Hypoxia-Inducible Factor Stabilization as an Emerging Therapy for CKD-Related Anemia: Report From a Scientific Workshop Sponsored by the National Kidney Foundation

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Abstract

The National Kidney Foundation convened an interdisciplinary international workshop in March 2019 to discuss the potential role of a new class of agents for the treatment of anemia in patients with chronic kidney disease (CKD): the hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs). International experts with expertise in physiology, biochemistry, structural chemistry, translational medicine and clinical management of anemia participated. Participants reviewed the unmet needs of current anemia treatment, the biology of hypoxia-inducible factor, the pharmacology of prolyl hydroxylase inhibitors, and the results of phase 2 clinical trials of HIF-PHIs among patients with both non-dialysis dependent and dialysis-dependent CKD. The results of key phase 3 clinical trials of HIF-PHIs in the public domain as of this writing are also presented in this article although they appeared after the workshop was completed. Participants in the workshop developed a number of recommendations for further examination of HIF-PHIs which are summarized in this article and include long-term safety issues, potential benefits, and practical considerations for implementation including patient and provider education.

Key words: anemia, chronic kidney disease, hypoxia inducible factor, erythropoiesis

Introduction

Anemia is a common complication of chronic kidney disease (CKD).[1] The treatment of CKD-associated anemia was revolutionized by the advent of recombinant human erythropoietin (EPO) more than 30 years ago and the subsequent development of EPO derivatives collectively termed erythropoiesis stimulating agents (ESAs). All ESAs require parenteral administration and concern about safety of ESAs arose when high doses were used to target hemoglobin (Hb) concentrations in the near normal range in large clinical trials.[2-4] The postulated mechanism for the association between higher Hb targets and adverse outcomes may involve off-target effects of administering ESA to supraphysiologic blood levels.[5]

Over the last 2 decades, significant progress has been made in identifying the role of hypoxia-induced gene expression, for which the EPO gene is paradigmatic, including discovery of a widespread cellular oxygen-sensing mechanism that operates through oxygen-dependent proteolysis of hypoxia-inducible transcription factors (HIF).[6-8] A critical step in this pathway consists of oxygen-dependent hydroxylation of two prolyl residues of the HIFα subunits, which requires 2-oxoglutarate as substrate. Small molecule 2-oxoglutarate analogues can serve as competitive inhibitors of HIF degradation and thus function as HIF-stabilizers. According to their molecular mechanism, these compounds are called prolyl hydroxylase (PH) inhibitors (PHIs).[9-11]

Several of these orally administered compounds are in development or have been approved outside the US as a new class of anti-anemic medication. Phase 3 programs with 6 PHIs are ongoing or have been completed, the results of some of which have been published.[12-20] As of this writing 4 of these agents (roxadustat, vadadustat, daprodustat and enarodustat) have been licensed in Japan; roxadustat is licensed in China and Chile. Properties of the three PHIs with development programs in the US are summarized in Table 1.

The National Kidney Foundation convened an interdisciplinary, international workshop March 22-23, 2019 in Philadelphia, PA to discuss the biological background, trial designs, and published evidence related to the potential use of HIF-PHIs, with the objective of developing recommendations on future research, education, and clinical implementation. International experts with expertise in physiology, biochemistry, structural chemistry, translational medicine and clinical management of anemia participated. This report

summarizes some of the presented data and the discussions which followed and provides updates to reflect the advancement of knowledge since the workshop.

Three scientists who spearheaded the discovery of the oxygen sensing pathway, William G. Kaelin, Gregg L. Semenza and Peter J. Ratcliffe, the latter two having participated in the workshop, were awarded the 2019 Nobel Prize in Physiology or Medicine [https://www.nobelprize.org/prizes/medicine/2019/summary/].

HIF Biology

Organisms must respond to decreases in oxygen availability and the HIF family is central to this response.[21-23] The HIF pathway operates in virtually all cells and controls the rate of transcription of hypoxia-responsive genes. The spectrum of responses to HIF pathway activity is focused on cell, tissue and organism survival and adaptation under hypoxic conditions, such as metabolic pathways which control the switch from aerobic to anaerobic metabolism, angiogenesis, ventilation, ATP production and erythropoiesis. The HIF pathway has also been shown to be involved in the inflammatory response, cell proliferation and cancer biology.[22, 24] Of major interest to the nephrology community is the central role of HIF-induced effects on the entirety of the erythropoietic process (Figure 1).

The peritubular interstitial cells located in the corticomedullary area of the kidneys are responsible for EPO production.[25, 26] Additional cells capable of producing EPO are perisinusoidal cells of the liver and, potentially, astroglial cells in the central nervous system.[27, 28] In the healthy adult, the peritubular renal EPO producing cells (REP) are the main source of circulating EPO. As chronic kidney disease progresses, a portion of circulating EPO appears to be of hepatic origin.[29, 30]

The location of a preponderance of REP cells in in a zone of the kidney with relative hypoxia[31] results in the sensing of small decreases in blood oxygen content, leading to increased transcription of the EPO gene and increased levels of circulating EPO. Although both HIF-1 and HIF-2 are present in the kidney, the controlling isoform of EPO production is HIF-2.

In addition to the impact of the HIF pathway on EPO production is the significant role of HIF activity in controlling iron homeostasis including iron absorption, transport, oxidation, and recycling. HIF-2 stimulates iron absorption in the duodenum by increasing iron transporting enzymes (divalent metal transporter, duodenal cytochrome B), and by indirect suppression of

hepcidin.[32] Hepcidin is the regulator of ferroportin, the sole membrane transporter of iron from enterocytes as well as storage cells such as macrophages.[33, 34] Ceruloplasmin, required for oxidation of ferrous to ferric iron, and transferrin are HIF-1 targets.[35] HIF activation leads to increased erythropoietin and transferrin receptor expression on erythroblasts, as well as increased survival/proliferation of erythroid progenitors in bone marrow erythroid tissue.[33]

Before this exquisite oxygen sensing mechanism was elucidated, it was shown that production of EPO was linked to proximal tubular sodium absorption, the process predominantly responsible for renal oxygen consumption.[36] This link between EPO production and kidney oxygen utilization may in part explain the apparent disordered oxygen sensing which results in the relatively deficient production of EPO in patients with CKD. As CKD progresses, decreased renal blood flow and anemia lead to diminished oxygen delivery. However, there is also a decrease in filtered sodium load leading to decreased sodium reabsorption and, in turn, decreased oxygen utilization. This creates a state of tissue "pseudonormoxia," with diminished production of EPO despite the presence of anemia.[10, 31] In addition, there is probably relative deficiency of REP cells available for EPO production as a consequence of parenchymal fibrosis.[28]

Nevertheless, the site of increased endogenous EPO consequent to pharmacologic manipulation by PHIs is at least to some extent the kidneys. A study utilizing an early version of PHI resulted in increased EPO production in hemodialysis patients who were anephric which was likely hepatic in origin.[37]

Results of HIF-PHI Clinical Studies

At the time of this writing, approximately 2 years following the Scientific Workshop, phase 3 global trials have been completed for roxadustat and vadadustat and are nearing completion for daprodustat. Efficacy and safety have been evaluated through comparisons with ESAs or placebo. The greatest safety focus is on cardiovascular events, resulting in large phase 3 programs powered to determine whether these drugs differ from ESAs with respect to cardiovascular safety.[2-4]

A phase 3 study from China of 305 dialysis dependent (DD) patients randomized 2:1 to roxadustat or epoetin alfa was published in 2019. During a 26-week treatment period roxadustat demonstrated noninferior efficacy to epoetin alfa. Adverse events were similar between the groups except for an increase in hyperkalemia with roxadustat.[18] In a phase 3 Chinese study of 154 CKD patients without kidney replacement therapy (KRT), roxadustat

was compared to placebo. Among patients randomized to roxadustat, there was an approximate 2 g/dL increase in Hb, significantly greater than placebo. Adverse events were similar between groups except for an increase in hyperkalemia and metabolic acidosis with roxadustat.[19] Hyperkalemia had been reported in earlier phase studies of HIF-PHIs.[38-40]

In the roxadustat global phase 3 program there were 8 studies involving over 9,000 patients. Three global phase 3 CKD without KRT studies were pooled to analyze efficacy and safety comparing roxadustat to placebo.[41] 4,270 patients were included, with mean baseline Hb 9.1 g/dL and eGFR 17.0 mL/min/1.73m^2. The mean exposure in the pooled roxadustat group was 1.62 years vs. 1.23 years in the pooled placebo group. Roxadustat produced an increase in Hb of 1.85±0.94 g/dL vs. 0.13±1.01 g/dL for the placebo group. There was a greater need for rescue therapy (ESA treatment, IV iron or transfusion) in the placebo group (reduced 81% with roxadustat) and a greater need for blood transfusion (reduced 74% with roxadustat). The increase in Hb with roxadustat was not affected by iron status.[41, 42]

The time to first major adverse cardiovascular event (MACE, defined as all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke) in the pooled phase 3 studies in patients without KRT was similar for roxadustat vs. placebo (HR, 1.10 [95% CI: 0.96, 1.27]), which met the definition for noninferiority. The overall rate of adverse events (AEs) was found to be similar between roxadustat- and placebo-treated patients (89.4% versus 85.4%). The rate of hyperkalemia was 10.9% vs. 7.1% with roxadustat compared to placebo. Follow-up adjusted incidence rate of serious AEs were also similar for roxadustat and placebo at 45.9 vs. 43.9 per 100 patient-years.[41, 42]

The efficacy and safety of roxadustat in DD-CKD patients was evaluated in three phase 3 pooled studies[41, 42] comparing roxadustat to epoetin. The mean treatment exposure in the roxadustat group was 1.71 years (up to 4.4 years) compared to 1.92 years in epoetin-treated patients. Among 3,880 patients, roxadustat was demonstrated to be noninferior to epoetin in change in Hb. The Hb increase was numerically greater among roxadustat-treated patients, but this may have reflected different dose adjustment protocols in the two groups. Blood transfusions occurred in 12.8% and 9.5% of the epoetin and roxadustat groups, respectively, P=0.046. There was an 11% reduction in intravenous iron treatment in the roxadustat arm, which may have reflected different iron treatment protocols between the groups.

In the pooled analysis of patients with DD-CKD, the time to first MACE was similar for roxadustat vs. epoetin (HR, 1.02 [95% CI: 0.88, 1.20]), which met the definition for noninferiority.[41, 42] In a prespecified subset analysis of 1,526 incident dialysis patients,

treatment with roxadustat was noninferior to epoetin in MACE (HR, 0.82 [95% CI: 0.60, 1.11])[42, 43]. The overall rate of adverse events (AEs) was similar between roxadustat- and epoetin-treated patients (at least one AE in 86.6% vs. 86.0%) in the pooled DD-CKD analysis. Hyperkalemia occurred in 7.1% of patients in both treatment groups. The arteriovenous fistula thrombosis incidence rate was 5.2 vs. 3.9 per 100/patient-years for roxadustat and epoetin, respectively. Deep vein thrombosis occurred in 24 roxadustat-treated patients compared to 7 epoetin-treated patients (0.7 vs. 0.2 per 100 patient-years). There was also a difference in the rate of seizures, occurring in 2.0% and 0.7% of roxadustat- and epoetin alfa-treated patients, respectively.[41]

In one of the CKD without KRT studies patients in the roxadustat group experienced 29.9% decrease in hepcidin compared to 4% decrease in the placebo group.[41] In the DD-CKD program, roxadustat led to a greater reduction in hepcidin than the comparator, epoetin. Among both CKD without KRT and DD-CKD patients, the increase in Hb was similar irrespective of C-reactive protein levels (an indicator of inflammation).[41] In the CKD without KRT pooled studies, roxadustat led to a 17.26 mg/dl decrease in LDL-cholesterol.[41]

The efficacy and safety of vadadustat in DD-CKD patients was evaluated in two studies, one in incident and one in prevalent patients totaling 3,923 subjects.[44] The mean change in Hb from baseline between vadadustat and darbepoetin was compared in two different evaluation periods. In the study in incident dialysis patients the mean differences (SEM) between groups were -0.31±0.11 g/dL (95% CI: -0.53, -0.10) and -0.07±0.13 g/dL (95% CI: -0.34, 0.19) in weeks 24-36 and weeks 40-52, respectively. In the study in prevalent dialysis patients the mean differences were -0.17±0.03 g/dL (95% CI: -0.23, -0.10) and -0.18±0.03 g/dL (95% CI: -0.25, -0.12) for vadadustat and darbepoetin, respectively.

Cardiovascular safety for vadadustat was evaluated by pooling the two DD-CKD studies, including 1,947 and 1,955 patients in the vadadustat and darbepoetin alfa groups, respectively.[44] A first MACE event occurred in 18.2% of patients in the vadadustat group and in 19.3% the darbepoetin alfa group (HR, 0.96; 95% CI: 0.83, 1.11), establishing noninferiority for vadadustat. Time to expanded MACE, (MACE plus hospitalization for heart failure or thromboembolic event, excluding vascular access failure) was similar between vadadustat and darbepoetin (HR, 0.96; 95% CI: 0.84, 1.10). There were no clinically meaningful differences between vadadustat and darbepoetin in the number of AEs and serious adverse events (SAEs).

Among CKD without KRT patients, vadadustat was compared to darbepoetin in two studies, one in ESA-naive patients (n=1751) with Hb <10 g/dL, and one in ESA-treated patients (n=1725) with Hb 8–11 g/dL in the US and 9–12 g/dL outside the US. In these studies vadadustat demonstrated noninferior efficacy compared to darbepoetin.[45] The mean change in Hb during the main evaluation period was 1.43 g/dL and 1.38 g/dL in the ESA-naive trial for vadadustat and darbepoetin, respectively. In the ESA-treated patients the mean Hb changes were 1.43 g/dL and 1.38 g/dL.

The primary safety endpoint in the CKD without KRT studies of vadadustat was MACE (time frame from baseline visit to end of study, event-driven, minimum 1 year).[45] A first pooled MACE event occurred in 22.0% in the vadadustat-treated group and 19.9% in the darbepoetin-treated group. The point estimate for the hazard ratio was 1.17, with a 95% confidence interval of 1.01 to 1.36. The upper bound to determine noninferiority was 1.25, so the MACE outcome with vadadustat did not meet the noninferiority definition. Although there was a numeric increase in each component of the composite outcome in the vadadustat-treated patients, the statistical and clinical significance appeared to be nominal. All the increase in MACE risk occurred among the non-US compared to the US study population, HR 1.29 vs. 1.01, respectively. The Hb entry criteria were somewhat higher ex-US and the Hb target during study was 10-12 g/dL ex-US compared to 10-11 g/dL in the US. The difference in safety outcomes between regions remains unexplained.

Daprodustat is the third HIF-PHI with a development program in the US moving through global phase 3 studies. In a phase 3 study conducted in Japan[15] 271 DD-CKD patients were randomized to either continuation with darbepoetin or conversion to daprodustat over 52 weeks. Hb response to daprodustat was demonstrated to be noninferior to darbepoetin. 32% of patients receiving daprodustat required IV iron during the treatment period compared to 43% with darbepoetin. The evaluation of safety was limited due to small sample size. At the time of this writing, 4 of 5 global phase 3 studies of daprodustat have been completed according to clinicaltrials.gov, but no results have been presented.

Recommendations for Future Research

Box 1 summarizes recommendations for future research, which are discussed in more detail in the following sections.

Further evaluation of potential adverse effects of HIF-PHI therapy

Although several large phase 3 programs are ongoing, published and ongoing phase 3 trials evaluate AEs in a relatively limited number of patients and over a relatively short treatment period (52-104 weeks). Phase 3 clinical trials have already or will provide sufficient evidence for some potential adverse effects associated with HIF-PHI therapy, such as:

- Evidence for MACE non-inferiority compared to ESA has been demonstrated in DD-CKD patients,[12, 15, 18, 41, 45] but questions remain in patients with CKD without KRT.[19, 45] Further evaluation of individual components of MACE may be required, as these consist of end points with different mechanism (e.g., ischemic vs. non-ischemic) that could be affected differently by HIF-PHIs.
- Thrombotic events are being evaluated in Phase 3 trials. The data generated thus far are reassuring.[12, 15, 18, 19]
- Lowering of total cholesterol, LDL and HDL has been shown in Phase 3 trials.[12, 15, 18, 19, 41] These effects could be perceived as potentially beneficial (total cholesterol and LDL) or harmful (HDL), but their clinical significance remains uncertain, as clinical trials of statin therapy have not been shown to effectively improve outcomes in dialysis patients[46, 47] and cholesterol levels show inverse (paradoxical) associations with outcomes in this population.[48]

However, some potential AEs cannot be sufficiently examined in phase 3 clinical trials, due to the longer exposure time needed for their occurrence or the need for specialized examinations. These will require future studies (e.g., phase 4 trials, registry data and/or meta-analyses).

- Malignancies are a concern, based on the putative mechanisms of action of HIF-PHIs (effects on cancer cell metabolism and VEGF stimulation) and data from genetic studies. Studies to date do not support this hypothesis,[49] but large, long-term studies focusing on these outcomes will be needed to reliably assess this potential with HIF-PHI therapy.
- Diabetic retinopathy: data available from some phase 3 trials[15, 50] is reassuring, but longer-term studies are needed.
- Pulmonary arterial hypertension (PAH) is common in patients on dialysis and theoretically may be aggravated by HIF-PHIs. Phase 3 trials may not offer sufficient certainty due to the high background frequency of the condition and the dedicated examinations needed for its evaluation. It is reassuring that the incidence of heart-failure related AEs and SAEs (which could be related to worsening PAH) was not significantly increased in phase 3 trials. [12, 15, 18, 19, 41]

- The risk of infections and inflammation is high in transplant recipients and dialysis patients and may be affected by HIF-PHIs based on their putative mechanisms of action.[51, 52] Data from mice with colitis suggest that inflammation may decrease with HIF-PHI therapy.[53] Results of available Phase 3 trials on the incidence of common infectious events is reassuring; [12, 15, 18, 19, 41] but more rare outcomes (such as the incidence of autoimmune disorders) may require larger studies with longer follow-up.
- Kidney fibrosis may be enhanced by the HIF pathway,[54] and hence clinical studies should examine the risk of HIF-PHI therapy on CKD progression. Experimental studies of HIF-PHIs did not suggest an increased risk of kidney fibrosis[55] and also showed beneficial effects on other organs (e.g. pulmonary fibrosis[56]) which should be studied in humans.
- HIF-PHIs may affect cyst growth and clinical progression of polycystic kidney disease (PKD), based on their putative mechanisms of action and studies in experimental animals.[57, 58] Some ongoing phase 3 trials include monitoring for cyst growth and should offer useful information. Dedicated studies in patients with PKD may be necessary.
- Hyperkalemia is an unexpected adverse effect of HIF-PHI therapy in phase 3 clinical trials.[18, 19, 41] The mechanism remains unexplained and requires further evaluation.

Further evaluation of potential benefits of HIF-PHI therapy

Currently available and soon-to-be-completed phase 3 trials have primarily examined the effects of HIF-PHIs on Hb concentration (efficacy) while also monitoring for the incidence of MACE and other events (safety). These trials were not of sufficient duration for the evaluation of long-term clinical events other than MACE, and their assessment of additional biochemical effects and effects in various subgroups of patients is exploratory in nature. Based on the mechanisms of action of HIF-PHIs, their application may result in several potential benefits which should be examined in future studies.

- Currently available data on the effects of HIF-PHIs in ESA-hyporesponsive patients is inconclusive.[17, 18, 59]
- HIF-PHIs may have beneficial effects on iron absorption and mobilization, which could complement their effects on EPO production. Currently available data from phase 2 and 3 clinical trials offer evidence of improved iron utilization in patients treated with HIF-PHIs.[12, 14, 15, 18, 38, 40, 41, 60-63] Going forward, current treatment paradigms for iron supplementation in dialysis patients may change.
- Because of the complex mechanisms of action of HIF-PHIs, it is possible that their impact on quality of life may dissociate from their effects on anemia therapy. Several Phase 3

clinical trials that have been completed or are in progress collect data on quality-of-life measures

- Experimental studies suggest that HIF-PHIs may be beneficial in alleviating hypoxic kidney injury.[64, 65] The effects of HIF-PHI therapy on the long-term progression of kidney disease in patients with CKD and on the incidence of AKI will require dedicated future studies.
- Experimental studies indicate the presence of preconditioning effects of HIF-PHIs under ischemic conditions,[66, 67] which could translate to clinical benefits such as lower coronary or cerebrovascular events. Currently available data from phase 3 trials do not support superiority with regards to MACE as compared to ESA and one trial failed to demonstrate non-inferiority with regards to MACE as compared to ESA in CKD without KRT patients.[45] However, these trials examined composite events that include both ischemic and non-ischemic components. Further analyses of data from multiple phase 3 trials to separate potentially divergent effects on ischemic events are recommended.
- While a biologic effect of HIF-PHI therapy on blood pressure may be present,[68] the magnitude and clinical relevance of such an effect remains unclear. The interpretation of such effects is made especially difficult by the complexity of blood pressure physiology and pathophysiology in hemodialysis patients and the uncertainty of the clinical benefits associated with antihypertensive therapies in this population. Nonetheless, the results of phase 3 studies to date have not shown any consistent effect of HIF-PHIs on blood pressure.
- EPO has insulin-sensitizing effects,[69] but the extent of anti-hyperglycemic effects and their clinical impact in patients treated with HIF-PHIs remains unclear. The clinical relevance of such putative effects is also clouded by the numerous uncertainties surrounding diabetes management in patients with ESKD.

Practical considerations for clinical implementation

There are many questions surrounding the implementation of HIF-PHI therapy that will not be answered by clinical trials, given their limited scope, study population and duration of treatment.

- Current trials have examined the efficacy and safety of HIF-PHIs under treatment paradigms established for ESA therapy. It remains unclear if the unique mechanisms of action of HIF-PHIs allow for the targeting of higher Hb concentrations. Conversely, higher doses of HIF-PHI needed to achieve higher Hb concentrations may result in a

higher rate of adverse effects specific to the HIF pathway (such as malignancies and effects on diabetic retinopathy).

- Because of the complex mechanisms of action of HIF-PHIs (which involve effects on iron metabolism and inflammation), it is conceivable they may be effective in combination with ESA therapy. The use of combination therapy may also allow lower doses of both agents, which could enhance safety. Without dedicated clinical trials the efficacy and safety of combination therapy can only be hypothesized, and its clinical application will likely be determined by other factors such as cost and individual patient characteristics.
- HIF-PHIs have complex mechanisms of action, which may result in differential efficacy and safety profiles based on certain clinical characteristics in treated patients. Potential effect modifiers include presence/absence of pre-existing cardiac disease, diabetes mellitus or inflammation, or the etiology of CKD (e.g., PKD, as discussed above). Phase 3 clinical trials will provide information on clinical efficacy in some subgroups, but safety profiles may require further examination (e.g., in patient-level meta-analyses or in registry studies).
- The novelty of the HIF-PHI class will require that healthcare providers and patients receive focused education about the class in general and about the individual drugs approved for clinical use. Cost considerations (relative to other options, such as iron supplementation or biosimilar ESAs) may hamper adoption. Uptake will be affected by how HIF-PHIs will be incorporated into hospitals'/dialysis facilities' formularies and treatment protocols.

Conclusions

Conference participants shared enthusiasm about a new treatment option for anemia through HIF stabilization that reflects the successful translation of recent basic science discovery into clinical practice. Participants recognized the potential of this novel pharmacological approach to improve patient well-being and prognosis beyond anemia correction. However, there was also agreement that this approach of inhibiting PH with 2-oxoglutarate analogues is not highly specific and may lead to induction of other HIF target genes as well as off-target effects mediated by other 2-oxoglutarate-dependent enzymes. There is a clear need for careful analyses of studies conducted so far and for a high level of vigilance as these agents enter the market. The spurred interest in anemia management through the availability of PHIs also provides an opportunity to redefine treatment goals, with less emphasis on Hb concentration and careful consideration of functional parameters, including patient-reported outcomes.

Since the ongoing study program on PHI use for management of renal anemia is one of the largest investigative programs in CKD management conducted so far, it offers huge opportunities to learn more about the course and outcomes of CKD beyond anemia treatment. Patient level meta-analyses should be encouraged to take full advantage of this promising data source.

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Figure 1: Hypoxia Inducible Factor Pathway

Abbreviations: HIF – hypoxia-inducible factor; PH – prolyl hydroxylase; EPO – erythropoietin; DMT1 – divalent metal transporter 1; DcytB – duodenal cytochrome B

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Table 1 Pharmacokinetic properties of Daprodustat, Roxadustat and Vadadustat

Compound	Effective daily oral doses in phase II trials	Dosing Schedule	Half-life	Plasma EPO (IU/L)	Metabolism
Daprodustat (GSK-12278863)	5-25 (also examined 50 and 100 mg)	QD	~1-7 hrs	24.7 and 34.4, 82.4	CYP2C8 with minor CYP3A4
Roxadustat (FG-4592, ASP1517)	0.7-2.5 mg/kg	TIW	12-15 hrs	113 and 397, 130	CYP2C8
Vadadustat (AKB-6548, *MT-6548*)	150–600 mg	QD (TIW)	4.7–9.1 hrs	32	n.r.

Abbreviations: CYP, cytochromeP450; DD-CKD, dialysis-dependent CKD; EPO, erythropoietin; HIF, hypoxia-inducible factor; IC50, half maximal inhibitory concentration; NDD-CKD, non-dialysis-dependent CKD; n.r., not reported/not published; PHD, prolyl hydroxylase domain; PHI, prolyl hydroxylase inhibitor; QD, once daily; TIW, thrice weekly

Box 1. Summary of Recommendations for Future Research

- Further evaluation of potential adverse effects of HIF-PHI therapy
    - Evidence examined in phase 3 clinical trials
        - Major adverse cardiovascular events
        - Thrombotic events
        - Effects on blood lipids and their consequences
    - Evidence not sufficiently examined in phase 3 clinical trials
        - Malignancies
        - Diabetic retinopathy
        - Pulmonary arterial hypertension
        - Infection risk
        - Kidney fibrosis
        - Cyst growth in polycystic kidney disease
        - Hyperkalemia
- Further evaluation of potential benefits of HIF-PHI therapy
    - Effects in ESA-hyporesponsive patients
    - Effects on iron metabolism
    - Effects on quality of life
    - Reduced rate of loss of kidney function
    - Protection against ischemic events
    - Lowering of blood pressure
    - Glucose tolerance
- Practical considerations for implementation of HIF-PHI into clinical practice
    - Potential normalization of hemoglobin concentration
    - Combination therapy with ESAs
    - Heterogeneity of treatment effects
    - Patient and provider education
    - Cost, formulary, and treatment protocol barriers
- Key recommendations for future studies
    - Patient-level meta-analyses to better define adverse effect profile
    - Patient-level meta-analyses to better define adverse therapeutic response phenotypes
    - Post-approval monitoring (registry) of rare adverse effects
    - Use of data from phase 3 clinical trials to inform design and focus of future clinical trials