Lost Without Directions: Lessons from the Anemia Debate and the Drive Study

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Growing concerns related to the potential hazards of erythropoiesis stimulating agents have led to downward adjustment in hemoglobin targets for patients with chronic kidney disease, including patients with ESRD on dialysis. These concerns, coupled with economic pressures and shifting cost structures in dialysis funding, have prompted new strategies directed toward the optimal management of anemia, including the call for more liberal use of intravenous iron (1). This article highlights the limited evidence base in support of alternative anemia management strategies and cautions against the injudicious use of iron in this patient population in the absence of sufficient data on long-term safety.

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Overall mortality in the U.S. ESRD population remains extremely high (>20%/yr), with little recent improvement despite advances in basic dialysis technology. Most published clinical research has been derived from secondary data analysis, typically from large registry databases, whereas adequately powered clinical trials have been few and far between. The major clinical controversies facing patients and providers including, determination of the optimal dialysis dose and the safety and most effective methods to control hypertension, disordered mineral metabolism, and anemia remain. In anemia management, the debate stems from the lack of adequately powered and controlled clinical trials to define an optimal hemoglobin range; no long-term safety data on intravenous (IV) iron therapy; and strong economic forces that include for-profit dialysis providers, government funding for dialysis care, and aggressive marketing campaigns by pharmaceutical companies.

Publication of the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) (2) trial, which demonstrated increased mortality in chronic kidney disease patients not receiving dialysis targeted to a higher hemoglobin and the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) (3) trial, which demonstrated no benefit in a similar population with regard to cardiac improvement, prompted a careful analysis of available literature and ultimately resulted in a black box warning for all erythropoiesis stimulating agents (ESAs). This was closely followed by changes in the Center for Medicare Services (CMS) reimbursement policy for ESA use. New legislative action is underway that will begin to bundle injectables used for dialysis care (ESAs, IV iron) into the payment to providers. This action will clearly apply new financial pressures on dialysis providers as these injectables move from profit items to cost items.

On the backdrop of this changing landscape came two pharmaceutical studies: Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) I (4) and DRIVE II (5). DRIVE I was a 6-wk study in which anemic (hemoglobin ≤11 g/dl) patients on hemodialysis with high serum ferritin concentrations (500 to 1200 ng/ml) and low iron saturation (transferrin saturation ≤25%) were randomized to receive 1 g of IV iron (125 mg ferrous gluconate × 8 consecutive dialysis treatments) *versus* no iron therapy. Subjects were excluded if they had active infection and/or were receiving antibiotics. All subjects received a 25% increase in their ESA dose. Patients who received IV iron had a greater increase in their hemoglobin at 6 wk than those not receiving iron. DRIVE II was a 6-wk observational extension of DRIVE I designed to evaluate ESA usage in the follow-up period. During this 6-wk period, 59% of patients in the original control arm received IV iron whereas 39% from the IV iron arm of the DRIVE I study received additional IV iron. Despite this difference in care during the 6-wk follow-up period, patients who received IV iron during DRIVE I had a decrease in the ESA dose in the subsequent 6 wk, whereas the control group did not. Immediate safety data showed that the IV iron was generally well tolerated with no difference in adverse events in the DRIVE I study. In DRIVE II a *post hoc* analysis of safety data for the entire 12 wk showed a lower frequency of serious adverse events in the iron administration group. What to make of this finding is unclear, because more patients in the DRIVE I control arm received iron in DRIVE II.

What Have We Learned from the DRIVE Studies?

The DRIVE studies have shown us that serum ferritin is a poor predictor of response to IV iron. Beyond that, they have helped very little in the management of anemia in chronic kidney disease. Twelve weeks of safety data are clearly inade-

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quate to justify the administration of IV iron to patients with underlying inflammatory processes, as seen in the DRIVE trials in which the average high-sensitivity C-reactive protein was 27.0 ± 33.7 mg/L. Although we have focused on the potential harm of overutilization of ESAs, we should be mindful that the long-term safety of unbridled IV iron administration has never been established. There is no evidence to support the assumption that achieving a target hemoglobin concentration in patients on dialysis with evidence of ongoing inflammation by using less ESA and more IV iron will prove safer than trying to achieve that target with more ESA or any other potential strategy. For better or worse, with the scepter of bundling looming on dialysis providers, assuming that target hemoglobin concentrations are still considered valid clinical performance measures, we will likely observe increased iron utilization to minimize ESA usage in the interests of reducing costs as suggested in a recent cost-savings analysis of the DRIVE study (6). What we have truly learned from the anemia debate and the DRIVE studies is that given the right environment, economic policy, pharmaceutical marketing, and open market forces may drive patient care without adequate attention to patient safety. As a scientific community we need to pay close attention to the limitations of the current data and begin to step up to our responsibilities by demanding adequately powered, well designed, randomized clinical trials with clinically relevant endpoints and the adequate collection of safety information. Perhaps it is time for CMS and/or the large dialysis organizations to sponsor these trials, ensuring that they are implemented and interpreted by experts drawn from diverse groups within and outside of the nephrology community.

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