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Anemia management in CKD/ESRD

Jae Yoon Park
Dongguk University Ilsan Hospital, Korea, Republic of

Anemia is a common complication in patients with chronic kidney disease (CKD), developing gradually and increasing in severity as kidney disease progresses. Anemia in CKD is associated with reduced quality of life and poor outcomes including increased cardiovascular disease, hospitalizations, cognitive impairment and mortality. Anemia of CKD is a multifactorial process due to relative erythropoietin (EPO) deficiency, uremic-induced inhibitors of erythropoiesis, shortened erythrocyte survival and disordered iron homeostasis. Until 1990, anemia of CKD, especially in patients with end-stage renal disease (ESRD), was managed with oral and/or intravenous iron administration, occasional androgens and blood transfusions for the severely anemic, which sometimes could cause complications such as transfusion reactions, sensitization and iron overload. The therapy of anemia in CKD was revolutionized with the introduction of erythropoiesis-stimulating agent (ESA) in 1989. Since then, the use of iron and ESAs has been a mainstay of treatment of anemia in patients with CKD/ESRD that improved the quality of life of patients with alleviation of complications associated with anemia. However, the US Food and Drug Administration has raised concerns about increased cardiovascular complications and mortality associated with the use of ESAs based on the recent randomized trials. Also, it has been reported that ESAs were not effective in treating anemia in 10-20% of patients with CKD. The main causes of ESA hyporesponsiveness are known as iron deficiency and chronic inflammation. These issues have recently increased the demand for new anemia treatments in CKD/ESRD.

Tissue hypoxia is the pivotal factor that increases EPO production as a final step in a signal transduction pathway involving several proteins, among which hypoxia-inducible factors (HIFs) play a central role. Prolyl-hydroxylase 2 has been identified as the key enzyme that regulates HIF-2 α stability. HIF-prolyl-hydroxylase 2 inhibitors or HIF stabilizers represent a novel therapeutic option in the future management of anemia of CKD. HIF stabilizers inhibit the prolyl-hydroxylase enzyme leading to increased levels of HIF and thus increased production of endogenous EPO. HIF stabilizers improve the iron metabolism by decreasing the level of ferritin and hepcidin. In addition, although the demand for ESAs was increased according to the elevated level of C-reactive protein, an indicator of inflammatory response, the requirement for HIF stabilizers was not changed significantly. These strengths of HIF stabilizers have led to the emergence of new treatment option for patients with ESA hyporesponsiveness who are no longer expected to benefit from ESAs. HIF stabilizers can be administered orally, unlike ESAs which requires injection, expected to have low production cost and high drug stability. To date, HIF stabilizers have been proved to be effective in improving anemia treatment of patients with CKD before dialysis through phase 2/3 clinical trials, and phase 3 trials are underway in dialysis patients. HIF stabilizers could be expected as a new treatment for anemia in patients with CKD/ESRD.