New options for the anemia of chronic kidney disease

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Anemia is a common complication of chronic kidney disease. Use of erythropoiesis-stimulating agents (ESA) has been a mainstay of treatment since 1990. A series of large trials demonstrated that ESAs have serious safety problems, including increasing cardiovascular and thrombotic events, and death. Analyses suggest high pharmacologic doses of ESAs, rather than the highly achieved hemoglobin, may mediate harm. Hypoxia-inducible factor (HIF) activators stimulate endogenous erythropoietin production and enhance iron availability. In early clinical trials, these oral agents appear to be capable of replacing ESA therapy and minimizing the need for i.v. iron therapy for chronic kidney disease–related anemia, while having other potentially advantageous actions. Large phase 3 trials are underway with several HIF activators. This commentary reviews trends in anemia management, the safety issues related to our present therapies, the role of HIF in regulating erythropoiesis, and the diverse actions of HIF activators.

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Anemia is a common complication in patients with chronic kidney disease (CKD), developing gradually and increasing in severity as kidney disease progresses.[1] Anemia is associated with poor outcomes, including higher mortality in patients with end-stage renal disease (ESRD)[2] and in those with non–dialysis-dependent CKD.[3] The major cause of anemia in CKD is a relative deficiency in erythropoietin (EPO) production,[4] although the complex clinical picture of most patients with CKD frequently includes additional conditions contributing to the development of anemia, such as inflammation and iron deficiency. Until approximately 1990, anemia of CKD, especially in patients with ESRD, was managed with oral and occasional i.v. iron administration, occasional use of androgens, and blood transfusions for the severely anemic. Transfusion complications included transfusion reactions, sensitization, and iron overload.[5] This resulted in lower hemoglobin levels in patients with ESRD until pharmacologic replacement of EPO with Epoetin in 1989 revolutionized the approach to CKD-related anemia.

The prevalence of anemia (hemoglobin ≤12 g/dl) is high (47.7%) in patients with nondialysis CKD and increases as CKD progresses, being present in approximately 42% of patients with stage 3 CKD, increasing to approximately 76% in stage 5 CKD.[6] The incidence of more severe anemia (hemoglobin ≤10 g/dl), which is the treatment level described in the package insert of erythropoiesis-stimulating agents (ESAs), is less common: 5.6% prevalence in stage 3 CKD and 27.2% in stage 5 nondialysis CKD.[7] Even though anemia is very common in patients with advanced CKD, relatively few of these patients receive treatment for it: among patients with CKD stages 4 and 5, only 20% and 42%, respectively, were on any treatment for anemia defined using gender-specific thresholds (<12 g/dl for female patients and <13 g/dl for male patients).[7]

Anemia treatment trends in CKD have shown a secular trend, perhaps as a result of clinical trials changing clinical practices and changes in the regulatory environment. Hemoglobin levels reported in patients initiating chronic dialysis peaked at the end of 2006 in the United States at approximately 10.5 g/dl in ESA-treated patients with CKD, and approximately 10.0 in the remaining patients. Subsequently, mean hemoglobin has fallen steadily in these groups and is approximately 9.5 g/dl in 2013 (Figure 1). This decline comes in the wake of clinical trials showing no benefit or even harm from normalizing hemoglobin with ESA therapy.[8]

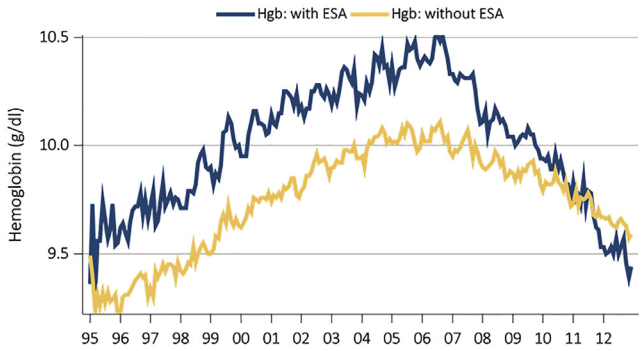

Figure 1 | Changes in initial hemoglobin in US incident dialysis patients. Adapted from the USRDS (US Renal Data System) Annual Report, Volume 2, 2014. ESA, erythropoiesis-stimulating agents; Hgb, hemoglobin.

Similar to the trends seen in hemoglobin concentration, ESA use before starting dialysis has also fallen since 2006 and is now below 15% utilization in the United States (Figure 2).[8] Use of i.v. iron, in contrast, increased in dialysis patients, with mean ferritin levels steadily increasing. Nondialysis CKD and patients on dialysis have disordered iron metabolism due to increases in hepcidin, the regulator of iron absorption and release from reticuloendothelial cells. Clinically, physicians have compensated for this disordered iron metabolism by administering i.v. iron, but this may have adverse long-term effects due iron increasing oxidative stress.

In addition to the trends observed in predialysis patients, decreases in hemoglobin levels and ESA dose have also been observed in dialysis patients. The average ESA dose in the United States is now approximately 8000 units per week.[9] Due to a more conservative approach to ESA therapy in the past decade, a concomitant rise in blood transfusions from approximately 2.5% to 3.0% has also been observed. Some increase in transfusion rates may reflect appropriate clinical decisions to avoid ESAs in some patients, such as those with cancer or history of strokes, but the concern remains that increased transfusions may have adverse effects, especially among transplant-eligible patients. In summary, disordered iron metabolism and EPO insufficiency contribute to anemia in CKD, whereas treatment of anemia across the CKD stages is less frequent and less aggressive, resulting in lower hemoglobin levels and higher transfusion rates. The growing concerns about the safety of ESA products are a major driver in the shift toward worsening anemia in patients with CKD.

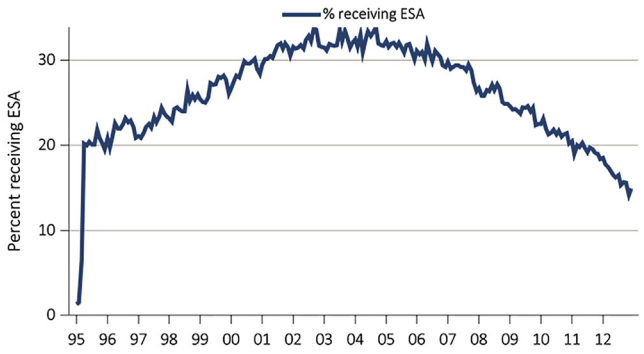

Figure 2 | Changes in ESA use before initiation of dialysis in US patients. Adapted from the USRDS (US Renal Data System) Annual Report, Volume 2, 2014. ESA, erythropoiesis-stimulating agents.

Pathophysiology and epidemiology of anemia of CKD

Before the ESA era, patients with CKD and particularly dialysis patients were routinely maintained at a low hematocrit level because interventions available to clinicians were relatively ineffective. During this time, anemia therapy consisted of iron supplements, androgen therapy, and blood transfusions; however, there were predictable complications to these interventions, including iron overload, infections, allosensitization, and cardiovascular complications. The therapy of anemia of CKD was revolutionized with the introduction of Epoetin, the first ESA, in 1989. This led to a major reduction in the burden of illness suffered by patients with CKD. In particular, ESA use led to the virtual elimination of patients with transfusion-dependent anemia. Notwithstanding the major advancement of ESA therapy, its therapeutic application can be considered to be unphysiological regarding the dose, timing, and mode of administration. The early therapeutic paradigm for ESA had been to administer high doses, which were then escalated every 2 to 4 weeks if a desired increase in hemoglobin concentration was not achieved. This strategy ran counter to the human body's natural response to anemia, which is a short-term rise in endogenous EPO levels (Figure 3), and likely increases the possibility of significant toxicities.[10]

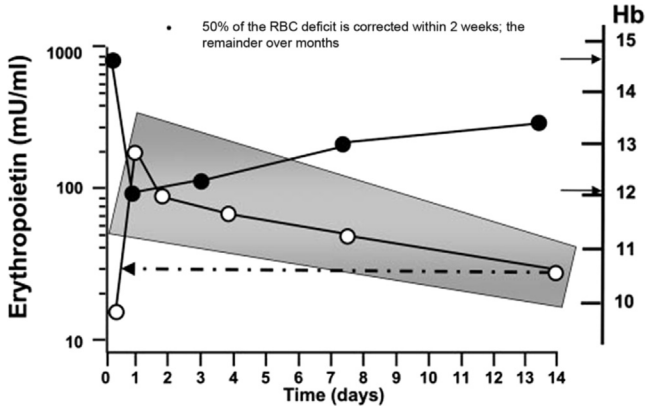

Figure 3 | Epoetin concentration-time profile following 2-unit phlebotomy in normal male volunteers. The shaded area reflects the 95% confidence interval of the data. The arrows pointing right show the baseline and post-phlebotomy hemoglobin values, while the dotted line and arrow highlights that erythropoietin levels are still above baseline 14 days after phlebotomy. Adapted with permission from Fishbane S, Besarab A. Mechanism of increased mortality risk with erythropoietin treatment to higher hemoglobin targets. *Clin J Am Soc Nephrol.* 2007;2:1274–1282.[10] Copyright © American Society of Nephrology. Hb, hemoglobin; RBC, red blood cell.