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Pleotropic Effects of HIF-PHIs, Are There Clinical Relevant ?

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Anemia is a major complication of chronic kidney disease (CKD), which is mainly caused by the impaired ability of erythropoietin (EPO) production. Hypoxia-inducible factor (HIF) has been demonstrated to regulate gene expression of erythropoietin and this process is mediated by prolyl hydroxylase domain (PHD) proteins. PHD inhibition can stabilize HIF. Therefore, various PHD inhibitors have been developed for the treatment of renal anemia. Recent clinical trials have shown the promising EPO production under using of PHD inhibitors as well as non-inferior effect for anemia correction in patients with or without dialysis compared to erythropoietin stimulating agents (ESAs) or placebo. Moreover, HIF is induced by hypoxia and HIF stabilization increases gene transcription by binding to hypoxia response elements (HREs), thus upregulating EPO and other genes, which leads to EPO production and pleotropic effects.

These pleotropic effects include iron metabolism, metabolic change of glucose and lipid, fibrosis, inflammation, immune modulation, and cancer biology. Through these signaling pathways, several disease such as diabetic nephropathy, acute kidney injury, renal fibrosis, CKD progression, infection, and cancer development may be influenced by PHD inhibitors. In addition to the efficacy of PHD inhibitors, we also concern if there is any severe adverse effect such as cardiovascular risk or mortality would be induced by HIF-PHD pleotropic effect. Large size of patient number and longer study duration should be performed to evaluate these pleotropic effects.

Pleotropic effect of PHD inhibitors

Pleotropic effect	Current evidence of PHDi effect	Study model
Iron metabolism	Improve	Clinical
Glucose metabolism	Improve	In vivo
Lipid metabolism	Improve	Clinical
Renal fibrosis	Controversial	In vitro, in vivo
AKI	Protective	In vitro, in vivo
Inflammation	Induce	In vitro, in vivo
Cancer development	Controversial	In vitro, in vivo, clinical