

## Anemia Management in Chronic Kidney Disease: Bursting the Hemoglobin Bubble

Until the approval of recombinant erythropoietin therapy in 1989, many patients receiving dialysis were severely anemic and needed transfusions to maintain a hemoglobin level greater than 70 g/L (1–3). Recombinant erythropoietin was greeted as a panacea for anemia in chronic kidney disease (CKD) and was approved for use with considerable fanfare, relatively little clinical trial data, and few reservations. Early reports (4–6) described sustained increases in hemoglobin levels accompanied by improvements in exercise tolerance, quality of life, and cognitive functioning, with relatively few adverse events. These benefits were seen with only modest increases in target hemoglobin level, often to 90 to 100 g/L.

Current strategies for anemia management in CKD crudely attempt to mimic precise feedback mechanisms. Endogenous release of erythropoietin in response to anemia prevents apoptosis of early bone-marrow erythrocyte progenitors and permits proliferation, maturation, and increased output of erythrocytes, whereas erythropoietin suppression and subsequent increased apoptosis in erythroid progenitors occur in settings of higher erythrocyte mass (7). Because endogenous erythropoietin levels are often higher in persons with CKD than in control participants, most anemia in CKD must be multifactorial, with either concurrent bone marrow resistance to erythropoietin (often due to iron deficiency and inflammation) or increased erythrocyte destruction or loss contributing to anemia. For persons without substantial erythropoietin resistance, smaller epoetin doses will increase erythrocyte production and prolong erythrocyte life, whereas for persons with erythropoietin resistance, supraphysiologic doses of epoetin may be required to approach hemoglobin targets. Erythropoietin has effects beyond erythrocytosis, including hemoglobin-independent hypertension (8) and angiogenesis (9), which are probably promoted by exogenous non-physiologic administration.

The question that naturally followed the early trials of erythropoiesis-stimulating agents (ESAs) was whether further increases in hemoglobin levels would improve tissue oxygenation, thereby reducing the high rates of adverse events in patients with CKD. This prompted the Normal Hematocrit Trial (10), in which 1233 patients receiving hemodialysis with high cardiovascular risk were randomly assigned to a target of a normal hematocrit (42%) versus a lower hematocrit (30%). The hemoglobin-normalization group received very high epoetin doses (mean, 450 U/kg per week). Mortality and myocardial infarction were more common in the group with the higher hematocrit target ( $P = 0.06$ ), and the study was stopped early because of futility). Despite this result, ESA use and hemoglobin values both progressively increased over the subsequent de-

cade in U.S. patients receiving dialysis (3). Although this bubble was remarkable, it probably reflected results from large observational studies showing better outcomes with higher hemoglobin levels (11); post hoc analyses of clinical trials suggesting that not achieving the target hemoglobin level, rather than the target level itself, was associated with greater mortality (10, 12); and financial incentives promoting greater ESA use (13).

In 2006, CREATE (Cardiovascular Risk Reduction in Early Anemia Treatment with Epoetin) and CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) finally burst the high-hemoglobin bubble. These 2 large randomized trials (14, 15) that enrolled patients with stage 3 to 4 CKD found either no benefit or potential harm associated with targeting normal hemoglobin levels versus levels of 105 to 115 g/L. Concurrently, trials in patients with cancer were consistently finding increased mortality associated with ESA use (albeit at far higher doses than those used in CKD) (16). Of note, the largest ESA study to date (17) continued, despite calls that it should be stopped. Randomly assigning 4038 participants with stage 3 to 4 CKD, TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) compared hemoglobin normalization using darbepoetin with placebo, although salvage ESA could be given for hemoglobin levels less than 90 g/L. Published in late 2009, TREAT (18) revealed no difference between randomization groups in the primary outcome, although an increased risk for stroke was associated with targeting normalization.

The publication of TREAT prompted the updated systematic review and meta-analysis by Palmer and colleagues in this issue (19). This well-executed meta-analysis mostly confirms earlier findings, showing that higher hemoglobin targets are associated with fewer transfusions but increase hypertension, access thrombosis, and stroke. Of note, the meta-analysis revealed a trend toward increased risk for all-cause mortality and serious cardiovascular events with targeting hemoglobin levels greater than 130 g/L as compared with control participants with hemoglobin levels between 100 and 115 g/L.

Given the emphasis of recent clinical trials on targeting high hemoglobin levels, critical knowledge gaps remain, most notably the absence of information on lower hemoglobin targets (<125 g/L). The largest randomized, placebo-controlled outcome study to explore this range was the 1990 Canadian Erythropoietin Study Group (CESG) trial (5), which included 118 patients and lasted only 6 months. The placebo group in the CESG trial had a mean hemoglobin concentration of 74 g/L (SD, 12), compared with 2 treatment groups that achieved mean hemoglobin levels of 102 g/L (SD, 10) and 117 g/L (SD, 17), respec-

tively, by using 50% to 60% less epoetin than the normalization group in the Normal Hematocrit Trial. In the CESH trial, substantial benefits to quality of life and physical performance were associated with the 2 higher hemoglobin targets, although outcome measures did not differ between the 2 treatment groups. Subsequent larger clinical trials have not shown clinically meaningful sustained improvements in quality of life, although hemoglobin levels for the control groups in these studies were similar to those in the treatment groups of the CESH trial (10, 14, 15, 18). A second knowledge gap is the lack of data to facilitate individualization of therapies. Higher-functioning persons are probably more aware of the symptoms of anemia than more sedentary persons, thereby deriving greater benefit from higher hemoglobin targets (20). In this context, it is ironic that the major clinical trials focused on participants with prevalent cardiovascular disease or diabetes. A third gap, pertaining to the use of iron and other anemia-management agents, is the lack of data on concurrent administration of multiple anemia therapies.

We cannot disentangle the effects of higher hemoglobin targets from the higher cumulative ESA (and iron) administration required to achieve those targets, which leaves us uncertain about whether higher hemoglobin levels are the wrong goal or whether we lack the proper means to safely get there. What we definitively know is limited: Targeting hemoglobin levels greater than 130 g/L with epoetin or darbepoetin is probably more harmful than beneficial for most persons. Critical questions remain:

- Is there a lower hemoglobin limit above which most patients derive a benefit with epoetin therapy, and what is that level?
- Is there a subset of persons who feel better with higher hemoglobin levels for whom higher levels should be targeted?
- Would risk be reduced if other agents, including iron, were increasingly used instead of high-dose erythropoietin or darbepoetin?
- Is low-dose ESA therapy safe?
- How should we treat persons with ESA resistance?

Before abandoning epoetin and darbepoetin and returning to the era of severe anemia and frequent transfusions, additional adequately powered clinical trials are needed to specifically address each of these questions and thereby balance the potential harms associated with ESAs against benefits that were noted in the earliest placebo studies. Until then, the bursting of the hemoglobin bubble is another cautionary reminder that observational data may be misleading and that medicine is the art of treating the individual patient, which requires extrapolation of available knowledge to individuals' clinical circumstances while recognizing deficits in existing knowledge, maximizing limited resources, and involving patients in their own care decisions.

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