Navigating Anemia Therapy in CKD With Hypoxia-Inducible Factor Activators: A Review

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The clinical challenges and safety concerns associated with the use of erythropoiesis-stimulating agents (ESAs) have provided the rationale for developing novel therapeutic approaches that address the complex pathophysiology of anemia in chronic kidney disease (CKD). Hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) are a new class of oral agents that effectively increase and maintain hemoglobin levels in patients with CKD. These agents stimulate the endogenous production of erythropoietin and enhance iron metabolism by activating hypoxia-inducible factors. Despite their efficacy, the use of some HIF-PHIs has been limited to patients on maintenance dialysis in some countries, including the United States, due to unresolved cardiovascular safety concerns in patients with CKD not on dialysis. In this review, we examine the mechanisms of action and erythropoietic effects of HIF-PHIs, evaluate undesirable on-target and off-target effects, and address cardiovascular and other safety concerns that have been raised in comparison to ESAs. We discuss how this novel class of oral anemia drugs may impact clinical practice, including their potential use in kidney transplant recipients.

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Rationale for Novel Anemia Therapies

Anemia is a common complication of chronic kidney disease (CKD) that profoundly affects a patient's well-being. Anemia in CKD results primarily from relative erythropoietin (EPO) deficiency, i.e., the inability to produce sufficient EPO to sustain normal erythropoiesis.[1] EPO is the principal glycoprotein required for red blood cell (RBC) production in the bone marrow, where it promotes the survival of erythroid progenitor cells.[2] The second major factor contributing to CKD-related anemia is absolute and/or functional iron deficiency, which limits the synthesis of heme, the essential component of hemoglobin that binds and transports oxygen.[3]

Before the introduction of hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) into clinical practice, anemia therapy in CKD consisted of oral or intravenous iron therapy and, after assurance of iron repletion, EPO replacement therapy administered intravenously or subcutaneously as recombinant human EPO or its glycosylated derivatives, collectively known as erythropoiesis-stimulating agents (ESAs).[4] The cardiovascular (CV) safety concerns associated with ESA use reinforced interest in therapies that address the broader pathophysiology of CKD-associated anemia.[3,5,6]

HIF-PHIs Mimic Physiological Responses to Hypoxia

HIF-PHIs are oral agents that activate hypoxia-inducible factors (HIFs), heterodimeric transcription factors that orchestrate cellular adaptation to hypoxias such as anemia-induced hypoxia. HIFs increase the expression of numerous genes, including those encoding EPO and proteins involved in iron transport and utilization such as transferrin (Fig 1). Under normoxic conditions, HIF-prolyl hydroxylase domain (PHD) dioxygenases (PHD1, PHD2, and PHD3) hydroxylate the oxygen-sensitive HIF-α subunits (HIF-1α, HIF-2α, and HIF-3α), marking them for proteasomal degradation.[7] When PHD activity is reduced by limited oxygen availability or pharmacologic inhibition, HIF-α subunits are less efficiently degraded, accumulate in the cell, and heterodimerize with HIF-β to form active transcription factors that activate gene transcription (Fig 1).[5]

From ESAs to HIF-PHIs: A Global Transition

HIF-PHIs are increasingly replacing ESAs in patients with dialysis-dependent (DD) and non-dialysis-dependent (NDD) CKD (Table 1), marking a worldwide shift in the management of CKD-related anemia.[8] ESAs require refrigeration, and their parenteral administration can pose logistical challenges in certain outpatient settings, but this important limitation does not apply to oral HIF-PHIs. Of the HIF-PHIs evaluated in global CV safety studies (Tables 2 and 3), daprodustat (GlaxoSmithKline) and vadadustat (Akebia Therapeutics) have received US Food and Drug Administration (FDA) approval in the United States but only for patients on maintenance dialysis.[9,10] Roxadustat was not approved for anemia due to CKD.[11] Following the market withdrawal of daprodustat, vadadustat remains the only HIF-PHI currently available to US patients with anemia due to CKD.

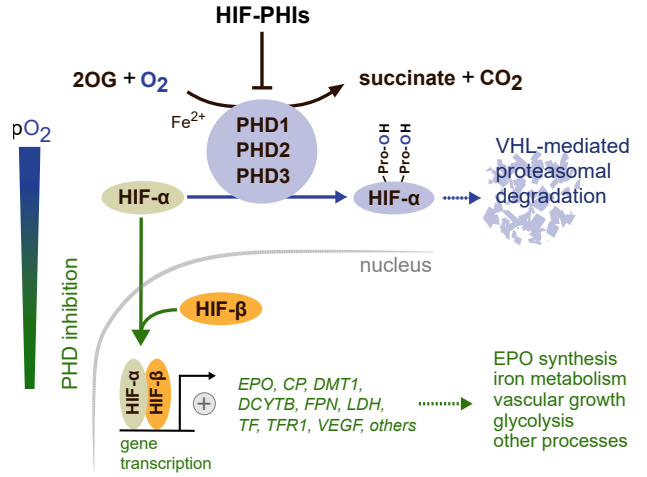

Figure 1. Reversible HIF activation by pharmacologic HIF-prolyl-hydroxylase inhibition. Schematic overview of HIF regulation. The oxygen-sensitive HIF-α subunit is continuously synthesized and rapidly degraded under normoxic conditions. Proteasomal degradation of HIF-α is initiated by PHD dioxygenases and mediated by the VHL-E3-ubiquitin ligase complex. PHD dioxygenases (PHD1, PHD2, and PHD3) use molecular oxygen and 2OG as substrates to hydroxylate the oxygen-sensitive HIF-α subunit at specific Pro residues, with PHD2 being the main regulator of HIF activity in most cells. Hypoxia or pharmacological PHD inhibition with HIF-prolyl hydroxylase inhibitors (HIF-PHIs) reduce PHD catalytic activity by competing with 2OG for binding the catalytic site. This impairs the degradation of HIF-α, resulting in its cellular accumulation and nuclear translocation. In the nucleus, HIF-α heterodimerizes with HIF-β, forming the active HIF transcription factor, which increases the expression of oxygen-regulated genes, including erythropoietin (*EPO*), ceruloplasmin (*CP*), divalent metal transporter 1 (*DMT1*), duodenal cytochrome b (*DCYTB*), ferroportin *(FPN)*, transferrin (*TF*), transferrin receptor 1 (*TRF1*), lactate dehydrogenase (*LDH*), vascular endothelial growth factor (*VEGF*) and others. Abbreviations: HIF, hypoxia-inducible factor; PHD, prolyl hydroxylase domain; Pro, proline; 2OG, 2-oxoglutarate; VHL, von Hippel-Lindau.

Hemoglobin Targets and Cardiovascular Safety

Hemoglobin targets for HIF-PHI therapy are informed by CV safety trials that have assessed whether normalization of hemoglobin with ESAs reduces anemia-related CV risks.[12,13] The trials demonstrated that targeting hemoglobin levels > 13 g/dL, compared with lower hemoglobin targets (9-11.5 g/dL), increased CV and cerebrovascular events, vascular access thrombosis, progression to end-stage kidney disease (ESKD), and all-cause mortality.[14-17] Based on these findings, the FDA issued a Black Box warning for ESAs that advised clinicians to administer the lowest effective dose to avoid RBC transfusions and not to raise hemoglobin levels above 11 g/dL.[18] The FDA issued identical recommendations for daprodustat and vadadustat, citing the same safety concerns.[9,10]

Regional guidelines recommend different hemoglobin targets. The European Renal Best Practice board of the European Renal Association (ERA) supports individualized hemoglobin targets of up to 12 g/dL, citing the absence of definitive evidence for harm below this threshold.[19,20] Likewise, the Japanese Society for Dialysis Therapy recommends upper hemoglobin limits of 13 g/dL for NDD-CKD patients and 12 g/dL for those receiving dialysis.[21] These region-specific practices are also reflected in the different hemoglobin targets chosen for US and non-US populations in global CV safety trials designed to establish noninferiority for HIF-PHI compared with ESAs (Tables 2 and 3). In line with FDA recommendations, KDIGO (Kidney Disease: Improving Global Outcomes) advises against intentionally exceeding hemoglobin values of 11.5 g/dL and recommends initiating ESA or HIF-PHI therapy when hemoglobin falls below 10 g/dL.[22]

Secondary analyses of ESA safety trials have revealed that patients receiving high doses of ESAs are at greater risk for death and serious CV and cerebrovascular complications, raising concerns that ESAs contribute to harm directly.[23,24] The supraphysiologic increase in serum EPO levels after parenteral ESA administration has been proposed as a potential mechanism for ESA-associated CV harm.[25] However, this explanation seems less likely because HIF-PHIs achieve target hemoglobin levels at substantially lower circulating EPO levels compared with ESAs[26] but have shown no improvement in CV outcomes.[27]

Clinical Implications of Pharmacologic HIF Activation

Because HIFs regulate a wide range of biological processes, systemic PHD inhibition can elicit nonerythropoietic on-target effects. These include reductions in total serum cholesterol, low- and high-density lipoprotein cholesterol, and triglycerides; these findings are consistently observed with both roxadustat and daprodustat.[5,6] HIF-regulated genes differ in their sensitivity to hypoxia and HIF stabilization; for example, *EPO* transcription is induced under milder hypoxic conditions than vascular endothelial growth factor (*VEGF*),[28] so higher doses of HIF-PHIs are more likely to activate additional HIF-responsive genes such as *VEGF*.[29,30] Moreover, because HIF-PHIs are competitive structural analogs of 2-oxoglutarate (2OG), they may interfere with the activity of other 2OG-dependent dioxygenases, potentially resulting in clinically relevant HIF-independent effects.[31-33] Some adverse effects may be agent-specific, such as roxadustat-associated suppression of thyroid function, which may be related to structural interactions between roxadustat and the thyroid hormone receptor.[34]

Given these considerations, we recommend initiating HIF-PHI therapy at the lowest effective dose to reduce the likelihood of adverse on- and off-target effects. Clinicians should also carefully review concurrent medications for potential drug interactions that could alter the bioavailability or pharmacokinetics of HIF-PHIs.[5]

Table 1. Overview of Approved Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitors

HIF-PHI	Recommended Starting Dose	Maximum Dose	Dosing Frequency	Examples of Countries With Approval for Marketing
Daprodustat	• ND-CKD: 2～4 mg (ESA naive), 4 mg (switch from ESA) • DD-CKD: [Japan] 4 mg, [US] 1～4 mg (ESA naive), 4-12 mg (switch from ESA)	24 mg	QD	• Approved for DD-CKD and NDD-CKD: Japan • Withdrawn in US (FDA-approved for DD-CKD) and the EU (was recommended for EMA approval)
Desidustat	• ND-CKD: 100 mg (ESA naive), 100, 125, or 150 mg (switch from ESA) • DD-CKD: 100 mg	150 mg	TIW	India
Enarodustat	• ND-CKD and DD-CKD-PD: 2 mg • DD-CKD: 4 mg	8 mg	QD	China, Japan, South Korea
Molidustat	• ND-CKD: 25 mg (ESA naive), 25～50 mg (switch from ESA) • DD-CKD: 75 mg	200 mg	QD	Japan
Roxadustat	• [EU] 70 mg for BW < 100 kg, 100 mg for BW ≥ 100 kg • [Japan] 50 mg (ESA naive), 70～100 mg (switch from ESA)	3.0 mg/kg BW	TIW	China, Chile, Egypt, EU, Iceland, Japan, Kuwait, Lichtenstein, Mexico, Norway, Russia, Saudi Arabia, South Africa, South Korea, Turkey, United Arab Emirates, UK
Vadadustat	300 mg	600 mg	QD	• Approved for DD-CKD: US, Australia, EU, South Korea, Taiwan, Switzerland • Approved for both DD-CKD and NDD-CKD: Japan

ESA naive is defined as no previous use of ESA. Abbreviations: BW, body weight; CKD, chronic kidney disease; DD, dialysis-dependent (maintenance); EMA, European Medicines Agency; ESA, erythropoiesis-stimulating agent; EU, European Union; ND, non-dialysis-dependent; QD, once daily; TIW, 3 times weekly.

HIF-PHIs in the Regulation of Erythropoiesis in CKD

Induction of Endogenous EPO

The primary sites of EPO production relevant to erythropoiesis are the kidney and liver, where its expression is regulated by hypoxia-inducible factor 2 (HIF-2).[35,36] In the kidney, EPO is synthesized by perivascular interstitial fibroblast-like cells, which respond to tissue hypoxia, such as in anemia, with the stabilization of the HIF-2α subunit (Fig 1). In patients with CKD, these cells are functionally impaired, leading to lower-than-expected EPO production for the degree of anemia.[37]

In the liver, EPO is produced by hepatocytes, which synthesize a more basic and less glycosylated version of EPO when hypoxia and/or anemia are severe.[36] In patients with ESKD, hepatocytes can produce >50% of circulating EPO.[38,39] However, hepatic EPO production cannot fully compensate for the loss of renal EPO in CKD, necessitating either ESA therapy or pharmacologic stimulation of endogenous EPO with HIF activators in most patients.

HIF-PHIs stimulate the production of endogenous EPO in both kidney and liver. Although the relative contributions of kidney- and liver-derived EPO to circulating EPO in HIF-PHI-treated patients has not been established, animal models and observations in anephric patients suggest that the contribution of hepatic EPO production may be substantial.[36,40,41] Furthermore, animal studies suggest that HIF-PHI-induced kidney EPO production is limited by interstitial fibrosis and the conversion of EPO-producing cells into myofibroblasts.[42] Thus, in patients with minimal kidney function, the effectiveness of HIF-PHIs may depend, at least in part, on their ability to stimulate EPO production in the liver.

Effects on Iron Metabolism and Erythrocyte Homeostasis

The second major factor in CKD-related anemia is iron deficiency, due to blood loss from repeated laboratory testing, retention in hemodialysis apparatuses, hemorrhage from gastrointestinal lesions, or functional impairment of iron uptake and mobilization. Iron deficiency is detected clinically by lower-than-normal serum ferritin, decreased serum iron, and increased serum transferrin measured as total iron binding capacity (TIBC).[3,43,44]

Clinical studies have shown that HIF-PHIs improve iron availability to the erythron. HIF activation increases duodenal iron absorption and iron mobilization from hepatocytes and macrophages by transcriptional up-regulation of iron metabolism genes (Fig 2). Furthermore, HIF-PHIs decrease serum hepcidin and increase serum iron and TIBC.[6] The hepatic 25-amino acid peptide hepcidin, which regulates intestinal iron absorption and mobilization from internal stores, reduces the surface expression of ferroportin, the only membrane iron exporter found on all cell types, by promoting its

internalization and degradation. Adequate ferroportin surface expression is required for efficient export of iron into the plasma from duodenal epithelial cells, reticuloendothelial cells, and hepatocytes (Fig 2).[45] The effects of HIF-PHIs on hepcidin are indirect and result from the stimulation of erythropoiesis in the bone marrow.

Both ESAs and HIF-HPIs decrease hepcidin during the expansion of erythroblast populations, through erythroblast production of erythroferrone, a hormone that suppresses hepcidin production in the liver (Fig 2).[45,46] However, compared to ESAs, HIF-PHIs have greater hepcidin suppression extending beyond the period of erythroblast proliferation, most likely from HIF-mediated increases in TIBC and decreases in transferrin saturation (TSAT), which can reduce liver hepcidin production.[47,48]

Compared with ESA therapy, the improved iron availability with HIF-HPI is associated with increased RBC mean corpuscular volume and mean corpuscular hemoglobin but decreased RBC distribution width, indicating production of a more uniform population of larger RBCs, each containing more hemoglobin.[49] This HIF-PHI effect may be a therapeutic advantage over escalating ESA dosing and/or intravenous iron.[49,50] Because of iron's crucial role for erythropoiesis, it is recommended to initiate HIF-PHI therapy only in patients who are iron-replete.[22]

Although intravenous iron use was not a primary end point and the studies were not adequately controlled, data from global trials have indicated that patients on HIF-PHIs may require less intravenous iron supplementation over time.[3,6] Other reported effects of HIF-PHIs include early release of marrow reticulocytes and lengthening of RBC life span.[49,51] Microvascular effects including angiogenesis in the marrow are likely related to early reticulocyte release,[52,53] but HIF effects on more widespread microvessels may be responsible for lengthening RBC life span.[54]

HIF-PHIs in ESA Hyporesponsiveness

ESA hyporesponsiveness, defined as failure to achieve target hemoglobin levels despite substantial ESA dose escalation,[4,19] is often transient and more common in dialysis patients.[55-60] It is associated with increased risks for CV events, ESKD, and death.[56,57,59,61-65] The most common cause and strongest predictor of ESA hyporesponsiveness is inflammation.[66] Inflammatory cytokines suppress erythropoiesis by impairing EPO production and

Table 2. Overview of Global Phase 3 Trials in Non-Dialysis-Dependent CKD

Study, Location, Sponsor	Study Design; No. of Patients, Randomization	Treatment, Starting Dose,[a] Study Duration	Hb Targets
Daprodustat (GlaxoSmithKline)			
ASCEND-ND[75] (NCT02876835); global	R, OL, AC; ESA naive and ESA treated; n = 3,872, 1:1	DAPRO 1-4 mg QD[b] for ESA naive and 1-24 mg QD[c] for ESA users vs DARBE, 148 wk	Hb target:10-11 g/dL
Roxadustat (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)			
ALPS[115] (NCT01887600); Europe; Astellas	R, DB, PC; ESA naive; n = 594, 2:1	ROXA 70 or 100 mg TIW[d] vs PBO, 104 wk	Hb target: 10-12 g/dL
ANDES[116] (NCT01750190); global (no European sites); FibroGen	R, DB, PC; ESA naive; n = 922, 2:1	ROXA 70 or 100 mg TIW[d] vs PBO, 52 wk	Hb target: 10-12 g/dL
OLYMPUS[117] (NCT02174627); global; AstraZeneca	R, DB, PC; ESA naive; n = 2781, 1:1	ROXA 70 mg TIW vs PBO, 164 wk	Hb target: 10-12 g/dL
DOLOMITES[118] (NCT02021318); Europe; Astellas	R, OL, AC; ESA naive; n = 616, 1:1	ROXA 70 or 100 mg TIW[d] vs DARBE, 104 wk	Hb target: 10-12 g/dL
Vadadustat (Akebia Therapeutics; Otsuka Pharmaceuticals)			
PRO2TECT[119] (NCT02648347); global	R, OL, AC; ESA naive; n = 1,751, 1:1	VADA 300 mg QD, then adjusted to 150, 450, or 600 mg QD vs DARBE,168 wk	Hb target ranges: US, 10-11 g/dL; non-US, 10-12 g/dL
PRO2TECT[119] (NCT02680574); global	R, OL, AC; ESA treated; n = 1,725, 1:1	VADA 300 mg QD, then adjusted to 150, 450, or 600 mg QD vs DARBE, 168 wk	Hb target range: US, 10-11 g/dL; non-US, 10-12 g/dL

Based on information in Haase.[5] Funding sources are indicated with drug name or with individual studies. ESA naive is defined as no use of ESA for a study-defined period before start of study. Abbreviations: AC, active-controlled; CKD, chronic kidney disease; DAPRO, daprodustat; DB, double-blind; DARBE, darbepoetin alfa; EBP, epoetin beta pegol; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; maintenance; NC, noncomparative; NR, not reported; OL, open label; PBO, placebo; PC, placebo controlled; QD, once daily; R, randomized; ROXA, roxadustat; TIW, 3 times weekly; VADA, vadadustat.

[a]Starting dose, then titrated to maintain target Hb levels (right column).

[b]Starting dose based on baseline Hb level.

[c]Starting dose based on prior ESA dose.

[d]Weight-based dosing: 70 mg for weight of 45 to <70 kg; 100 mg for ≥70 kg.

Table 3. Overview of Global Phase 3 Trials in Dialysis-Dependent CKD

Study, Location, Sponsor	Study Design; No. of Patients; Randomization	Treatment: Starting Dose[a] and Study Duration	Hb Targets
Daprodustat (GlaxoSmithKline)			
ASCEND-ID[120] (NCT03029208); global	R, OL, AC; ESA naive and ESA treated (limited exposure <6 wk), I-DD; n = 312, 1:1	DAPRO 1-4 mg QD[b] vs DARBE, 52 wk	Hb target: 10-11 g/dL
ASCEND-D[70] (NCT02879305); global	R, OL, AC; ESA-treated, M-DD; n = 2,964, 1:1	DAPRO 4-12 mg QD[c] vs ESA (epoetin alfa for HD, DARBE for PD, 52 wk	Hb target: 10-11 g/dL
Roxadustat (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)			
HIMALAYAS[121] (NCT02052310); global, FibroGen	R, OL, AC, ESA naive and ESA limited use (≤3 wk), I-DD; n = 1,043, 1:1	ROXA 70-100 mg TIW[d,e] vs epoetin alfa, 52 wk	Hb target: 10-12 g/dL
PYRENEES[122] (NCT02278341); Europe; Astellas	R, OL, AC, ESA treated, M-DD; n = 838 (836 treated), 1:1	ROXA 100-200 mg TIW[c] vs ESA (epoetin alfa or DARBE), 52-104 wk	Hb target: 10-12 g/dL
ROCKIES[123] (NCT02174731); global; AstraZeneca	R, OL, AC; ESA naive and ESA treated, M-DD and I-DD (n = 416); n = 2,133, 1:1	ROXA 70-200 mg TIW[c,e] for ESA treated and 70 or 100 mg TIW[d] for ESA naive vs epoetin alfa, 52-164 wk	Hb target: 10-12 g/dL
SIERRAS[68] (NCT02273726); US; FibroGen	R, OL, AC; ESA treated, M-DD and I-DD (n = 71); total n = 741, 1:1	ROXA 70-200 mg TIW[c,e] vs epoetin alfa, 52 wk	Hb target: 10-12 g/dL
Vadadustat (Akebia Therapeutics; Otsuka Pharmaceuticals)			
INNO2VATE[78] (NCT02865850); global	R, DB, AC; ESA naive and ESA treated; I-DD; n = 369, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg vs DARBE, 116 wk	Hb target ranges: US, 10-11 g/dL; non-US, 10-12 g/dL
INNO2VATE[78] (NCT02892149); global	R, DB, AC; ESA naive and ESA treated; M-DD; n = 3,554, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg vs DARBE, 116 wk	Hb target ranges: US, 10-11 g/dL; non-US, 10-12 g/dL

Based on information in Haase.[5] Funding sources are indicated with drug name or with individual studies. ESA naive is defined as no use of ESA for a study-defined period before start of study. Abbreviations: AC, active-controlled; CKD, chronic kidney disease; DAPRO, daprodustat; DB, double blind; DARBE, darbepoetin alfa; ESA, erythropoietin-stimulating agent; Hb, hemoglobin; I-DD, incident dialysis (hemodialysis and peritoneal dialysis); M-DD, maintenance/stable dialysis (hemodialysis and peritoneal dialysis); OL, open-label; QD, once daily; QW, once weekly; R, randomized, ROXA, roxadustat; TIW, 3 times weekly; VADA, vadadustat.
[a]Starting dose, then titrated to maintain target Hb levels (right column).
[b]Depending on study, starting dose is based on either recent Hb measurements or weight or both.
[c]Initial dose according to prior ESA dose.
[d]Dosed at 70 mg for weight of 45 to 70 kg; 100 mg for weight of >70-160.
[e]Titrated to achieve a Hb level of 11 g/dL and to maintain Hb levels of 10-12 g/dL.

receptor signaling, erythroid progenitor differentiation, and iron utilization.[67]

Although animal studies suggest HIF-PHIs may be more effective than ESAs under inflammatory conditions,[5] the clinical data are less compelling. Whereas studies with roxadustat indicate that patients with inflammation may achieve hemoglobin maintenance with less dose escalation,[68] post hoc analyses of daprodustat and vadadustat did not show greater efficacy than ESAs in patients with high C-reactive protein.[69-71] In a small prospective study, 15 of 32 dialysis patients with ESA hyporesponsiveness responded to roxadustat; the nonresponders had the highest inflammation markers, suggesting reduced efficacy with more severe inflammation.[72]

Because ESA hyporesponsiveness is often transient, clinical studies remain challenging. Nonetheless, randomized trials are necessary to establish whether HIF-PHIs provide a clinical benefit in this setting. In the absence of such data, we believe that HIF-PHI therapy should be considered as an alternative to ESAs in patients with inadequate hemoglobin response if treatable causes cannot be identified. However, the decision to initiate HIF-PHI therapy should be based on an individualized assessment of potential risks and benefits, and the dosing should not exceed the recommended upper dose limits. In cases where ESA hyporesponsiveness is driven by intrinsic hematologic disorders, such as hemoglobinopathies or bone marrow-based malignancies, desirable responses to HIF-PHI therapy are less likely.

Clinical Risk Profile of HIF-PHIs

Cardiovascular Risk Profile

The association between high-dose ESA therapy and increased CV risk led to the notion that HIF-PHIs might provide safety advantages due to their ability to achieve hemoglobin targets with lower circulating EPO levels.[73] Furthermore, a substantial number of preclinical studies in animals supported the notion of cytoprotective effects and possible CV benefit.[5] However, none of the global safety

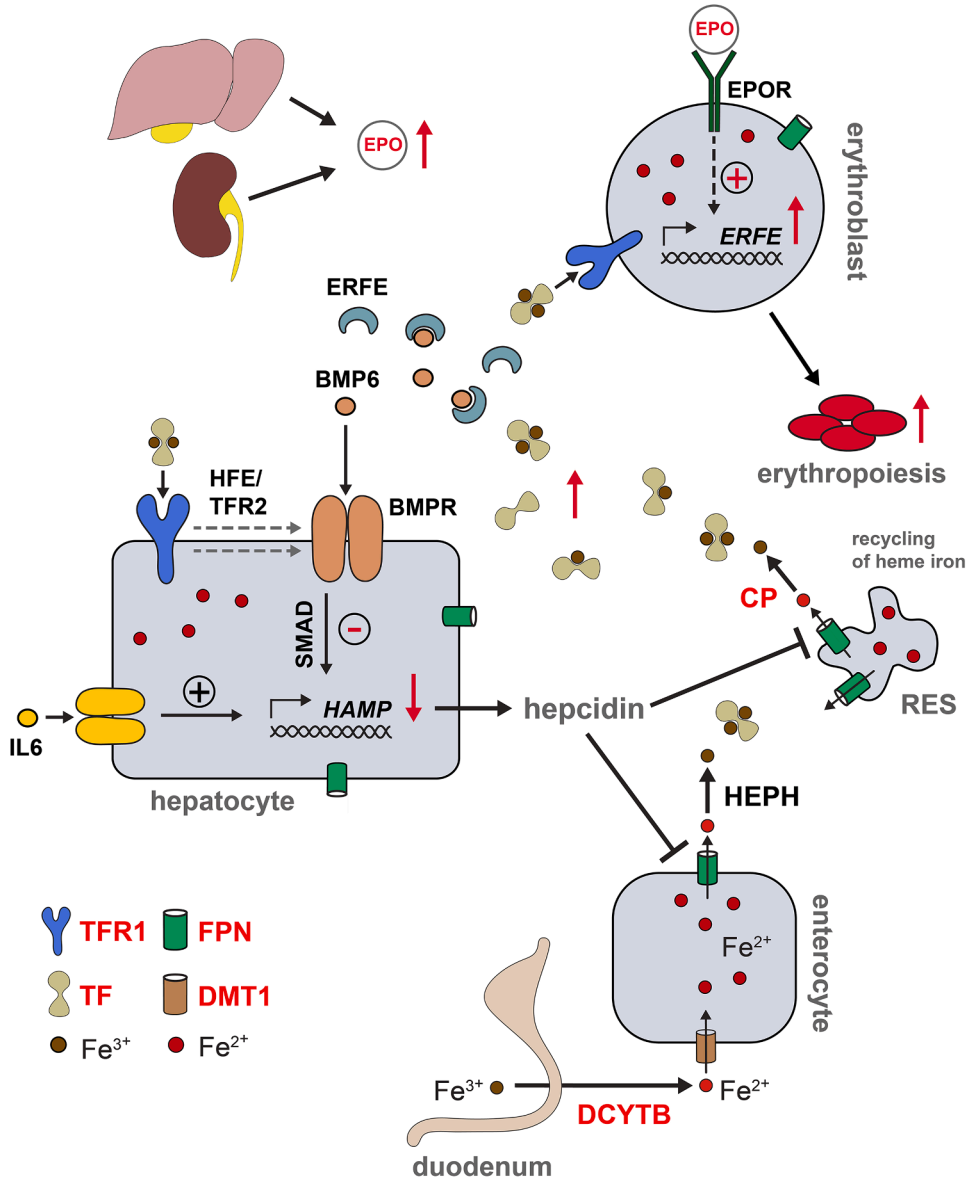

Figure 2. HIF-dependent coordination of erythropoiesis. Schematic illustrating the relationships between HIF signaling, EPO synthesis, and systemic iron homeostasis. HIF-PHIs stabilize HIF-α, resulting in increased transcription of genes involved in erythropoiesis and iron metabolism. HIF-regulated genes are highlighted by red font, and HIF-PHI effects are indicated by red arrows and red plus or minus signs. HIF-PHIs stimulate endogenous EPO production in the kidney and liver. EPO binds to its receptor (EPOR) on erythroblasts, promoting erythroid survival and proliferation by preventing apoptosis. In response to increased erythropoietic activity, erythroid precursors secrete erythroferrone, which suppresses hepcidin production by sequestering BMP6. BMP6, produced by liver endothelial cells, normally promotes transcription of *HAMP*, the gene encoding hepcidin, via activation of the SMAD pathway. In the duodenum, DCYTB reduces ferric iron (Fe^{3+}) to its ferrous form (Fe^{2+}), which is then transported into the cytosol of enterocytes by DMT-1. DCYTB and DMT1 are primarily regulated by HIF-2.[124,125] Absorbed Fe^{2+} is exported into the circulation via FPN, the only known cellular iron exporter. FPN surface expression is suppressed by hepcidin, and its transcription is HIF-2-regulated.[126] Exported Fe^{2+} is oxidized to Fe^{3+} by HEPH or by plasma CP in the case of hepatocytes and RES cells. Fe^{3+} then complexes with *TF* for systemic delivery. *TF*, a HIF-regulated gene, is consistently increased in patients receiving HIF-PHIs, resulting in increased TIBC.[5] Circulating TF-Fe^{3+} complexes are internalized via cell surface transferrin receptors. TFR1 is a transcriptional target of HIF-1 and most likely co-regulated by HIF-2.[127] In CKD anemia, plasma hepcidin is increased at baseline due to diminished renal clearance and presence of proinflammatory cytokines such as IL6, a very potent inducer of hepcidin.[45,46] Furthermore, inflammation suppresses erythropoiesis by inhibiting erythroid progenitor cells in the bone marrow,[128-132] and EPO production in the kidney,[133] contributing to anemia in CKD. Iron overload from intravenous administration can induce hepcidin by a complex interaction (indicated by dashed arrows) involving TF-bound iron, TFR1, TFR2, the homeostatic iron regulator protein HFE, hemojuvelin, BMP2 and BMP6, and their respective receptor complexes.[45,46] TFR2 participates in iron sensing and regulates hepcidin production in an iron-dependent manner through its interaction with HFE and the BMPR/hemojuvelin signaling complex. Under high-iron conditions, iron-bound

studies (Tables 2 and 3) demonstrated that HIF-PHIs were superior to ESAs.[6] Prespecified noninferiority for major adverse CV events (MACE) was met in DD patients for roxadustat (pooled analysis), daprodustat and vadadustat.[6] In contrast, noninferiority was not consistently met in patients with NDD-CKD in primary or secondary analyses.[6] The reasons for these results remain unclear but likely include geographic differences in practice patterns, standard of care, access to health care, hemoglobin targets, and differences in how safety analyses were conducted. For example, relative MACE risk for vadadustat in the US population was comparable to ESA but higher outside the United States.[74] In the safety analysis for daprodustat, MACE risk in the secondary on-treatment analysis in NDD-CKD was dependent on whether adjustments were made for the differences in dosing intervals between the short-acting daily administered HIF-PHI and long-acting darbepoetin-alfa.[75]

Due to these unresolved concerns for CV safety and the need for further postmarketing studies, current KDIGO guidelines do not recommend HIF-PHIs as first-line agents; instead, they favor an individualized approach[22] because patients, after a review of the risks and benefits, may decide to choose an oral over a parenteral agent for the treatment of their anemia. While advising caution regarding unresolved safety concerns, less conservative recommendations for HIF-PHI use are made by the UK Kidney Association,[43] the ERA,[76] and the Asian Pacific Society of Nephrology.[77]

Like ESAs, some HIF-PHIs have been associated with serious thrombotic events. Roxadustat has shown a higher risk of thrombosis compared with ESAs or placebo.[5,6] In the FDA safety analysis, this was attributed in part to relatively high starting doses, which led to a rapid rise in hemoglobin and overshooting of target range.[11] With vadadustat, thromboembolic events (excluding access failure) occurred in 1.2% of patients versus 1.4% with darbepoetin, and arteriovenous fistula thrombosis in 5.7% versus 4.5%, respectively.[78] Further studies are needed to clarify these risks and understand underlying mechanisms.

Cancer Risk

Pharmacologic HIF activation by HIF-PHIs could theoretically promote tumor formation, growth, or metastasis. These concerns stem from the observation that hypoxia is a common and salient feature of the tumor microenvironment, leading to activation of HIF in tumor cells, the degree of which correlates with disease progression and poor prognosis. Tumor cells co-opt HIF-regulated processes, such as angiogenesis and anaerobic metabolism, to support growth and survival under hypoxic conditions.[79,80] Therapeutic targeting of the HIF pathway can therefore be beneficial in certain oncologic contexts. For example, belzutifan, a selective HIF-2 inhibitor that blocks the dimerization of HIF-2α with HIF-β, was recently approved for the treatment of advanced clear cell renal cell carcinoma (CCRCC). CCRCC is characterized by constitutively high expression levels of HIF-2α, which has been shown to promote its growth in animal models.[81,82] Other tumors associated with dysregulated HIF oxygen sensing include neuroendocrine neoplasms such as pheochromocytomas, duodenal somatostatinomas, and paragangliomas, which carry variants in either *HIF2A* or *PHD2*. A relatively high and constitutive expression of HIF-2α appears to be required for the development of these tumors.[83,84]

Given current clinical trial results and insights from experimental studies, HIF-PHIs are unlikely to be oncogenic. HIF-PHIs result in transient and low-level HIF activation in nontransformed cells, which appears insufficient to drive tumorigenesis. In Chuvash polycythemia, which is due to germline variants in the von Hippel-Lindau (*VHL*) gene and characterized by low level levels of systemic HIF activation, patients exhibit increased erythropoiesis and thrombotic complications but not elevated cancer risk.[85] Animal studies have provided no evidence that prolonged exposure to HIF-PHIs is oncogenic,[86-88] and global phase 3 trials have not detected a significant cancer signal. One exception was the ASCEND-ND trial in nondialysis patients, where cancer-related events were slightly more common in the daprodustat group compared with darbepoetin alfa (3.7% vs 2.5%; relative risk, 1.47 [95% CI, 1.03-2.10]).[75] However, this difference became

transferrin releases HFE from complex with TFR1. The TFR2/HFE interaction potentiates SMAD-dependent signal transduction and stimulates hepcidin production. Hepcidin binds to FPN, inducing its internalization and degradation. This limits iron absorption from the duodenum, iron recycling from macrophages (which process ~1% of senescent RBCs daily), and iron release from hepatocytes, resulting in decreased iron availability for erythropoiesis.[45,46] This decreased iron availability does not cause microcytosis because hepcidin suppresses erythroblast FPN expression, thereby preserving iron and heme in erythroblasts.[134,135] In contrast, absolute iron deficiency is characterized by reduced erythroblast iron and heme content. Inflammation-associated iron deficiency in CKD-related anemia is characterized by elevated serum ferritin, decreased serum iron and TIBC, and reduced hemoglobin density, as indicated by low mean corpuscular hemoglobin concentration.[136] Abbreviations: BMP6, bone morphogenetic protein 6; BMPR, bone morphogenetic protein receptor; CP, ceruloplasmin; DCYTB, duodenal cytochrome b; DMT-1, divalent metal transporter 1; EPO, erythropoietin; EPOR, erythropoietin receptor; ERFE, erythroferrone; FPN, ferroportin; *HAMP*, hepcidin antimicrobial peptide; HEPH, enterocyte hephaestin; HFE, homeostatic iron regulator (High FE); HIF, hypoxia-inducible factor; HIF-PHIs, HIF-prolyl hydroxylase inhibitors; IL6, interleukin-6; RBCs, red blood cells; RES, reticuloendothelial; SMAD, suppressor of mothers against decapentaplegic; TIBC, total iron-binding capacity; *TF*, transferrin; TFR, transferrin receptor.

attenuated with post hoc adjustment for differences in dosing frequency and pharmacokinetics between daprodustat and darbepoetin alfa.[75] Notwithstanding these findings, longer drug exposure and extended follow-up of patients treated with HIF-PHIs are necessary for a more definitive assessment of cancer risk.

Safety Concerns in Special CKD Subpopulations

The safety and efficacy of HIF-PHIs have not been adequately studied in several CKD subpopulations. In patients with polycystic kidney disease (PKD), activation of the HIF pathway has been shown to promote cyst expansion in animal models.[89] Although it is unknown whether HIF-PHIs accelerate cyst growth in humans, the absence of long-term safety data supports avoiding their use in PKD patients.[90] Children and pregnant or breastfeeding women also represent populations for whom clinical trial data are lacking.[5,6] Similarly, caution is advised in patients with pulmonary hypertension or diabetic retinopathy. Sustained HIF activation has been linked to pulmonary hypertension in both animal and human genetic studies.[91] Likewise, proliferative retinal diseases such as diabetic retinopathy and age-related macular degeneration are associated with increased HIF and VEGF activity.[92,93] Although phase 2 and 3 trials did not report increases in serum VEGF or worsening of retinopathy, localized HIF-VEGF signaling could potentially promote retinal disease progression.[5,6]

In summary, while oral HIF-PHIs offer therapeutic benefits for most patients with CKD, their use in specific subpopulations may increase the risk of harm. Until more robust safety data are available, caution or avoidance is warranted in these groups.[5,27] Table 4 summarizes some of the risk benefit considerations related to HIF-PHI use.

Expanding the Use of HIF-PHIs: Considerations in Posttransplant Anemia

Posttransplant anemia (PTA) is a common and understudied complication affecting 20% to 51% of kidney transplant recipients (KTR).[94] Based on time of onset, patients can be classified into those with early (<6 months after transplant) and those with late PTA.[95] In most cases, PTA results from reduced EPO production and/or iron deficiency.[96,97] Other factors, some of which are unique to KTR, contribute to lower hemoglobin, including perioperative blood loss, acute rejection, infections, and immunosuppressive therapy.[98] Serum EPO levels exhibit a biphasic peak pattern following transplant surgery, with an initial peak within the first few days followed by a second peak between weeks 2 to 4. This pattern is influenced by factors such as delayed graft function and immunosuppressive therapy.[99] However, variability in endogenous EPO production has also been demonstrated in normal allograft function, for reasons that remain unclear.[100] Early PTA typically resolves without therapeutic intervention within several months after successful kidney transplantation.[99,101] Persistent anemia is frequently associated with decreased allograft function, which delays the restoration of endogenous EPO production in the posttransplant period.[101] In addition, chronic inflammation with impaired EPO response and bone marrow suppression caused by immunosuppressive therapy contribute to a slower rate of RBC production.[98] Parvovirus B19 is a less frequent cause of PTA and should be ruled out in refractory anemia.[102]

The correction of anemia is a crucial aspect of posttransplant care. The primary goals of PTA management are to avoid blood transfusions, alleviate symptoms, and support allograft recovery, with the potential benefit of improving transplant function and quality of life.[103] Blood transfusions are associated with the development of donor-specific antibodies and increase the risk of antibody-mediated rejection.[104] They are to be avoided in PTA unless in an emergency.

The consensus for PTA management has been largely adapted from data in nontransplant CKD. Current strategies emphasize the use of iron and ESAs to facilitate anemia correction, reduce blood transfusions, and potentially

Table 4. Summary of Risk and Benefit Considerations for Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitors Use in Patients With CKD

Advantages and Potential Benefits	Potential Disadvantages and Theoretical Risks
Oral agent: beneficial for patients on HD or PD and patients with NDD-CKD (not approved in the US and several other countries)	Possible increase in CV risk; lack of noninferiority compared to ESAs in NDD-CKD in CV safety trials (depending on type of analysis and geographical region)
Beneficial effects on iron metabolism (absorption and utilization)	Potential drug-drug interactions due to polypharmacy and increased pill burden with potential for overdosing or underdosing, narrow therapeutic window
No cold storage needed	Compliance monitoring may be more difficult
Potential benefit in patients with ESA hyporesponsiveness not clear and needs further study	Nondesirable on- and off-target effects and compound-specific effects; theoretical risk of promoting malignancy or kidney cyst growth, proliferative retinopathy and pulmonary arterial hypertension
Potential cytoprotective effects (predicted from preclinical models)	Lack of studies on use in children and kidney transplant patients

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; ESAs, erythropoiesis-stimulating agents; HD, hemodialysis; NDD, non-dialysis-dependent; PD, peritoneal dialysis.

accelerate recovery of allograft function and improve CV outcomes, although the associations between PTA and CV outcomes are less clear.[105-107] For the management of PTA, the KDIGO guidelines recommend applying the same principles and therapeutic goals used in nontransplant CKD patients with the exception of HIF-PHIs, which are currently not recommended for KTR.[22]

HIF-PHIs have not been adequately studied in PTA because KTR were excluded from clinical safety trials. Although a rigorous re-evaluation will be required to establish the efficacy and safety of HIF-PHIs in KTR, some limited insights have emerged from postmarketing analyses in Asia, mostly in patients with late PTA. In a randomized placebo-controlled study of Chinese KTR, roxadustat was found to increase hemoglobin without major adverse events such as allograft dysfunction or rejection.[108] Several smaller studies and case series, including one report with daprodustat from Japan, showed similar results.[109-111] Nevertheless, robust data regarding CV safety and cancer risk in KTR are not available. Additional caution is warranted due to the metabolic profile of HIF-PHIs, which are processed by cytochrome P450 enzymes or uridine 5′-diphospho-glucuronosyltransferases,[5] raising concerns about potential drug interactions with commonly used immunosuppressive agents such as calcineurin inhibitors and mycophenolic acid.

Preclinical studies in animal models suggest that donor pretreatment with HIF-PHIs may reduce allograft injury and improve graft survival.[112] This observation aligns with findings from human kidney transplant biopsies, where higher postengraftment HIF-1α expression was associated with better allograft function compared with low expression.[113,114] Even though these potential cytoprotective effects remain speculative, they provide a rationale for further clinical studies.

Summary and Future Directions

HIF-PHIs are oral medications that effectively treat anemia in CKD by stimulating endogenous EPO production and facilitating iron transport and utilization. Due to CV safety concerns, approval of some agents is currently limited to patients on maintenance dialysis in the United States and other countries. Therapy initiation should be guided by careful patient selection and individualized risk-benefit assessment. Given the relatively narrow therapeutic window of HIF-PHIs, use of the lowest effective dose is essential to minimize adverse on- and off-target effects. Long-term safety should be evaluated through postmarketing surveillance efforts. Whether HIF-PHIs are efficacious and safe in certain subpopulations of patients with CKD, including patients with kidney transplants, remains to be established.

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