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REVIEW ARTICLE

Erythropoiesis-stimulating agents in chronic kidney disease: What have we learned in 25 years?

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Since the pioneering studies by Eschbach et al in 1987, erythropoiesis-stimulating agents (ESAs) have become the mainstay of anemia therapy in chronic kidney disease (CKD) patients. The introduction of ESAs 25 years ago markedly improved the lives of many patients with CKD, who until then had severe, often transfusion-dependent anemia. However, randomized controlled trials demonstrate an increased risk for cardiovascular events such as stroke, thrombosis, and death at nearly normal hemoglobin concentrations and higher ESA doses in CKD. By contrast, kidney transplant recipients may represent a unique population of CKD patients who may benefit from ESA therapy. This review discusses potential mechanisms involving the erythropoietic and nonerythropoietic effects of ESA treatment and ESA resistance. Further research aimed at elucidating the causal pathways is strongly recommended. Given current knowledge, however, clinical practice should avoid disproportionately high dosages of ESAs to achieve recommended hemoglobin targets, particularly in those with significant cardiovascular morbidity or ESA resistance. The key to CKD anemia management will be individualization of the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm.

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Introduction

Erythropoiesis-stimulating agents (ESAs) and adjuvant iron therapy have been the primary treatments for anemia in chronic kidney disease (CKD). It was assumed that increasing hemoglobin concentrations would not only improve patient-perceived quality of life (i.e., fatigue, energy level, and physical functioning) and reduce the need for blood transfusions, as shown in early trials[1–3] but also reduce morbidity and mortality. However, multicenter trials have challenged this traditional paradigm, particularly in regard to ESAs. Use of ESAs to normalize hemoglobin levels has repeatedly been shown to be associated with an increased risk of cardiovascular events and death. Anemia management patterns have changed markedly between 2002 and 2008 in hemodialysis patients in the USA.[4] Clinicians are prescribing fewer ESAs and more intravenous iron after changes to ESA drug labels and a new prospective payment system for dialysis services. The clinical impact of these changes needs further evaluation.

Over the past 2 decades, ESAs, particularly recombinant human erythropoietin (rHuEPO), have become the mainstay of renal anemia therapy (Table 1).[51,52,7,8,14,1,9,15,53,16,17,34,18,21,22,12,13] Erythropoietin (EPO) is the principal hormone involved in the regulation and maintenance of a physiological level of circulating erythrocyte mass. EPO exerts its biological effect primarily by attaching to the EPO receptors on erythroid progenitor cells, which leads to differentiation into mature erythrocytes. Human EPO is a 165-amino acid glycoprotein mainly produced by the liver during fetal life and by fibroblast-like peritubular interstitial cells in the kidney in adulthood. Interstitial pericytes are myofibroblast progenitors in fibrotic kidney disease. It is possible that in the progression of CKD, the EPO-producing abilities of pericytes are abated during the pericyte—myofibroblast transition, leading to the decreased production of EPO. It is also possible that uremic toxin accumulation can induce DNA methylation, a kind of epigenetic modification, which is involved in the silencing of the EPO gene.[5]

Recent evidence suggests that CKD anemia might be due to defective hypoxic signaling rather than an inability of the EPO-producing cells to synthesize EPO. Bernhardt et al[6] demonstrated that pharmacologic hypoxia-inducible transcription factor (HIF) stabilization using competitive prolyl-hydroxylase inhibitors (PHIs) can induce endogenous EPO in dialysis patients. The clinical trial of HIF-PHIs for patients with CKD anemia is ongoing. The long-term safety of therapeutic activation of the HIF system requires further study because of the broad biological potential of HIF in mediating hypoxia responses.

Development of ESA

In 1977, Miyake et al[7] purified EPO from the urine of patients with severe aplastic anemia. In 1983, Dr Fu-Kuen Lin[8] from Taiwan successfully established the genetic code for EPO, which led to the development of rHuEPO. Epoetin α and β, the first generation rHuEPOs, are composed of an identical amino acid sequence, but differ in their degree of glycosylation and the types of glycan moieties. Initially, rHuEPO was only given intravenously. The preferred route of application has been subcutaneous in recent years because it facilitates self-administration and is associated with substantial dose reduction. Subsequently, two second-generation ESAs with an extended duration of action were developed—hyperglycosylated version of epoetin α, darbepoetin α, and a pegylated version of epoetin β, methoxy polyethylene glycol-epoetin β (also known as continuous erythropoietin receptor activator or CERA). Darbepoetin α is approved for dosing every 2 weeks and CERA for dosing once a month. Dosage requirements of darbepoetin α and CERA do not appear to differ between the intravenous and subcutaneous routes of administration.

An extremely rare but serious adverse effect of the long-term administration of rHuEPO is pure red cell aplasia (PRCA).[9] rHuEPO, although weakly immunogenic, may induce the production of immunoglobulin (Ig)G antibodies against not only the recombinant molecules, but also residual endogenous EPO. Therefore, the resulting anemia is much more severe than prior to the onset of therapy. Bone marrow examination shows almost complete absence of erythroid precursors, but normal white cell and platelet precursors. PRCA has been observed predominantly with subcutaneous use of epoetin α after human serum albumin was removed from the formulation and replaced with Tween 80 to avoid potential contamination by viruses and prions. It has been postulated that this change in formulation might have reduced its stability.[10]

Peginesatide, a synthetic peptide-based ESA, is immunologically distinct from EPO and has been used as a rescue therapy in patients who develop rHuEPO-induced PRCA.[11] Recent trials demonstrated that peginesatide was as effective as epoetin α in maintaining hemoglobin levels and had a comparable cardiovascular safety profile in patients undergoing hemodialysis.[12] However, cardiovascular events and mortality were increased with peginesatide, as compared with darbepoetin, in patients with CKD stages 3, 4, or 5 who were not undergoing dialysis.[13]

ESA, once a promising cure for CKD anemia

In 1986, Winearls et al[14] found that rHuEPO was effective for treating anemia in patients who were on chronic hemodialysis. Nevertheless, important safety concerns arose even in this first report of the human use of EPO. During treatment, 1 of 10 study patients had an episode of hypertensive encephalopathy and 2 patients had clotting in their arteriovenous fistulas. The authors concluded that longer-term observations are needed to determine the consequences of increasing the hematocrit. In 1989, a Phase III multicenter clinical trial by Eschbach et al[3] was conducted to determine the effectiveness and safety of rHuEPO in anemic patients with end-stage renal disease. In a single-arm study, 333 hemodialysis patients with uncomplicated anemia (hematocrit 30%) were enrolled to receive epoetin α intravenously, three times/week at 150 U/kg or 300 U/kg body weight, which was then reduced to 75 U/kg