

Management of IDA in Chronic Kidney Disease

CKD is a progressive disease that gradually impairs kidney function, usually over a period of years. According to the National Kidney Foundation (NKF), approximately 8 million people in the US are living with moderate (stage 3) or severe (stage 4) CKD and are not yet receiving dialysis.¹ CKD often progresses to end stage renal disease (ESRD), where the kidneys fail and renal replacement therapy such as dialysis or transplantation is required to sustain life. The primary goal of treatment for CKD is to slow the progression of the disease, mainly by controlling the underlying common causes: hypertension and/or diabetes. Patients with CKD suffer from a myriad of complications, which may also affect CKD progression. These include malnutrition, bone disease and anemia, usually accompanied by iron deficiency.

Iron deficiency and anemia, often multifactorial in its etiology, are significant complications of CKD and ESRD, developing early in the course of the disease and progressing with loss of renal function.²⁻³ Published data indicate that approximately 44% of patients with CKD stage 3 or 4 are anemic (defined as Hb <13.5 g/dL for men and Hb <12.0 g/dL for women), and the prevalence of anemia increases to 75% in patients reaching CKD stage 5 (ESRD).¹ The cause of this anemia is, as mentioned, multifactorial, and includes the inability of the failing kidney to produce enough erythropoietin to stimulate adequate hematopoiesis, iron deficiency, and shortened red blood cell survival. Iron deficiency is a common and often predominant cause of anemia in CKD patients. Iron deficiency and iron deficiency anemia can be due to both poor nutrition and blood loss and can be exacerbated by use of erythropoietic stimulating agents (ESAs). ESA therapy depletes iron stores as iron needs are increased to produce iron-containing red blood cells (RBCs). The DRIVE study showed IV iron potentiates the response to ESAs even when the patients had normal or elevated ferritin and TSAT >25%.

Left untreated, anemia can have adverse effects on cardiac function, CKD progression, and survival.⁴⁻⁷ Anemia has also been shown to be an independent

predictor and risk multiplier for increased mortality in CKD patients who have not progressed to ESRD. Patients diagnosed with CKD and anemia have a risk of death that is equivalent to that in patients diagnosed with both diabetes and congestive heart failure combined.⁵⁻⁸ Treatment of iron deficiency anemia in CKD stages 1 through 4 may be critical to reducing associated cardiovascular morbidity and mortality, since anemia-associated left ventricular hypertrophy may be irreversible if therapy is delayed until the beginning of dialysis.⁹

Evidence suggests that aggressive treatment of iron deficiency anemia earlier in the progression of CKD can improve quality of life (QOL) as well as disease outcome and may possibly slow the progression to complete renal failure.¹⁰⁻¹³

In 2014, the Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) seemed to validate an association between high intravenous iron doses and mortality. The DOPPS results suggested that case-mix-adjusted mortality was higher when monthly doses of intravenous iron exceeded 300 mg. Hospitalization risk was also elevated. The authors called for a well-powered clinical trial to evaluate the safety of different IV iron-doing strategies in hemodialysis patients.¹⁴

The results of just such a trial was published in late 2018. The Proactive IV Iron Therapy in Haemodialysis Patients or PIVOTAL trial compared 400 mg monthly of IV iron sucrose administered proactively unless the ferritin was > 700 ng/ml or the transferrin saturation was > 40% to low dose iron sucrose, 0-400 mg monthly for ferritin < 200 ng/ml or transferrin saturation less than 20%. The proactive, high dose regimen was found to be non-inferior for the primary endpoint of a composite of non-fatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death, assessed in a time-to first-event analysis. The high-dose regimen resulted in a reduction in the dose of erythropoiesis-stimulating agents required, no difference in infection rates, a lower rate of hospitalization for heart failure and a lower rate of transfusion.¹⁵ The authors concluded: *“Given the absence of harm that was observed with the high-dose intravenous iron regimen in our trial, the safety*

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and efficacy of even higher doses of iron might be explored in further trials.”

Intravenous iron remains a mainstay of anemia management in patients with CKD and ESRD. In earlier stage CKD, anemia can often be managed with IV iron alone. When an ESA is required to maintain an adequate hemoglobin level, a lower dose will be required when adequate, proactive IV iron is given.

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