**ABSTRACT**

Anemia on Chronic Kidney Disease: The Role of Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors

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Anemia is one of the homeostatic abnormalities caused by chronic kidney disease and also frequently problem encountered in end-stage renal disease patients, regardless of the hemodialysis treatment. Anemia in chronic kidney disease significantly impairs the quality of life, increases morbidity and mortality risk, and deteriorates the physiological response to lower tissue oxygen levels. Chronic kidney disease's patients who are contraindicated or are hyporesponsive to therapy with erythropoiesis-stimulating drugs may utilize this mechanism as an alternative.

**Keywords:** anemia, chronic kidney disease, erythropoietin, hypoxia sensing system.

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**INTRODUCTION**

Anemia is a frequent complication of people with chronic kidney disease (CKD) and its increasing as the CKD progression. Kidney Disease Improving Global Outcome (KDIGO) 2012 defines anemia in chronic kidney disease (CKD) as a hemoglobin (Hb) level of <13 g/dl in men and <12 g/dl in women. Anemia in CKD will accelerate the disease progression, decrease the quality of life, and increase the risk of hospitalization and cardiovascular complication. A decrease in hemoglobin in CKD patients can be found in the early stages of the disease and worsen as kidney function declines; The prevalence of anemia in CKD in the United States ranges from 18.2% in stage 3A of CKD to 72.8% in stage 5.

Sir Robert Christison observed the rapid progression of anemia in CKD patients for the first time in 1839. Anemia in CKD is caused by two primary mechanisms: erythropoietin deficiency (EPO) and functional iron deficiency anemia (IDA). Functional IDA is characterized by impaired iron mobilization and inadequate iron transportation to the erythroid precursor despite adequate iron reserves, whereas absolute IDA is identified by severely diminished or absent iron stores.

Correction of iron deficiency and erythropoiesis-stimulating agent (ESA) therapy is the standard of care for treating anemia in CKD (EPO recombinant or its analogs). However, it has been demonstrated that using ESAs to achieve average or near-normal hemoglobin concentrations in CKD patients increases the risk of a cardiovascular event. The current best practice guidelines recommend using ESAs cautiously and only for partial anemia correction. Also, specific subgroups of anemic patients may be refractory or hyporesponsive to ESA. Therefore, an alternate therapy is required for these populations.

Endogenous EPO stimulation is a promising novel treatment for CKD anemia. Oral administration of Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor (HIF-PHI) could stimulate erythropoiesis by increasing endogenous EPO synthesis and modulating iron metabolism. These treatments are expected to alleviate cardiovascular complications from high ESA doses and benefit ESA hyporesponsive patients. This article aimed to review the mechanism of action and advantages of HIF-PHI therapy over ESA.

**Hypoxia-inducible factor mechanism of action**

The kidney is vulnerable to hypoxic conditions, and increasing the number of red blood cell production is feedback mechanism to respond the hypoxia conditions. Several factors, including the rate of cellular metabolism and the hypoxia-inducible factors activity, affect the susceptibility of kidney cells to hypoxia. HIFs are transcription factors that stimulate the expression of specific genes in response to hypoxia. The Prolyl hydroxylase domain enzymes (PHD) 1-3 and an asparaginyl hydroxylase (factor-inhibiting HIF, or FIH) regulate the HIF Pathway.
HIF is a heterodimer composed of two subunits (Figure 1): the α-subunit (oxygen-sensitive subunit) and the β-subunit (oxygen-insensitive subunit). Prolyl hydroxylase domain (PHD) enzymes, also known as HIF-prolyl hydroxylases (HPHs), use molecular oxygen as their substrate to hydroxylate proteins. Under adequate oxygen levels, HIF-α is continuously produced and promptly degraded by PHDs via hydroxylation. Von Hippel-Lindau (vHL) mediates this degradation, followed by ubiquitination and proteasomal destruction.

Hypoxia lowers the enzymatic activity of PHDs, this situation allows HIF-α to accumulate and transactivate multiple target genes, such as those involved in erythropoiesis, angiogenesis, iron metabolism, and glycolysis, glucose transport, cell proliferation, and survival. The accumulation of HIF formed a heterodimer with HIF-α. This heterodimer subsequently moves to the nucleus, and then continues binded to hypoxia-responsive elements (HRE), activating EPO synthesis in the kidneys and liver. By increasing erythrocyte count and capacity, EPO will prevent cell death induced by hypoxia, improving oxygen transport, and enhancing O₂ carrying capacity.

Another mechanism of anemia in CKD is functional iron deficiency mediated by hepcidin which reduces the absorption of the iron in intestine and releases from internal storage (enterocytes, hepatocytes, and macrophages) by promoting the degradation and endocytosis of ferroportin, the sole known iron exporter. HIF also affects the metabolism of iron and handling by increasing the expression of duodenal cytochrome b and divalent metal transporter-1, an essential gene that regulates iron absorption in the intestine. In addition, HIF upregulates transferrin, transferrin receptor-1, ceruloplasmin, and increasing tissue iron transport. By improving iron absorption and transport to the bone marrow, it can complement EPO’s effect on erythropoiesis by combining the stimulation of erythrocyte formation with increased iron availability. EPO-driven erythropoiesis caused by HIF also indirectly suppresses hepcidin.

Hypoxia-Inducible Factor in chronic kidney disease

AKB-6548 (Vadadustat) is one of the oral HIF-PHI that is presently being researched for its potential efficacy in the treatment of anemia in CKD in both nondialysis-dependent (NDD)-CKD or dialysis-dependent (DD)-CKD patients. Phase 1 studies observed an increase in serum EPO in healthy subjects, while the result of phase 2a single-ascending dose study in CKD patients who were not on dialysis (NDD-CKD) demonstrated a moderate increase in serum EPO. As reported in an open-label study, hemoglobin levels in the group of patients were increased by Vadadustat treatment. According to a study by Martin et al., Vadadustat increased hemoglobin and enhanced mobilization and iron utilization biomarkers levels when administered to a group of CKD stage 3 or 4 patients with secondary anemia. Phase 3 trials in CKD patients with and without dialysis are still ongoing.

Four phase-3 studies are being held to understanding more about Vadadustat’s hematological efficacy (mean change in hemoglobin concentration from baseline) and major adverse cardiovascular events (MACE; composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke). These studies include two studies in dialysis-dependent (DD)-CKD patients (the INNO2VATE trial) and two in nondialysis-dependent (NDD)-CKD patients (the PRO2TECT trials).

The PRO2TECT trials by Chertow et al. showed us that Vadadustat was non-inferior to darbepoietin alpha for improvement the hematologic feature, with the mean differences in the change in Hb concentration at weeks 24 - 36 being 5-fold higher in ESA-untreated patients compared to ESA-treated patients. However, Vadadustat failed to meet the predetermined noninferiority criteria for cardiovascular safety in NDD-CKD patients.

The difference in the safety of Vadadustat between NDD-CKD and DD-CKD was shown by the INNO2VATE trial. Eckardt et al. showed that Vadadustat was non-inferior to darbepoetin alfa in cardiovascular safety, also the hemoglobin correction and to maintain the optimal level of hemoglobin in dialysis patients with anemia. The mean differences in hemoglobin levels between Vadadustat and Darbepoetin alfa were -0.31 g/dL at weeks 24 to 36 and -0.07 g/dL at weeks 40 to 52 in the incident DD-CKD trial; and -0.17 g/dL and -0.18 g/dL, respectively in the prevalent DD-CKD trial.

Chen et al. studied oral administration FG-4592 (Roxadustat) as a HIF-PHI inhibitor agent. In this phase 2 study, FG-4592 was proved to be an effective alternative therapy for anemia in CKD, as 80% of the patients receiving low-dose therapy (1.1 – 1.75 mg/kgBW) and 87% of the patients receiving high-dose therapy (1.7 – 2.3 mg/kgBW) had an increase in Hb level 1 g/dl from baseline. In a 2019 study on the administration of Roxadustat, Akizawa et al. found that administration of Roxadustat for six weeks was well tolerated, and the difference in the safety of Roxadustat between NDD-CKD and DD-CKD was shown by the INNO2VATE trial.
CONCLUSION

Hypoxia-inducible factor has important role in providing a physiological response to a reduction in the level of oxygen tissue by promoting the expression of specific genes. This HIF-PH pathway inhibitor is a novel treatment that could serve as an alternative for CKD patients unable to receive ESAs or hyporesponsive to ESA therapy due to elevated hepcidin levels.

CONFLICT OF INTEREST

We declare that there were no conflicts of interest in this study.

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AUTHOR CONTRIBUTIONS

All of authors are equally contributed to the study.

REFERENCES


