arm compared to the darbepoetin arm.

Secondly, more aggressive anemia management does not yield better outcomes, at the very least, and may actually be harmful in some patients. Thus, the value proposition in favor of using ESAs to treat patients with CKD towards more normal hemoglobin concentrations compared with strategies that maintain more moderate hemoglobin concentrations is not supported by the evidence.

The difficult question faced by clinicians and payors is what level of ESA treatment or what hemoglobin target may optimize the balance among benefits, risks and costs. The answer to this question is currently unknown.

It remains an important treatment and policy goal to avoid transfusions in the CKD population. This is based on the very important consequences of immune sensitization in these patients. Many CKD patients will eventually reach end-stage renal disease, with kidney transplantation being the preferred option both from a patient and from a payor perspective. Each transfusion that these patients receive may reduce the likelihood of receiving a transplant, and those who receive a transplant face diminished chances of long-term function of their transplant kidney. Thus, it is clinically of the utmost importance to avoid transfusions in order to not jeopardize these patients' prospects of receiving and maintaining a kidney transplant.

Of note, considerations of equity also come into play. Women and African Americans are at increased risk of requiring transfusions and these population subgroups would be particularly endangered by any unreasonable barriers to receiving ESAs.

In addition, we still cannot rule out that an intermediate hemoglobin target DOES yield clinical benefits in terms of reduced morbidity, mortality, or increased quality of life. The three major ESA trials in CKD patients do not inform these considerations, as patients in their respective less aggressive treatment arms uniformly had hemoglobin concentrations that were in the intermediate range, on average (10.5-11.5 g/dL), which is perfectly compatible with current guideline recommendations. Thus, the crucial question of whether conservative ESA treatment with intermediate target hemoglobin concentrations, as currently recommended, may yield important clinical and patient-reported benefits over no treatment or bare-bone rescue treatment strategies remain unanswered.

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While observational in nature, a recent study in JAMA has hinted that such benefits may actually arise. Dialysis facilities treating patients with severe anemia aggressively had lower mortality among their patients compared to those using less aggressive ESA treatment. While this analysis cannot establish causality, it clearly indicates that ESAs used in moderation among severely anemic patients may be beneficial, a hypothesis that ought to be tested in future trials.

In summary, we derive from the available evidence that current ESAs may be dangerous if used for overly aggressive treatment targets compared with practices that are compatible with current treatment guidelines. Continued access to these medications is required, however, to give patients with CKD a fair chance at first receiving and then maintaining the function of a kidney transplant. Swift action is needed to support comparative effectiveness research that closes the evidence gap in the optimal role of ESAs in the treatment of relatively severe anemia and to more modest treatment targets while maintaining these patients transfusion-free.