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Treatment of anemia in CKD patients

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Anemia is a severe complication of chronic kidney disease (CKD) that is seen in more than 80% of patients with impaired renal function. Although there are many mechanisms involved in the pathogenesis of renal anemia, the primary cause is the inadequate production of erythropoietin (EPO) by the damaged kidneys. EPO is produced in the peritubular cells of the kidney and is the major hormone involved in the production of red blood cells (erythropoiesis). When EPO levels are low, an inadequate number of oxygen-carrying red blood cells are produced. Anemia starves the body of oxygen and causes decreased exercise capacity, cognitive impairment, and diminished quality of life. Anemia has also been implicated in the development of congestive heart failure and left ventricular hypertrophy.

Until approximately 1990, anemia of CKD, especially in patients with end stage renal disease (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. This resulted in lower hemoglobin (Hb) levels in patients with ESRD until pharmacologic replacement of EPO with epoetin in 1989 revolutionized the approach to CKD-related anemia.

Today, an erythropoiesis-stimulating agent (ESA) and adjuvant iron therapy are the main tools for treating the anemia associated with CKD. Available ESAs are very effective drugs, usually obtaining significant increases of Hb levels. However, they are administered by the parenteral route. Especially with frequent subcutaneous administrations, this may be cumbersome for long-term treatment in non–dialysis-dependent patients with CKD. In hemodialysis (HD) patients, the issue is more complex because intravenous administration increases nurse workload but improves treatment adherence. In addition, in the past several years, clinical trials have shown that higher Hb targets and/or application of high ESA doses may increase cardiovascular risk.

The development of new strategies to treat anemia is still an evolving and fascinating area of experimental and clinical research. At present, the most promising class of agents seems to be a hypoxia-inducible factor (HIF) stabilizers, as evident in the number of molecules currently under development. This class of drug stimulates erythropoiesis by physiologic concentrations of endogenous EPO, which may translate into a clinical advantage because concerns for ESA safety are higher at the high doses. However, these theoretical advantages will need to be demonstrated clinically in large trials. Conversely, the class needs to be proved safe in light of the potential risks for increases in levels of VEGF and related factors and the possibility of widespread stimulation of complex pathways leading to unexpected side effects. The final judgment of benefits/risks of these agents will be possible only after the completion of large long-term safety studies testing hard end points.

The role of iron preparations is well accepted in CKD patients with an acceptable safety profile. While hepcidin inhibitors represent a new promising therapeutic target for anemia, this may be

associated with adverse events such as tissue calcification and inflammation. New phosphate iron binders may have the potential of treating simultaneously anemia and hyperphosphatemia; iron absorption is significant only with iron citrate.