KSN 2021
FULLY VIRTUAL MEETING
September 02 (Thu) - 05 (Sun)

Abstract Submission No. : 9033

New Expectation of Renal Anemia Management

Jwa-Kyung Kim
Hallym University Sacred Heart Hospital, Korea

Anemia is an extremely common complication in chronic kidney disease (CKD), and is associated with a reduced quality of life, and an increased morbidity and mortality. The mechanisms involved in anemia associated to CKD are diverse and complex. They include a decrease in endogenous erythropoietin (EPO) production, absolute and/or functional iron deficiency, and inflammation with increased hepcidin levels, among others. Patients are most commonly managed with oral or intravenous iron supplements and with erythropoiesis stimulating agents (ESA). The goal of treatment is to mitigate any symptoms due to anemia and to reduce the likelihood of needing a blood transfusion. The long-term clinical experiences with ESAs have clearly proven that correction of anemia not only reduces blood transfusion and improves patients' QOL but has multiple benefits for the concurrent complications of CKD such as Cardio-Renal–Anemia (CRA) syndrome and/or malnutrition-inflammation-atherosclerosis syndrome. However, these treatments have associated risks, and sometimes are insufficiently effective especially for patients with chronic ESA hyporesponsiveness.

In the last years, there have been some remarkable advances in the treatment of CKD-related anemia, which have raised great expectations. A novel family of drugs has been developed: the hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs). Unlike other ESAs that replace endogenous erythropoietin, HIF-PHIs stimulate transcription of the EPO gene in the kidneys and liver, leading to increased levels of endogenous EPO. These agents also improve iron availability and reduce hepcidin levels. They are administered orally, which may be a more favorable route for patients not undergoing hemodialysis.

The phase 2 and 3 clinical studies have shown that HIF-PHIs are as efficacious as ESAs in ameliorating renal anemia. The safety and efficacy of HIF-PHIs among prevalent dialysis patients were examined in a trial of 3554 patients who were randomly assigned to receive the HIF-PHI, vadadustat, or darbepoetin-alfa. Vadadustat (at a dose of 150 to 600 mg) and darbepoetin were titrated to target an Hb of 10 to 11 g/dL among patients in the United States and 10 to 12 g/dL among patients in other countries. All trial participants were also offered treatment with iron to maintain a transferrin saturation (TSAT) >20 percent and serum ferritin >100 ng/mL. Between weeks 40 and 52 after randomization, prevalent

dialysis patients assigned vadadustat were less likely to maintain target Hb (44 versus 51 percent), although rates of red cell transfusion were similar (2.0 versus 1.9 percent of prevalent dialysis patients). Findings from a corresponding trial of 369 incident dialysis patients with the same study design reached similar conclusions. Combining patients from both trials, rates of mortality (13.0 versus 12.9 percent), non-fatal stroke (1.3 versus 1.9 percent), hospitalization for heart failure (3.9 versus 4.0 percent), and non-fatal myocardial infarction (3.9 versus 4.5 percent) were similar. Other adverse events (eg, hypertension, diarrhea, pneumonia) were lower in the vadadustat group, both among prevalent (55 versus 58 percent) and incident (50 versus 57 percent) dialysis patients. Other smaller trials of dialysis patients, which tested a different HIF PHI (roxadustat), reported similar findings.

However, guideline-oriented strategies on how to use HIF stabilizer is not available at this limited point due to scant clinical information. And whether the same clinical benefits on CRA and MIA syndrome hold true in patients given HIF stabilizers is a matter for future debate. Since HIF-PHIs pathways regulate or interact with many biologic processes, there is concern about non-erythropoietic adverse effects, such as increased risk of cancer, thrombosis, cardiovascular disease, progression of diabetic retinopathy, and CKD, among others, which will require long-term follow-up of treated patients. Nevertheless, HIF stabilizers can preferably be indicated for CRA syndrome at pre-dialysis stage, ESA resistant anemia at advanced CKD stage, and perhaps for dysregulated iron metabolism akin to MIA syndrome in patients on dialysis.