Editorial Perspective

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

Patrick S. Parfrey

Division of Nephrology, Health Sciences Centre, Memorial University, St. John's, Nfld., Canada

The decision to prescribe erythropoiesis-stimulating agents (ESAs) in chronic kidney disease should be based on the results of randomized controlled trials (RCTs) with clinically meaningful outcomes. For intervention with ESAs, these outcomes include mortality, cardiovascular and renal outcomes, safety, quality of life, and transfusions. Outcomes should not include surrogate markers such as left ventricular hypertrophy. The RCT evidence base is heterogeneous, with variation in types of patients included, baseline hemoglobin, target hemoglobin, duration of follow-up, types of outcomes assessed, measures of clinically meaningful benefit and research design.

Dialysis patients are different from predialysis patients because often without ESA treatment the hemoglobin level will fall below 8 g/dl, whereas prior to dialysis, hemoglobin levels will not usually fall below 10 g/dl until patients are close to dialysis. A return to a transfusion-dependent strategy for the management of severe anemia in the dialysis unit would be retrograde. However, the hemoglobin level at which ESAs should be initiated is unclear, as there is no RCT data on hard clinical outcomes or safety in patients with severe anemia at baseline (Hb <10 g/dl). Recent systematic reviews/meta-analyses suggest that improvement in quality of life is maximized in the 10–12 g/dl range [1–3].

Treatment of moderate anemia ($10 < \text{Hb} < 12$ g/dl) with ESAs to a target hemoglobin of around 13 g/dl is harmful. TREAT is important in making this statement because it is nearly 3 times bigger than the next biggest

RCT, and has a double-blind research design, which limits its bias associated with open-label RCTs (table 1) [4].

TREAT identified a very significantly increased hazard of stroke in diabetic predialysis patients, but the risk attributable to the high Hb target was small, about 6/1,000 patients per year [4]. The Canada-Europe study of 596 hemodialysis patients without symptomatic cardiac disease at baseline also reported a significantly increased number of strokes in the high Hb arm [5]. TREAT also reported an increased incidence of thromboembolic events in the high Hb arm and a signal that cancer outcomes may be worse [4].

The normal hematocrit study in dialysis patients revealed significantly increased vascular access thrombosis and loss in the high Hb arm [6], although even in a later analysis with longer follow-up, the primary outcome (death or myocardial infarction) was not significantly increased [7]. TREAT did not observe increased risk for cardiovascular events reported by CHOIR, or increased risk for renal events reported by CREATE in the high Hb arm.

The increased cardiovascular risk reported by CHOIR [8] may have been related to different rates of baseline cardiovascular disease in the high Hb arm compared to the low Hb arm, as the outcome was no longer significant when these imbalances were taken into account [9]. The increased risk of renal events in CREATE [10] may have resulted from the open-label design of the study, where the decision to prescribe dialysis in the high Hb arm may have been influenced by knowledge that symptoms were not related to anemia. This suggestion is supported by the

Table 1. What is important about TREAT?

1. By far the largest RCT of ESAs undertaken
2. Best research design: placebo-controlled, double-blind RCT
3. High Hb vs. rescue <9 g/dl
 - HR for stroke = 1.9
 - Risk attributable to high Hb arm small
 - Modest improvement in fatigue
 - Fewer blood transfusions
 - No increased risk for cardiac events
 - No increased risk for renal events

fact that the rate of fall of eGFR was the same in the high and low Hb arm [10].

The quality of life benefits from normalization of hemoglobin compared to partial correction of anemia are inconsistent. Improvement in fatigue of modest clinical relevance was observed in TREAT [4], no improvement in quality of life was observed in CHOIR [8], and improvement of clinical relevance in some domains was reported in CREATE [10] and the Canada-Europe study [5, 11]. As expected, the higher the target Hb, the less the transfusion requirements. However, in the high Hb arm this benefit is not large. For example in the Canada-Europe study, the number of transfusions per patient per year in the high Hb arm was 0.7 and 0.3 in the low Hb arm [12].

The utilization of cohort studies to make therapeutic conclusions is not wise. It is highly likely that the associations between clinical outcomes and higher ESA dose/ESA hyporesponsiveness are related to comorbidity and that no statistical technique can account for the differences in patients who require high and low doses of ESA to achieve a particular Hb target. Consequently, it is not surprising that several studies have shown an inverse relationship between Hb achieved and the primary outcome. Indeed this relationship has been seen in both the high and low Hb arms in the normal hematocrit study [6]. This suggests dose-targeting bias, a phenomenon reported in the HEMO study, where in both high and low KT/V arms, an inverse relationship was observed between KT/V achieved and the primary outcome [13]. Further research is necessary to determine whether high ESA doses are toxic. However, it seems reasonable to cap ESA doses in hyporesponsive patients.

In my opinion, ESAs are not usually indicated for the treatment of moderate anemia ($10 < \text{Hb} < 12$ g/dl). The Hb level at which ESAs should be prescribed requires assessment of risks and benefits for individual patients. For treatment of severe anemia, current guidelines suggesting a hemoglobin target of 10–12 g/dl seem reasonable. However, it should be remembered that the transfusion benefits and improvement in quality of life associated with ESAs were achieved at a target Hb of 9.5–11 g/dl, with little additional benefit when the target was above 11 g/dl [14].

References

- 1 Gandra SR, Finkelstein FO, Bennett AV, Lewis EF, Bragg T, Martin ML: Impact of erythropoiesis-stimulating agents on energy and physical function in nondialysis chronic kidney disease patients with anemia. A systematic review. *Am J Kidney Dis* 2010;55:519–534.
- 2 Johansen KL, Finkelstein FO, Revicki DA, Gitlin M, Evans C, Mayne TJ: A systematic review of physical functioning and meta-analysis of exercise tolerance in patients on dialysis with erythropoiesis-stimulating agents. *Am J Kidney Dis* 2010;55:535–548.
- 3 Parfrey PS, Wish T: Quality of life in CKD patients treated with erythropoiesis-stimulating agents. *Am J Kidney Dis* 2010;55:423–425.
- 4 Pfeffer MA, Burdmann EA, Chen CY, et al; the TREAT Investigators: A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;361:2019–2032.
- 5 Parfrey PS, Foley RN, Wittreich BH, et al: Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol* 2005;16:2180–2189.
- 6 Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;339:584–590.
- 7 Besarab A, Goodkin DA, Nissenson AR, Normal Hematocrit Cardiac Trial Authors: The normal hematocrit study – follow-up. *N Engl J Med* 2008;358:433–434.
- 8 Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D; CHOIR Investigators: Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;355:2085–2098.
- 9 Clinical study report PROO-06-014 (CHOIR): P5. www.clinicaltrials.gov, [http://Clinical_study_report_PROO-06-014\(CHOIR\):P5](http://Clinical_study_report_PROO-06-014(CHOIR):P5). Accessed May 6, 2010.
- 10 Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A; CREATE Investigators: Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006;355:2071–2084.
- 11 Foley RN, Curtis BM, Parfrey PS: Erythropoietin therapy, hemoglobin targets, and quality of life in healthy hemodialysis patients: a randomized trial. *Clin J Am Soc Nephrol* 2009;4:726–733.
- 12 Foley RN, Curtis BM, Parfrey PS: Hemoglobin targets and blood transfusions in hemodialysis patients without symptomatic cardiac disease receiving erythropoietin therapy. *Clin J Am Soc Nephrol* 2008;3:1669–1675.
- 13 Greene T, Daugirdas J, Depner T; Hemodialysis Study Group: Association of achieved dialysis dose with mortality in the hemodialysis study: an example of ‘dose-targeting bias’. *J Am Soc Nephrol* 2005;16:3371–3380.
- 14 Canadian Erythropoietin Study Group: Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving hemodialysis. *BMJ* 1990;200:573–578.