Chronic Kidney Disease Anemia Management: What Should Be Done?

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Key Words

Anemia · Chronic kidney disease · Hemoglobin

Abstract

A transition in the approach to anemia management in nephrology occurred when randomized trials demonstrated that higher hemoglobin targets do not result in better outcomes and may arguably cause harm. Contradicting the speculative conclusions drawn based on earlier observational data, this has resulted in hypotheses regarding the cause of these seemingly disparate but substantively similar messages. The renal community now must struggle with how to incentivize quality care and maximize patient quality of life while minimizing the real safety signal of which we are now aware.

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The management of anemia in chronic kidney disease (CKD) has got considerably more complicated. Prior to the publication of the CHOIR and CREATE trials in 2006 [1, 2], the observational data demonstrating that higher hemoglobin measurements are associated with better outcomes drove much of clinical practice. However, since then the results of three clinical trials (CHOIR, CREATE, and TREAT) [1–3] have reminded us how observational data cannot prove cause and effect and have brought to-

gether the nexus of observational data, clinical trials, clinical practice guidelines, and provider performance metrics.

The observational data are quite consistent. Regardless of the population, higher hemoglobin levels are associated with better outcomes. This relationship has been demonstrated in the elderly, patients with congestive heart failure, population-based samples, patients on dialysis, and patients with CKD. Among a population-based sample of patients with congestive heart failure, 22.9% were found to have a hematocrit between 36 and 40%, 33.2% had a hematocrit between 30 and 35%, and 13.6% had a hematocrit of <30% [4]. Thirty-eight percent of this population had CKD defined as a serum creatinine of >1.4 and >1.5 mg/dl for women and men, respectively, and the increased risk of mortality associated with anemia was additive and independent of the presence of kidney disease. As compared to patients with a hematocrit of greater than 40%, the relative risk of death was 1.08, 1.17, and 1.60 ($p = 0.007$, test for trend) for individuals with hematocrits of 36–39, 30–35 and <30%, respectively. In a similar study of patients after acute myocardial infarction, 60% of patients were noted to have CKD [5], and 54% had a hematocrit of <40%. Again, independent of CKD, odds ratios for mortality were 1.35, 1.94, and 3.16 ($p = 0.007$, test for trend) for individuals with hematocrits of 36–39, 30–35 and <30%, respectively. The consistency of the message across populations, albeit not demonstrating

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cause and effect, provided sufficient equipoise to justify randomized trials to examine the reasonable question, 'if higher hemoglobin between individuals was associated with different outcomes, could increasing hemoglobin (i.e. treating anemia) lower a single individual's risk?'

To address the question of whether the between-person decrement in risk associated with a greater hemoglobin can translate to a within-person decrement in risk if anemia is treated and hemoglobin rises, three large clinical trials in CKD were performed. CHOIR and CREATE were published simultaneously in 2006 [1, 2]. CREATE randomized 603 patients with an estimated glomerular filtration rate of 15.0–35.0 ml/min and anemia to one of two target hemoglobins (13.0–15.0 vs. 10.5–11.5 g/dl). Times to one of eight cardiovascular events were compared between groups. Over the study's 3 years of follow-up, there was no difference in the rate in which participants in either target experienced a cardiovascular event (hazard ratio (HR) = 0.78; 95% CI 0.53–1.14; $p = 0.20$). CHOIR randomized 1,432 patients with CKD to achieve a hemoglobin level of 13.5 versus 11.3 g/dl. The participants were followed for a median duration of 16 months before the study was stopped by the data and safety monitoring board. Participants in the high hemoglobin group experienced the primary composite endpoint of death, myocardial infarction, hospitalization for congestive heart failure, or stroke at a greater frequency than the low hemoglobin group (HR = 1.34; 95% CI 1.03–1.74; $p = 0.03$).

While CHOIR and CREATE examined the effect of hemoglobin targets in patients with CKD irrespective of its cause, TREAT was unique in that it enrolled only participants with type 2 diabetes mellitus. Additionally, TREAT also had different target hemoglobin levels, randomizing 4,038 patients to darbepoetin alfa to achieve a hemoglobin of 13 g/dl or to placebo with rescue darbepoetin alfa when the hemoglobin level was less than 9.0 g/dl. There was no difference in the primary end point of death or cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) between arms (HR = 1.05; 95% CI 0.94–1.17; $p = 0.41$). There were however differences in one secondary endpoint and in one additional secondary analysis. Participants in the active treatment arm experienced fatal or nonfatal stroke at a higher rate than those assigned to placebo (HR = 1.92; 95% CI 1.38–2.68; $p < 0.001$). Additionally, there were a greater number of deaths among the subgroup of patients in the active treatment group as compared to placebo among those with preexisting malignancies.

To reconcile these findings, it has been suggested that there may be a direct relationship between increasing cardiovascular risk and epoetin alfa dose [6]. While it is clear that dose can also be marker of comorbidity and inflammation as suggested when this relationship was demonstrated in observational studies [7], the significance of this relationship in a randomized trial, where the goal of randomization is to evenly distribute comorbidity and inflammation between groups, supports that in addition to its role as a marker there may also be a direct effect.

'What should be done about this' is really an issue of patient safety. The full question should therefore be, 'what should be done to maximize patient safety while research more definitively explains the disconnect between the observational and trial data?'. A proper strategy at this point should approach the question with the potential that the hypothesis of a direct dose-risk relationship could be either proven or rejected in subsequent years as the result of additional research. So the strategy should be designed to maximize safety while disrupting efficacy as little as possible.

Operating under the assumption that the hypothesis of a direct dose-risk relationship exists, a potential strategy to mitigate this risk is quite simply to limit the administration of higher doses. This is, however, where the clinical data and what may be best to minimize risk for an individual patient do not mesh with current performance benchmarks entirely. Minimizing the dose of epoetin alfa when a patient is within the hemoglobin goals that define the benchmark can be done with attention to reversible factors that affect erythropoietin responsiveness such as the use of intravenous catheters, iron stores, vitamin D administration, etc. In general, strategies that increase responsiveness to erythropoietin will help achieve other benchmarks of care and will likely improve outcomes. In a patient who is currently at hemoglobin goal, strategies to lower dose while still keeping the patient within goal are easily implemented.

However, where a patient is receiving higher doses of epoetin alfa and is not within the benchmark of care (i.e. goal), the strategy is really no different but the implications of implementing the strategy are. This stems from the fact that clinical practice guidelines meant to guide clinicians as to individual patient goals have been transposed verbatim to apply to populations of patients in a performance model. For a measure that the physician or healthcare team had near complete control as to whether or not the benchmark was achieved, such as the administration of a vaccination, this would be appropriate. However, in the setting of anemia management where pa-

tient-specific factors such as intercurrent illness or inflammation intervene, it may not be possible to reach the benchmark due to these factors even in a setting of the highest quality of health care. So again, operating under the assumption that the hypothesis of the dose-risk relationship with epoetin alfa exists, the clinical strategy is the same as in the patients who achieved their benchmark (i.e. lowering dose of epoetin alfa utilized), but the health services issue related to the benchmark is placed in center stage. To potentially maximize safety in this scenario, one must take an action that is potentially counter to the benchmarks that grade the quality of care delivered.

In this scenario, the strategy must be expanded to request a careful examination of the quality metrics. Is a minimum hemoglobin of 10 g/dl achievable in all patients? Are there some in whom the risk associated with attempting to achieve this hemoglobin does not justify the benefit to them individually? If the hypothesis that a dose-risk relationship between epoetin alfa and cardiovascular outcomes is true, the answer to this may be yes.

If this hypothesis goes on to be disproven, one must consider the downside to this strategy designed to maximize safety in the interim. The downside appears to be focused in potentially lowering the hemoglobin levels of patients with lesser responsiveness to epoetin who currently cannot achieve their hemoglobin goals. This must be taken into account as one structures the approach to these patients in a manner focused on interventions to improve responsiveness and lower dose rather than just lower dose.

In this current era and based on the evidence that we have available to guide our decisions in anemia management, the studies and trials may fit together in a complicated manner, but the conclusions and actions that can be drawn from them are far simpler. Strategies to improve responsiveness and lower dose may be the proper approach, and vigorous discussion within the renal community as to how best to translate our clinical practice guidelines into quality incentive metrics will be essential.

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