Hot Topics in Nephrology: A Debate

American Journal of Nephrology

Am J Nephrol 2010;31:552–556
DOI: 10.1159/000314628

Published online: May 21, 2010

Debate: PRO Position

Should Hemoglobin Targets for Anemic Patients with Chronic Kidney Disease Be Changed?

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Four randomized controlled trials (RCTs) have demonstrated that erythropoiesis-stimulating agents (ESAs) targeted to normalize hemoglobin (Hb) in chronic kidney disease (CKD) patients result in a higher rate of death and/or cardiovascular complications. In the Normal Hematocrit study, the point estimate of risk in the direction of harm was 30% [1]; in CREATE, it was 22% (95% CI: 0.53–1.14) [2]; in CHOIR, it was 34% (95% CI: 1.03–1.74) [3], and in TREAT it was 5% (95% CI: 0.94–1.17) [4]. Several observational analyses [5–9] implicate exposure to high dosages of ESAs in explaining these adverse outcomes. Studies in nonrenal settings confirm the direct risk conferred by ESAs. The case for ESA toxicity in explaining the risk of targeting a higher Hb in CKD patients is strong. The case is weak for a continued obsession with the current target range for Hb of 10–12 g/dl (the FDA recommendation) or 11–12 g/dl (K-DOQI). The status quo must change.

The anemia RCTs demonstrate that the Hb is a flawed surrogate end point, fundamentally undermining the current focus on an Hb target range. Fleming and DeMets [10] emphasize that a valid surrogate should both correlate with the true clinical outcome and fully capture the net effect of treatment on the clinical outcome. Hb does not do this because targeting a higher Hb in the trials is not associated with a reduction in mortality or a lower rate of cardiovascular complications. On the contrary, the RCTs demonstrate there is increased risk in targeting a higher Hb in dialysis patients. Aiming for an Hb of >9 g/dl as a minimum threshold is commensurate with the placebo arm of the TREAT study as well as the lower Hb arm of the Normal Hematocrit study. Having an upper limit for Hb (i.e. a target range) is not supported by evidence and encourages targeting with ESAs to just below 12 g/dl and within the target range, but beyond the prevailing evidence with respect to safety. The focus needs to be either avoiding ESAs entirely where possible, or reducing exposure to high ESA dosage where necessary.

Intervention in these four trials (comprising over 7,000 patients) involved 'targeting a higher Hb concentration'. This 'targeting' of higher Hb embodied treatment with ESAs. In fact, in all of the four trials, an algorithm controlled ESA dosage. In addition, in all of the trials, achieving a higher Hb concentration was associated with better outcomes compared to achieving a lower Hb level. In other words, targeting a higher Hb with ESA, not the actual achieving, is the problem. Thus, the singular focus on an Hb range misses the point. There is no evidence to indicate increased mortality or cardiovascular risk with other interventions in targeting a higher Hb – blood transfusions or iron. Indeed, dialysis patients with higher Hb because of high altitude have better outcomes than patients with lower Hb [9]. Regardless of the achieved Hb, treatment with high dosages of epoetin independently predicts death and cardiovascular complications.

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Table 1. Design characteristics for anemia RCTs

	Normal Hematocrit	CREATE	CHOIR	TREAT
Design	randomized, open-label	randomized, open-label	randomized, open-label	randomized, double-blind
Sponsor/agent	Amgen/Epogent® (epoetin-α)	Amgen/Aranesp® (darbepoetin-α)	J&J/Procrit® (epoetin-α)	Amgen/Aranesp® (darbepoetin-α)
Dosing	unclear	2,000 weekly	initiate 10,000 weekly when stable go to bi-weekly	0.75 mcg/kg/Q2W double dose when stable and go to monthly
Dosing frequency	3 times weekly on dialysis	de novo to weekly	de novo to weekly to bi-weekly	de novo to bi-weekly to monthly
Hb target(s), g/l	arm 1 9–11 arm 2 13–15	13.0–15.0 10.5–11.5	13.0 placebo (rescue for Hb <9.0)	13.0 placebo (rescue for Hb <9.0)
Regions	USA	global	USA	global
Inclusion criteria				
Hb, g/l	9–11.0	11.0–12.5	<11.0	≤11.0
eGFR/CrCl	ESRD	15–35	15–50	20–60
Diabetes	≈44%	≈25%	48.5%	100%

Evidence that Targeting a Higher Hemoglobin with ESA Therapy Is Harmful

The design characteristics of the four large RCTs are shown in table 1, and have been discussed in detail elsewhere [11].

The Normal Hematocrit study [1] enrolled symptomatic high-risk dialysis patients, who were randomized to either an Hb of 13–15 g/dl or an Hb of 9–11 g/dl. The mean epoetin dosage was 460 U/kg/week and 160 U/kg/week, in the high versus low Hb arms, respectively. The Data Safety Monitoring Board halted the study for safety reasons. At 29 months, there were 183 deaths and 19 first nonfatal myocardial infarctions in the higher Hb versus 150 deaths and 14 nonfatal myocardial infarctions in the lower Hb group (RR: 1.3; 95% CI: 0.9–1.9). There was also a higher rate of vascular thrombosis and strokes in patients in the higher Hb arm compared to patients randomized to the lower Hb arm.

Three RCTs have evaluated nondialysis CKD patients: CREATE, CHOIR and TREAT (table 1). All three trials demonstrated increased risk in targeting higher Hb with higher doses of ESAs.

The CREATE study evaluated the effect of complete versus partial correction of anemia in 603 patients with CKD (12). The achieved Hb was 13.49 g/dl in the high Hb group versus 11.6 g/dl in the low Hb group. A median dose of 5,000 versus 2,000 units of epoetin-β per week was used in the higher versus lower Hb group, respectively. At 4 years, complete anemia correction was not associated with a higher rate of the first cardiovascular event (HR: 0.78; p = 0.20), although there was a trend towards harm. There was a significantly higher risk of developing end-stage renal disease in patients randomized to the higher Hb concentration.

The CHOIR study [3] enrolled 1,432 patients with CKD anemia and compared the effect of raising Hb to high (13.5 g/dl) as compared to low (11.3 g/dl) levels on outcomes. The median epoetin dose used in the trial was 10,952 U/week in the high Hb group and 5,506 U/week in the low Hb arm. There were 125 composite events (death, myocardial infarction, congestive heart failure hospitalization and stroke) in patients in the higher Hb group versus 97 events in the low Hb group (HR 1.337; p = 0.03). The higher rate of composite events was explained largely by a higher rate of death (48% higher risk; p = 0.07) and congestive heart failure hospitalization (41%; p = 0.07).

The TREAT study [4] was a double-blind trial comprising 4,038 subjects. Patients were randomized to either darbepoetin or placebo, with a target Hb of 13 g/dl in the darbepoetin treatment arm and an Hb above 9 g/dl in the placebo arm. A median dose of 176 μg/month was used in the darbepoetin-treated arm compared to 0 μg/month in the placebo rescue arm. The trial was neutral for the

primary composite of death or a cardiovascular event (HR for darbepoetin vs. placebo: 1.05; p = 0.41), but there was a significantly higher rate of strokes in the darbepoetin-treated patients (HR: 1.92; p < 0.001). Death or end-stage renal disease occurred in 652 patients in the darbepoetin-α group (32.4%) and in 618 patients in the placebo group (30.5%; HR for darbepoetin-α versus placebo: 1.06; 95% CI: 0.95–1.19; p = 0.29). A higher rate of both thromboembolism and cancer-related deaths among patients with a history of cancer in the darbepoetin-treated patients was also observed.

Taken collectively, the anemia RCTs prove the inadequacy of Hb as a valid surrogate end point and point to the targeting of a higher Hb with ESA as being the key problem. The next question is whether exposure to epoetin, especially at high dosage levels, independently predicts adverse outcome.

In a secondary analysis of the CHOIR study [12], the question of whether exposure to epoetin-α explained the higher risk of adverse events observed with anemia treatment was evaluated. Landmark analyses at 4 and 9 months was used to avoid some of the biases and confounding inherent in post-hoc studies. In unadjusted analyses, both the inability to achieve target hemoglobin and the requirement of high-dose epoetin were significantly associated with an increased hazard of the primary end point (p = 0.05 and 0.003, respectively). In adjusted models, the increased hazard associated with randomization to the high hemoglobin arm from the primary trial was no longer significant (p = 0.49), while high-dose epoetin was associated with a 57% increased hazard to the primary end point (HR: 1.57; 95% CI: 1.04–2.36; p = 0.03). Thus, exposure to high doses of epoetin and not the targeted Hb independently predicted adverse outcomes in CHOIR.

Observational Studies Support ESA Toxicity

Several observational analyses have examined the relationship between epoetin exposure and adverse risk in treating anemia in the CKD population. Zhang et al. [5] studied the relationship between epoetin and all-cause mortality in 94,569 prevalent hemodialysis patients using Cox proportional hazard regression analysis with adjustment for baseline variables. For every hematocrit strata studied, patients administered higher doses of epoetin had significantly lower hematocrit values and greater mortality rates. Using the cubic spline function, a significant nonlinear relationship between increased epoetin dose and mortality was found regardless of hematocrit (p < 0.0001), with the steepest increase in relative risk for death found after the 72.5 dose percentile.

Bradbury et al. [6] explored a Fresenius North America cohort of 22,955 prevalent hemodialysis patients using Cox proportional hazard models and time-dependent models fitted with time-varying log EPO and Hb concentration. In the unadjusted model, after adjustment for baseline patient characteristics, an increased mortality risk with increasing epoetin dose was observed (HR: 1.31 per log unit increase; 95% CI: 1.26–1.36). However, adjustment for baseline patient characteristics resulted in attenuation of the mortality risk estimate (HR: 1.21; 95% CI: 1.15–1.28) that became more attenuated in lagged time-dependent analyses.

Streja et al. [7] explored the relationship between epoetin exposure, iron deficiency and thrombocytosis in 40,787 DaVita maintenance hemodialysis patients. A higher Hb >13 g/dl was associated with greater mortality (case-mix-adjusted death relative risk of 1.21; 95% CI: 1.02–1.44; p = 0.03) in the presence of thrombocytosis (platelet count >300,000/μl), but not in the absence of thrombocytosis. However, there was an association between epoetin exposure at very high doses of >20,000 units/week, and mortality over 3 years (relative risk of death: 1.59, 95% CI: 1.54–1.65; p < 0.001).

Servilla et al. [8] evaluated 12,733 epoetin-exposed incident hemodialysis patients. A proportional hazards modeling with time-varying covariates was used. Epoetin doses <8,000 U/week were associated with decreased risk. Higher epoetin doses were associated with increased mortality at Hb concentrations of 10–12.9 g/dl and with increased hospitalization at all Hb concentrations of 10 g/dl or greater. Higher epoetin doses were also associated with increased mortality and hospitalization within each tertile of serum albumin concentration.

Winkelmayer et al. [9] used instrumental variable modeling to examine the relationship between epoetin and outcome in 269,717 subjects in 4,500 dialysis units in the United States. Mortality was low among patients with a low Hb exposed to high doses of epoetin. However, mortality rates were increased in centers that used larger ESA doses in patients with hematocrit between 33 and 35.9% (highest vs. lowest quintile of predicted dose, HR: 1.07; 95% CI: 1.03–1.12) and in those with hematocrit of 36% or higher (highest vs. lowest quintile of predicted dose, HR: 1.11; 95% CI: 1.07–1.15).

Synthesizing the observational studies, the evidence suggests that there is indeed a relationship between ESA exposure and adverse outcome, but since confounding cannot be excluded, causality cannot be established.

Evidence of ESA-Associated Adverse Outcomes in Nonrenal Populations

Demonstrating that ESA therapy used in nonrenal settings can be harmful lends further support to the case for ESA toxicity. ESA therapy has been used in a variety of nonrenal settings, including the treatment of cancer-induced anemia, anemia of critical illness and in preventing blood transfusions prior to spine surgery.

Bohlius et al. [13] did a meta-analysis of 53 trials comprising 13,933 patients with cancer-induced anemia who received epoetin or darbepoetin plus red blood cell transfusion for treatment of anemia compared to patients receiving only transfusion. High doses of ESAs were used (21,000–63,000 IU of epoetin or 100–157 μg of darbepoetin per week for 8–52 weeks). ESAs increased all-cause mortality by 17% in all patients compared to control groups, and by 10% in patients undergoing chemotherapy compared to control groups. In another meta-analysis, Bennett et al. [14] evaluated 51 phase 3 trials comprising 13,611 patients with cancer (venous thromboembolism risk was evaluated in 8,172 patients with cancer from 38 phase 3 trials). The risk of mortality was also greater in ESA-treated patients (HR: 1.10; 95% CI 1.01–1.20). A significantly increased risk of venous thromboembolism in patients treated with ESAs (334 events /4,610 patients) versus control patients (173 events/3,562 control patients; RR: 1.57; 95% CI: 1.31–1.87) was observed. Furthermore, there was increased mortality among those with chemotherapy-induced anemia (HR: 1.29; 95% CI: 1.00–1.67, p = 0.05) and chemotherapy-associated anemia (HR: 1.09; 95% CI: 0.99–1.19).

The most convincing evidence of a direct adverse effect of ESA is from a prospective, multicenter, open-label, randomized, parallel group trial by Stowell et al. [15]. Subjects received either epoetin-α 600 U/kg subcutaneously once weekly starting 3 weeks before spinal surgery plus standard of care for blood conservation or standard of care alone, regardless of baseline Hb concentration. There were 340 in each treatment group (n = 680): 16 subjects (4.7%) in the epoetin-α group and 7 subjects (2.1%) in the standard of care group had a diagnosis of deep vein thrombosis and 1.5% and 0.9%, respectively, had other clinically relevant thrombovascular events.

In summary, evidence from ESA treatment in nonrenal populations taken together with the CKD data implicates exposure to high doses of ESAs as the likeliest reason for the increased risk of adverse outcomes.

Conclusion

Targeting a higher Hb concentration with high dosage of ESA in CKD patients is associated with increased risk. Aiming for an Hb of >9 g/dl is commensurate with the placebo arm of the TREAT study as well as the lower Hb arm of the Normal Hematocrit study. However, rather than focusing on the Hb, which at best is an unreliable surrogate, attention needs to be directed at minimizing exposure to high ESA dosage. The evidence for ESA exposure particularly at high dosage is strong, albeit more circumstantial. However, as Henry David Thoreau is famously quoted saying, 'Some circumstantial evidence is very strong, as when you find a trout in the milk'.

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