ORIGINAL INVESTIGATIONS

Pathogenesis and Treatment of Kidney Disease and Hypertension

Effect of Early Correction of Anemia on the Progression of CKD

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• ***Background:*** **This study is designed to assess the effect of early and complete correction of anemia by using recombinant human erythropoietin (epoetin) alfa on the progression of chronic kidney disease (CKD).** ***Methods:*** **Patients were randomly assigned to achieve high (13 to 15 g/dL [130 to 150 g/L]) or low (11 to 12 g/dL [110 to 120 g/L]) hemoglobin-level targets during 4 months of stabilization, followed by 36 months of maintenance. Glomerular filtration rate (GFR) decrease was measured by using iohexol clearance. Quality of life, nutrition, and safety also were monitored.** ***Results:*** **Because of labeling changes for subcutaneous administration of epoetin alfa (Eprex; Johnson and Johnson, Schaffhausen, Switzerland), the study was terminated prematurely. There were 195 patients enrolled in each group; 108 high-hemoglobin and 133 low-hemoglobin patients entered the maintenance phase. Mean maintenance duration was 7.4 months for the high-hemoglobin group and 8.3 months for the low-hemoglobin group. GFR decrease was numerically, but not statistically significantly, lower with the high-hemoglobin group (0.058 versus 0.081 mL/min/1.73 m^2/mo [<0.01 mL/s/1.73 m^2/mo]). Physical quality-of-life measures showed trends (Role–Physical, $P = 0.055$; Physical Function, $P = 0.083$) or statistically significant improvement (Vitality, $P = 0.042$) with high hemoglobin levels at the end of the stabilization phase. Adverse events were similar between groups. Cardiovascular adverse events occurred in 25% of the high-hemoglobin and 18% of the low-hemoglobin patients ($P = 0.137$). Neither epoetin dosage nor hemoglobin level was associated with cardiovascular adverse events or death.** ***Conclusion:*** **These data suggest that normalization of hemoglobin levels in patients with CKD is safe. Longer duration studies are needed to clarify efficacy benefits with high hemoglobin levels.** ***Am J Kidney Dis*** **47:738-750.**

INDEX WORDS: Anemia; chronic kidney disease (CKD); epoetin alfa; erythropoietin.

PROGRESSIVE CHRONIC KIDNEY disease (CKD) is a significant public health issue. Data from population surveys estimate that 11% of the adult population in the United States has CKD and approximately 16% of the population in Australia has at least 1 indicator of kidney damage.[1,2] In Europe, prevalences of patients on renal replacement therapy range from 438.2 per million in Iceland to 1,080.9 per million in the Valencia region of Spain.[3] CKD, especially in patients with at least a moderately decreased glomerular filtration rate (GFR; <60 mL/min/1.73 m^2 [<1.00 mL/s/1.73 m^2]), is associated with anemia,[4-6] increased risk for decreased quality of life, cardiovascular disease, and death.[7-10]

Human recombinant erythropoietin (epoetin) corrects anemia in patients with CKD and is recommended for patients with CKD with hemoglobin (Hb) levels less than 11 g/dL (<110 g/L).[11] Epoetin treatment improves quality of life and decreases the number of hospitalizations and transfusions in patients with CKD with anemia.[12] Anemia correction with epoetin improves oxygen delivery to tissues and may protect against oxidative stress.[13,14] Hypoxia and oxidative stress induce tubular damage and fibrosis, both of which are linked to the progression of CKD.[13,14] These data led to the hypothesis that correction of renal anemia with

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epoetin may decrease the rate of decline in renal function.

Several studies evaluated the ability of epoetin to retard the progression of CKD. The largest studies, conducted with patients with moderate to severe renal impairment, showed that correction of anemia improved renal survival compared with no or deferred anemia treatment.[15-17] However, in the study by Roth et al,[15] this was statistically significant only when patients were analyzed after Hb levels reached target correction. Small studies showed mixed efficacy results.[18-20]

One study of high-risk dialysis patients suggested that greater correction of Hb level may be associated with vasoconstrictive effects, thrombosis, and increased blood pressure.[21] In 2 oncology studies that investigated the benefit of anemia correction, both disease progression and survival were worse in the epoetin-treated group, and vascular adverse events were more common in epoetin-treated patients.[22,23]

Studies to date have yielded conflicting results regarding the potential benefits and drawbacks of complete correction of anemia in patients with CKD.[24] The current study is designed as a large-scale long-term study to determine whether the observation that anemia correction with epoetin alfa (Eprex) safely and effectively decreases the progression of renal failure in patients with moderate to severe CKD can be extended to patients with mild to moderate CKD. Because of safety concerns in late 2002 related to the risk for epoetin-induced pure red cell aplasia and subsequent labeling changes for subcutaneous administration of Eprex, the study was terminated prematurely by the sponsor. Available data from limited follow-up in this randomly selected cohort provide important pilot information and thus are reported here.

METHODS

Patients

Adults aged 18 to 75 years with CKD and an estimated GFR (eGFR) of 25 to 60 mL/min (0.42 to 1.00 mL/s; calculated using the Cockcroft-Gault formula[25]) were included if they had at least 6 months of follow-up, anemia (Hb <13 g/dL [<130 g/L] for men and <12.5 g/dL [<125 g/L] for women) without active blood loss or iron deficiency, eGFR decrease less than 0.6 mL/min/mo (<0.01 mL/s/mo), and blood pressure of 160/100 mm Hg or less (with or without antihypertensive therapy). Iron deficiency is defined as transferrin saturation less than 20% (or >10% of hypochromic red blood cells) or serum ferritin level less than 100 ng/mL (<100 μg/L). Exclusion criteria were autosomal dominant polycystic kidney disease, current treatment with erythropoiesis-stimulating agents for anemia secondary to CKD with an Hb level greater than 12 g/dL (>120 g/L), blood pressure of 180/110 mm Hg or greater within 3 months before study entry, red blood cell transfusion within the preceding 30 days, history of renal transplant, New York Heart Association class III/IV congestive heart failure or ischemic heart disease within the preceding 2 years, chronic inflammatory condition, seizure within the preceding year, malignancy other than nonmelanoma skin cancer, or a medical condition likely to affect the response to epoetin.

Study Design

Before initiation of this randomized, multicenter, open-label, clinical trial, the protocol and consent forms were approved by independent ethics committees or institutional review boards. The study was conducted in accordance with the 1989 Declaration of Helsinki.

Patients were randomly assigned to 2 Hb target groups: high Hb (13 to 15 g/dL [130 to 150 g/L]) and low Hb levels (11 to 12 g/dL [110 to 120 g/L]). Randomization was stratified by sex and treatment center by using a computer-generated randomization schedule. The study design consisted of a 4-month stabilization phase followed by a 36-month maintenance phase. The stabilization phase was deemed necessary to increase Hb levels to the target range, correct iron and vitamin deficiencies, and optimize factors known to affect progression of CKD (ie, optimize treatment of hypertension, treat patients with proteinuria with 1 g/d or greater of protein with angiotensin-converting enzyme [ACE] inhibitors and/or angiotensin receptor blockers [ARBs], and advise patients to maintain a daily protein intake of 0.8 to 1.0 g/kg).

Patients randomly assigned to a high Hb level were treated with epoetin alfa (Eprex) to normalize Hb level to a target of 14 to 15 g/dL (140 to 150 g/L) for men and 13 to 14 g/dL (130 to 140 g/L) for women. Stabilization could be extended for a maximum of 2 additional months for patients failing to achieve the target Hb level during the initial 4 months. Patients randomly assigned to a low Hb level could be treated with epoetin, if needed, to achieve a target Hb level of 11 to 12 g/dL (110 to 120 g/L). For all patients administered epoetin, therapy was administered subcutaneously once per week. The suggested initial epoetin dose was 25 to 100 IU/kg. Dose adjustments were permitted in steps of 4 weeks as needed to achieve target Hb level, with a permitted increase in weekly dose of 25 IU/kg.

Outcome Assessments

The primary end point is rate of GFR decline, determined by measuring plasma iohexol clearance. Secondary end points are GFR less than 10 mL/min/1.73 m^2 (<0.17 mL/s/1.73 m^2), need for renal replacement therapy, number of hospitalizations, occurrence of cardiovascular and thrombotic adverse events and death, quality of life, nutritional status, blood pressure control, and safety of long-term epoetin therapy to normalize Hb concentrations.