EDITORIAL

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Should all patients with chronic kidney disease receive an EPO-type drug?

THE EASY ANSWER is, of course, no. But an erythropoietin (EPO)-type drug is appropriate for most patients with chronic kidney disease, especially those in stage 3, 4, or 5, since anemia becomes increasingly common as the glomerular filtration rate falls below 30 to 60 mL/minute, and the adverse sequelae of anemia become more important.

In the United States, the currently available EPO-type drugs (also known as erythropoietic-stimulating agents or ESAs) are epoetin alfa (Epogen, Procrit) and darbepoetin alfa (Aranesp). Darbepoetin alfa is modified from epoetin alfa, with several amino acid substitutions and a higher sialic acid content, conferring a pharmacologic half-life about three times as long.[1,2]

See related article, page 289

As Dr. Saul Nurko discusses in this issue of the *Journal*,[3] anemia has been variably defined by hemoglobin levels less than 12.0 to 13.0 g/dL, depending on age and gender. In the United States, the treatment goal most often recommended for anemia in patients with chronic kidney disease is a hemoglobin level of 11.0 to 12.0 g/dL.[4]

NOT ALWAYS DUE TO EPO DEFICIENCY

Not all anemia in patients with chronic kidney disease is due to deficiency of the native hormone EPO alone. But often in practice we see patients with anemia attributed to chronic kidney disease who have not been assessed for other causes of anemia such as deficiencies of iron, vitamin B_{12}, and folate.

Nephrologists have become very adept at treating anemia with iron and EPO-type drugs. However, internists, family physicians, and other primary care providers can and should be the ones to recognize and initially evaluate anemia in patients with chronic kidney disease, rather than the nephrologist. This evaluation should include, at a minimum, measurements of hemoglobin, red blood cell indices, serum ferritin level, iron transferrin saturation, stool for occult blood, and vitamin B_{12} and folate levels.[4]

ORAL OR PARENTERAL IRON?

No single test can reliably and with high sensitivity and specificity be used to detect iron deficiency in patients with chronic kidney disease. Nonetheless, patients with chronic kidney disease with a serum ferritin concentration lower than 100 ng/mL or an iron transferrin saturation less than 20% are often considered to be iron-deficient,[4] and are likely to respond to iron supplementation with an increase in hemoglobin or a decrease in the dose of ESA needed. Therefore, a trial of oral iron supplementation would be appropriate, although this is often poorly tolerated and is not always completely effective.

If iron deficiency persists despite treatment with typical oral iron preparations such as ferrous sulfate, or if the patient cannot tolerate this therapy, a course of treatment with oral heme iron polypeptide[5] or an intravenous iron preparation would be appropriate.

Unlike patients undergoing chronic hemodialysis, many of whom receive maintenance intravenous iron therapy one to three times weekly in doses of 25 mg to 125 mg while at dialysis, patients with chronic kidney disease who are not on dialysis (and patients on peritoneal dialysis) are usually treated with less frequent, larger doses.

Iron dextrans have been given intravenously in doses of 500 mg or more for many years. Concern about the risk of anaphylactic reactions to iron dextran has led to investigation of the use of other parenteral iron preparations in doses above those typically used as maintenance therapy in chronic hemodialysis.

Thus, iron sucrose has been safely given to patients with chronic kidney disease in doses of 200 mg as a 2-minute intravenous "push" and up to 300 mg as an intravenous infusion.[6–8] Higher doses have also been used but are more likely to cause side effects.

Sodium ferric gluconate complex can be safely given as an intravenous infusion of up to 250 mg in many patients; side effects limit use of higher doses.[9,10]

WHEN TO START AN EPO-TYPE DRUG

ESA therapy is expensive and can be inconvenient for those who must receive their injections in a doctor's office. Thus, it should be reserved for patients who are most likely to have important clinical benefit from it.

In most patients with chronic kidney disease, ESA therapy is started when the hemoglobin concentration falls to 11.0 g/dL or below. However, in patients with conditions such as active angina pectoris or congestive heart failure, starting treatment at a higher hemoglobin level would be reasonable.

I would not recommend starting therapy in patients with limited life expectancy, significantly impaired function due to comorbid conditions unrelated to chronic kidney disease or anemia, significant dementia, or other conditions that make it unlikely that the patient will clinically benefit from such therapy.

TREATMENT IS BENEFICIAL

Anemia has adverse consequences. Compared with patients with chronic kidney disease whose hemoglobin levels are normal, those with anemia have a lower quality of life, more fatigue, less exercise tolerance, more depression, more left ventricular hypertrophy, more left ventricular systolic dysfunction, higher rates of cardiac disease and stroke (and death due to these diseases), more hospitalizations, longer hospitalizations, and even faster decline in kidney function.

Treatment of anemia to achieve hemoglobin levels of at least 10.0 to 11.0 g/dL has been associated with improvement in each of these areas (reviewed elsewhere[11]). There is even some evidence that ESA therapy before starting dialysis is associated with lower healthcare costs compared with costs for patients who did not receive this therapy.[12]

A HIGHER HEMOGLOBIN GOAL?

Guidelines from the National Kidney Foundation (the Kidney Disease Outcomes Quality Initiative, or K/DOQI, now under revision[4]) recommend a target hemoglobin level of 11.0 to 12.0 g/dL.[4] Other guidelines are similar, although with some differences in the upper end of the range.

A few small, prospective studies[11,13,14] found that patients who achieved normal or near-normal hemoglobin levels while on ESA treatment had better quality of life, neurocognitive function, and exercise performance and a lower rate of congestive heart failure. For unclear reasons, however, prospective trials have failed to show improvement in regression of left ventricular hypertrophy or reductions in hospitalizations or deaths with hemoglobin normalization. As a result, debate continues as to the overall clinical benefit, safety, and cost-effectiveness of hemoglobin "normalization" in patients with chronic kidney disease. For now, I would not recommend routinely maintaining hemoglobin levels above 12.0 g/dL.

Many patients cannot tolerate oral iron supplements

IS LESS-FREQUENT DOSING EFFECTIVE?

One of the difficulties with ESA treatment is the need for weekly subcutaneous injections, which, for some patients, need to be given in the physician's office. Several studies have addressed less-frequent ESA dosing.

Provenzano et al[15] recently reported the initial results of the Procrit for Maintenance-Phase Treatment of Anemia Due to Chronic Kidney Disease (PROMPT) study, in which patients were randomized to receive open-label epoetin alfa in doses of 10,000 U weekly, 20,000 U every 2 weeks, 30,000 U every 3 weeks, or 40,000 every 4 weeks for 16 weeks. The primary end point was the final mean

hemoglobin concentration, and all groups had final mean hemoglobin concentrations greater than 11.0 g/dL. In addition, 93.5% of patients on weekly treatment maintained their hemoglobin above 11.0 g/dL throughout the study, as did 89.5% in the every-2-week group, 77.2% in the every-3-week group, and 76% in the every-4-week group.

Germain et al[16] performed a chart review to assess the efficacy of epoetin alfa given less often than once a week in patients with chronic kidney disease. About half the patients received it once every 2 weeks; others received it every 3 weeks, 4 weeks, or less often. Overall, 82% of the patients maintained hemoglobin levels greater than 11.0 g/dL.

Ling et al,[17] in an open-label study, changed the treatment of 97 patients with chronic kidney disease: they had been receiving darbepoetin alfa every 2 weeks, which was changed to once a month. Hemoglobin levels stayed between 10.0 and 12.0 g/dL in 85% of the patients who completed the 29-week study.

Jadoul et al[18] reported that a similar percentage of hemodialysis patients maintained their target hemoglobin levels when their darbepoetin alfa regimen was changed from every 2 weeks to once a month.

Thus, treatment with either epoetin alfa or darbepoetin alfa every 2 to 4 weeks is successful for many patients. Occasional patients can be treated with even less frequent dosing. This is of particular value for the many patients who must receive their injections in the office for insurance or other reasons.

TOWARD BETTER MANAGEMENT

Most patients with chronic kidney disease and anemia should receive an ESA to maintain a hemoglobin concentration of at least 11.0 g/dL. Several reports have clearly pointed out, though, that many patients do not receive an ESA before starting dialysis, or if they do, have suboptimal hemoglobin levels despite treatment.[12,19–21] Thus, there are significant opportunities for better anemia management in patients with chronic kidney disease before they need to start renal replacement therapy.

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