Mortality Risk in Dialysis Patients with Naturally Higher Hemoglobins

Antonia M. Harford* and Philip G. Zager†

*University of New Mexico Health Sciences Center, Albuquerque, New Mexico; and †Dialysis Clinics, Inc., Albuquerque, New Mexico

Pioneering studies by Eshbach1 demonstrated the effectiveness of treating the anemia of ESRD with erythropoietin-stimulating agents (ESAs). These results led to more aggressive treatment of anemia in an effort to improve quality of life and survival for dialysis and predialysis patients. Unfortunately, clinical trials do not confirm the benefits of an aggressive correction and rather suggest that it may be harmful,2-5 leading to calls to rethink the goals for ESA treatment of renal anemia.6-8

The Normal Hematocrit Trial studied 1233 hemodialysis patients with heart disease.2 Participants were randomly assigned to target hematocrit values of 42 and 30%. The primary end point was time to death or first nonfatal myocardial infarction. The study was stopped after 29 months, when the number of deaths and first nonfatal myocardial infarctions were higher in the normal hematocrit arm. Although the difference in event-free survival between groups did not reach the prespecified boundary for stopping the trial, the difference in mortality made it unlikely that continuing would reveal a benefit for the normal hematocrit arm. The mean dosage of epoetin was threefold higher in the normal hematocrit arm. These results suggested that using high dosages of epoetin to target a normal hematocrit may have adverse effects. However, within each arm was an inverse relationship between achieved hematocrit and mortality. The excess of prespecified events in the normal hematocrit arm may have occurred largely in resistant patients who received high epoetin dosages but failed to achieve the target hematocrit.

Three recent randomized clinical trials of patients with CKD also failed to demonstrate a benefit associated with targeting a normal hemoglobin concentration.3-5 The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study randomly assigned 1432 patients to receive epoetin alpha therapy to achieve a hemoglobin level of 13.5 versus 11.3 g/dl.5 The primary outcome was a composite of cardiovascular events. There were more composite events in the group targeted to achieve a hemoglobin level of 13.5 versus 11.3 g/dl. There was no difference in quality of life between the arms.

The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin β (CREATE) study explored the hypothesis that targeting hemoglobin levels of 13.0 to 15.0 g/dl versus 10.5 to 11.5 g/dl would reduce cardiovascular events in 603 patients with CKD and mild to moderate anemia (11.0 to 12.5 g/dl).3 The primary end point was a composite of cardiovascular events. The median weekly epoetin beta dosage was 5000 and 2000 IU in the arms targeted to full and partial correction of anemia, respectively. The trial was stopped after the second interim analysis because the conditional power for demonstrating a benefit in the normal hemoglobin group was <5%. However, neither the efficacy nor the futility boundaries had been crossed, but the risk for cardiovascular events favored the arm with the lower hemoglobin target. There was significant improvement in quality of life but an increased risk for ESRD in the normal hemoglobin arm.

The Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) randomly assigned 4038 patients with CKD, type 2 diabetes, and mild anemia to treatment with darbepoetin alpha versus placebo to target a hemoglobin level of 13 versus 9 g/dl.4 There were no significant differences in the occurrence of either of the composite end points—death and cardiovascular events or death and ESRD—between the arms. However, fatal and nonfatal strokes were increased significantly in the normal hemoglobin arm.

Only limited data are available from the preceding studies on the relationship of ESA dosage to cardiovascular events and all-cause mortality. Therefore, it is difficult to tease out the relative contributions of achieved hemoglobin and ESA dosage to the selected primary and secondary outcomes. It is possible that high
dosages of Epogen may contribute to the adverse outcomes associated with targeting high hemoglobin values.

The study by Goodkin et al. in this issue of JASN provides evidence that hemoglobin concentrations >12 g/dl, per se, may not be associated with increased mortality. These investigators used data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) to compare mortality and quality of life among hemodialysis patients who maintained hemoglobin concentrations >12 g/dl for 4 months without (endogenous EPO; n = 545) or with (other; n = 29,251) ESA therapy. Sensitivity analyses identified 86% of the endogenous EPO patients as not receiving ESAs in the 8 months after the study period. In aggregate, crude mortality was significantly lower among the endogenous EPO group compared with the other group. However, when stratified by hemoglobin concentrations of 10 to 12 g/dl and ≥12 g/dl, there were no significant differences in mortality in either stratum. Furthermore, after adjustment for case mix and region, mortality was similar in the endogenous EPO and other groups (relative risk 0.98; 95% confidence interval 0.80 to 1.19).

We need to exercise caution in interpreting the results from this important study. Because the investigators did not measure circulating epoetin in the endogenous EPO group, we cannot assess the relationship of epoetin level to mortality. Second, because data on epoetin administration were not collected between the time they entered DOPPS and the 4-month survey time, some patients in the endogenous EPO group may have received exogenous epoetin. Third, the causes of ESRD were quite different in the two groups. Cystic disease was more common in the endogenous EPO group and diabetes in the other group. The impact of ESRD etiology may not have been fully accounted for in the adjusted models. There also was considerable heterogeneity in the mean ESA dosage in the other group across countries, lowest in Japan and highest in North America; therefore, the results of this study may not be broadly generalizable across all racial or ethnic groups.

The results of this study are in concert with a recent study of 12,733 prevalent hemodialysis patients. In aggregate, mortality was increased among patients who received ≥20,000 U/wk epoetin but not in the subgroup of these patients who achieved hemoglobin concentrations of ≥12 g/dl.10 It is important to consider the relationship between ESA dosage and achieved hemoglobin level. It is reasonable to postulate that epoetin resistance may be a surrogate marker for comorbidities, which increase mortality.

Goodkin et al. have asked an important question with regard to anemia management in ESRD: Is a normal hemoglobin concentration, per se, associated with adverse outcomes? The results of their study suggest that we need additional data to develop updated guidelines for the optimal treatment of anemia in ESRD.

DISCLOSURES

Dr. Zager has served as a paid consultant for Amgen. Drs. Zager and Harford have received salary support from Dialysis Clinic, Inc. to the University of New Mexico.

REFERENCES
