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Efficacy, Safety of Hypoxia-Inducible Factor Activators in Renal Anemia

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Clinical trial evidence to date suggests that novel hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) may offer therapeutic advantages over existing treatments for renal anemia, according to a recent review published in *Advances in Chronic Kidney Disease*.

HIF-PHIs inhibitors promote endogenous erythropoiesis and iron metabolism. The authors of the review, Neil Sanghani, MD, and Volker Haase, MD, of Vanderbilt University Medical Center in Nashville, Tennessee, noted that these drugs also have the potential to produce beneficial effects beyond erythropoiesis. Currently, 3 oral compounds—daprodustat, roxadustat, and vadadustat—have advanced to global phase 3 development for patients with chronic kidney disease (CKD) patients not on dialysis.

Roxadustat, an orally administered, highly protein-bound small molecule from FibroGen and AstraZeneca, was just approved for use in China. It targets all 3

HIF-prolyl hydroxylase domains and is usually dosed 3 times weekly. Phase 2 and 3 trials showed that the drug increases hemoglobin levels and either directly or indirectly reduces hepcidin in CKD patients regardless of whether or not they are on dialysis. Roxadustat also reduced total cholesterol levels. Daprodustat from GlaxoSmithKline and vadadustat from Akebia Therapeutics showed similar effects.

Other HIF-PHIs also are under investigation, such as enarodustat, desidustat, and molidustat. The nonerythropoietic actions of each of these drugs still need to be defined.

HIF-PHIs may have therapeutic advantages over existing anemia treatments, according to the reviewers. Thus far, published phase 2 trial data indicate that HIF-PHIs are as effective as erythropoiesis-stimulating agents (ESAs) in increasing hemoglobin levels but at lower plasma erythropoietin levels. Other potential clinical benefits include better iron metabolism, anti-inflammatory effects, and efficacy in ESA-resistant patients. ESAs have been linked with adverse cardiovascular events. HIF-PHIs may help lower blood pressure and protect from ischemic events.

Research has identified some safety concerns, however. HIF-PHIs might promote tumorigenesis and angiogenesis that negatively affects retinal diseases or cancer. The drugs might contribute to pulmonary hypertension, thromboembolic complications, CKD progression, and renal and liver cyst progression in polycystic kidney disease. Hyperkalemia has been reported in phase 2 studies of these drugs. Hyperglycemia and hyperuricemia also have been observed.

Adverse events in CKD may depend on the pharmacokinetics and dosing of HIF-PHIs. Results from clinical studies on the long-term safety of HIF-PHIs in CKD patients are forthcoming, according to the reviewers.

"Although efficacious and not inferior to ESA therapy, phase III patient safety results pending, renal practitioners are not likely to switch patients who are stable on ESA therapy to HIF-PHIs, unless additional clinical trials clearly establish that HIF-PHI therapy has benefits that go beyond erythropoiesis," Drs Sanghani and Haase stated. "An important question for the renal practitioner will be how to choose among different HIF-PHIs once approved for marketing."

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Reference

Sanghani NS, Haase VH. Hypoxia-inducible factor activators in renal anemia: Current clinical experience. *Adv Chronic Kidmru Dis.* 2019;26:253-266. doi:10.1053/j.ackd.2019.04.004

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