Novel Agents to Treat Renal Anemic Patient

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"Anemia" is a condition where a lower-than-normal amount of red blood cells (RBC) or hemoglobin found in the blood. It may arise as a complication of some systemic morbidities renal diseases, particularly chronic kidney disease (CKD).[1] Most patients experience some symptoms of anemia when the hemoglobin drops below 7.0 g/dL.[2]

Erythropoietin (EPO), a glycoprotein hormone, naturally produced by the kidney that stimulates red blood cell production. Anemia is less common in early kidney disease, but if left untreated, it gets worse as kidney disease progresses.[3] A patient is in greater risk for kidney disease if he/she has diabetes or high blood pressure. CKD is a condition characterized by a gradual loss of kidney function over time, causes permanent damage of kidney function. This damage can cause wastes and fluid to build up inside the body which causes other health problems. CKD causes renal dysfunction which create obstacle to produce lower EPO which causes less production of hemoglobin in the body and patient experience anemia.[3,4]

Hypoxia-inducible factor (HIF) system is the most important factor to regulate EPO production. Its activity depends on the tissue oxygen levels. Decreased level of oxygen in cellular environment (hypoxia) increases the activities of HIF.[3,4] HIFs also regulate erythropoietic gene expression, iron absorption, energy metabolism, pH, and angiogenesis.

Anemia usually is grouped into 3 etiologic categories: i) decreased RBC production, ii) increased RBC destruction, and iii) blood loss.

Anemia of chronic diseases & CKD placed under the category of decreased RBC production.[2]

A data determined from a review of National Health and Nutrition Examination Survey (NHANES) that the prevalence of anemia increased with the stages of CKD, as follows:[4]

CKD stage	Prevalence
Stage 1:	8.4%
Stage 2:	12.2%
Stage 3:	17.4%
Stage 4:	50.3%
Stage 5:	53.4%

Treatment with available agents:

After receiving a patient with anemia of chronic illness like CKD, some important factors such as iron deficiency, concomitant blood loss, or deficiencies of vitamin B12 and/or folic acid is need to be addressed immediately.[5,6] Blood transfusions are reserved for severe cases. But before that, use of Erythropoiesis-stimulating agents (ESAs) such as Epoetin α, Epoetin β are the most recommended initial treatment for anemia of CKD.[5,7] Those are produced by recombinant DNA technology. Immediately after EPO, Darbepoetin alfa (DA) and methoxy polyethylene glycol-epoetin beta where developed with prolonged shelf-life. Although the administration of ESAs and iron supplementation are a well-established therapeutic approach for

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renal anemia, several studies have revealed that liberal administration and dosing of ESA was associated with risk of cardiovascular (CV) events, progression of CKD, vascular access thrombosis and overall mortality.[5,7] Moreover, there is a the strong association between labile iron and oxidative stress, bacterial growth, gastrointestinal abnormalities, hypersensitivity, risk of infection and mortality have been concerns related to iron supplementation in CKD patients.[6]

To minimize the adverse effects of ESAs and its resistances in the long-term use, alternative agents of exogenous ESAs have been developed that stimulate endogenous EPO production in the responsive tissues. Those investigational agents work to stabilize hypoxia-inducible factor (HIF) by inhibiting prolyl hydroxylase (PH) enzymes.[8] Being also known as HIF-prolyl-hydroxylase inhibitors (HIF-PHIs), they lead to an increase in the levels of HIF and stimulate the production of endogenous EPO. They induce considerably lower but more consistent blood erythropoietin levels than ESAs. HIF-PHIs improve iron mobilization to the bone marrow and iron metabolism resulting in effective anemia management in patients with CKD.[7] They also promote erythroferrone which reduce hepcidin interference, allowing for greater utilization of iron.

There are four oral HIF-PHIs recently invented and vast clinical trial is still ongoing. Those are Roxadustat, Daprodustat, Vadadustat, and Molidustat.[8] Among them, Roxadustat received its first global approval in China in December 2018.[9] It was approved for medical use in the European Union in August 2021.[10] Roxadustat exhibits erythropoietic activity involving both increased EPO secretion and mobilization of iron stores which makes this drug as the best treatment of anemia of CKD and iron deficiency related anemia. It maintained hemoglobin similarly to ESA with a comparable safety profile like cardiovascular safety.[9,10]

Although the use of ESAs and iron supplementation are a well-established therapeutic approach for renal anemia, there are several safety concerns as discussed earlier. Current findings suggest that HIF-PHIs especially roxadustat is clinically effective and well tolerated. Now-a-days, HIF-PHIs can be an alternative for the treatment of renal anemic patients. However, more studies are necessary regarding their safety in long-term use and possible side-effects.

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