Hypoxia-Inducible Factor-Proline Hydroxylase Inhibitor in the Treatment of Renal Anemia

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Keywords

Chronic kidney disease · Anemia · Hypoxia-inducible factor-proline hydroxylase inhibitor

Abstract

Background: Anemia is a common complication in CKD patients. Despite the use of iron and erythropoietin-stimulating agents, the control rate of anemia in CKD is not satisfying. Novel drugs are needed for anemia correction. **Summary:** HIF-PHI, hypoxia-inducible factor-proline hydroxylase inhibitor, a novel class of therapeutic agents, has been developed to treat anemia in CKD patients. Its main effects comprised boosting EPO production, enhancing iron utilization, and suppressing hepcidin production. Several stage 2 and stage 3 clinical trials have been run to test its efficacy and safety in both nondialysis and dialysis patients, of which the results are very encouraging. Here, we summarize the mechanism, clinical applications, and clinical trials of HIF-PHI in treating renal anemia in order to give an overview of the new drug in clinical practices. **Key Messages:** HIF-PHI is a novel therapeutic agent of treating renal anemia in CKD patients. It is quite effective in improving anemia, which is unaffected by inflammation. Besides, it may ameliorate lipid metabolism as

well. Furthermore, the oral form may improve patients' compliances with treatment. Thus, it may be a good alternative of anemia correction in CKD patients.

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Introduction

Chronic kidney disease (CKD) has grown to be a worldwide public health problem, affecting 10.8% patients in China. Anemia is a common complication in CKD patients, accounting for 18.50~22.20% in nondialysis CKD patients [1, 2] and 30~80% (DOPPS4 and CNRDS 2011 data) in dialysis patients. Previous studies showed that anemia was associated with mortality, quality of life, cognition deficiency, renal function progression, and cardiovascular events [3–7]. Thus, the European Renal Best Practice position statement [8] recommends that hemoglobin should be maintained around 11~12 g/dL in CKD patients. However, despite the use of iron and erythropoietin-stimulating agents (ESAs), the control rate of anemia in CKD patients is not satisfying, with only 63.1~90.7% meeting the goal, partly due to the

inflammation conditions in some patients [9]. Furthermore, the safety of ESAs remains a great concern in clinical practices. Several studies have shown that ESAs may provoke hypertension, thrombosis, cardiovascular events, and even death in CKD patients [10–13]. One of the reasons for these side effects was that ESA can bring non-physiological EPO level. Therefore, efforts should be taken in finding new drugs in treating renal anemia.

Anemia in CKD is mainly due to inadequate synthesis of erythropoietin, iron deficiency, inflammation, and reduced erythrocyte survival [14]. It is well recognized that HIF-2 α plays an important role in regulating the expression of the EPO gene in renal EPO-producing cells [15, 16]. Thus, the inhibition of the enzymes in the HIF-2 α -related pathway may boost EPO production, improving renal anemia. As a result, HIF-PHI, hypoxia-inducible factor-proline hydroxylase inhibitor, a novel class of therapeutic agents, has been developed to treat anemia in CKD patients. Several stage 2 and stage 3 clinical trials have been run to test its efficacy and safety in both non-dialysis and dialysis patients, of which the results are very encouraging. Here, we summarize the mechanism, clinical applications, and clinical trials of HIF-PHI in treating renal anemia in order to give an overview of the new drug in clinical practices.

Mechanism

HIF, first discovered in the 1950s, is an important intracellular modulator of hypoxia-induced reactions [17, 18]. It comprises 2 different subunits, α and β chains. α chains have 3 main forms, which are all oxygen sensitive, whereas the β chains are constitutively expressed [19, 20]. Previous studies [15, 16, 21, 22] show that HIF-2 α plays an important role in regulating erythropoiesis through 3 different mechanisms: EPO production, iron absorption, and hepcidin suppression. Once hypoxia triggers the activation of HIF-2 α , it facilitates the expression of EPO, increasing EPO production to stimulate erythropoiesis in bone marrow [23, 24]. Besides, HIF-2 α also enhances the enteral iron absorption by boosting production of divalent metal transporter 1 and duodenal cytochrome B, improving iron transportation from the intestinal lumen to the enterocytes [25, 26]. Furthermore, it inhibits the production of hepcidin which suppresses the iron uptake and mobilization [21, 27]. As a result, mature erythrocytes are produced for oxygen delivery to ameliorate the hypoxia in tissues. As soon as hypoxia is corrected, HIF-2 α is quickly hydroxylated by prolyl hy-

droxylase enzymes (PHD) and then degraded through ubiquitination by proteasomes, stopping the downstream reactions [28]. PHDs have 3 isoforms with PHD2 acting more on HIF1 α and PHD3 more on HIF2 α [29].

In CKD patients, there is a discrepancy between oxygen supply and demand in the kidneys, disturbing the hypoxia-induced signaling in renal EPO-producing cells [30]. Inhibition of PH will restore the HIF-2 α pathway and stimulate erythropoiesis in CKD patients, improving renal anemia. Thus, HIF-PHI has been developed and put into clinical trials to test its efficacy and safety in CKD patients.

Clinical Trials

The HIF-PHIs under investigation such as Roxadustat[®], Daprodustat[®], Molidustat[®], and Vadadustat[®] are currently in phase 3 studies and all proved to be quite effective in treating renal anemia in CKD patients. The main differences of the 4 drugs comprise their various activities against 3 HIF-PHDs and the diverse influence on iron and lipid metabolism. Here is a summary of the performances of 4 drugs in clinical trials (Table 1).

Roxadustat

Roxadustat is the first HIF-PHI developed by Fibrogen almost a decade ago. It inhibited all 3 HIF-PHIs equally. The first clinical trial was started in 2005. With its great efficacy in renal anemia correction, it has been approved by the National Medical Products Administration for renal anemia in China in 2019. Besides, the phase 3 clinical trials of Roxadustat in the treatment of anemia in Chinese CKD patients have just been released. There were 2 parallel clinical trials focused on anemia treatment by Roxadustat in NDD or DD patients, and both the trials were led by Prof Chen Nan from Shanghai Ruijin Hospital.

In NDD patients, one phase II Chinese study [31] conducted from 2011 to 2012 enrolled 91 CKD patients with eGFR 10~60 mL/min $\times$ 1.73 m² and randomized them into different Roxadustat starting doses or placebo. By the end of 8 weeks, the overall hemoglobin response rate (hemoglobin $\geq$ 1.0 g/dL from baseline) was significantly higher in the Roxadustat group than in the placebo one (83.6 vs. 23.3%). The mean maximum Δ Hb was 1.82 and 2.59 g/dL in the low- and high-dose cohorts, versus 0.65 g/dL in the placebo group. Another phase II study [32] from 2013 to 2015 recruiting 107 Japanese NDD patients

Table 1. Summary of 4 HIF-PHIs

Drug name	Activities against 3 HIF-PHDs	Ongoing phase study	Dosages reported	Frequencies reported	Comparison with ESA in DD	Comparison with ESA in NDD	Iron metabolism	Lipid metabolism
Roxadustat	PHD3 = PHD1 = PHD2	Phase 3	50–120 mg (based on weight)	TIW, BIW	Noninferior	NR	Both in DD and NDD	Both in DD and NDD
Daprodustat	PHD3 > PHD1 > PHD2	Phase 3	5–100 mg	Qd	Noninferior	NR	Both in DD and NDD	In DD and NR in NDD
Molidustat	PHD3 = PHD1 = PHD2	Phase 3	25~150 mg	Qd	Noninferior	Noninferior	In NDD	Not obvious
Vadadustat	PHD3 > PHD1 > PHD2	Phase 3	150–600	Qd	NR	NR	Both in DD and NDD	NR

NR, not reported; HIF-PHIs, hypoxia-inducible factor-proline hydroxylase inhibitors; PHD, prolyl hydroxylase enzyme; ESA, erythropoietin-stimulating agent.

showed that patients treated with different regimens of Roxadustat had a mean increase in hemoglobin of $0.20 \pm 0.16 \sim 0.57 \pm 0.24$ g/dL by the end of 6 weeks, much higher than that of the placebo group (-0.052 ± 0.142 g/dL). Provenzano et al.'s [33] phase II study completed in 2012 showed a mean Δ Hb varied from 0.6 to 1.7 g/dL based on different Roxadustat regimens in the first 4 weeks. Patients with different levels of baseline CRP shared similar mean Δ Hb values, indicating that Roxadustat-induced hemoglobin increases were independent of baseline CRP. All these studies confirmed Roxadustat's efficacy in improving renal anemia and demonstrated that Roxadustat augmented hemoglobin in a dose-dependent manner. Moreover, studies also showed that Roxadustat enhanced iron metabolism and reduced hepcidin in NDD patients. In Besarab et al.'s [34] phase II study conducted from 2008 to 2010, compared with the placebo group, patients with Roxadustat had an evident rise in total iron-binding capacity (TIBC) (41.8 ± 45.4 vs. -7.6 ± 26.6 μ g/dL), indicating an increased iron utilization. Besides, serum hepcidin level was significantly decreased in 1.5 and 2.0 mg/kg Roxadustat dose groups by -150 ± 89.5 and -225 ± 192 ng/mL, respectively, whereas it was only -17.8 ± 114 ng/mL in the placebo group. Iron deficiency and anemia were improved by more iron being absorbed from intestines and released from macrophages to participate in hemoglobin production due to TIBC improvement and serum hepcidin inhibition by Roxadustat. In addition to its effect on erythropoiesis, Roxadustat was reported to reduce cholesterol level as well. Provenzano et al. [33] reported a reduction in cholesterol by 26 ± 30 mg/dL after 8 weeks of treatment. Considering the relatively small-sample and short-time follow-up of the previous studies,

Chen et al. [35] have carried out phase 3 clinical trials in 2015~2016 by enlarged cohorts and prolonged follow-up to better demonstrate the efficacy and long-term effect of Roxadustat. In total, 154 NDD CKD patients from 29 renal centers were randomized to receive Roxadustat or placebo for 8 weeks in a double-blind manner and then all switched to Roxadustat for an 18-week open-label period. During the randomization phase, the patients in the Roxadustat group had a mean increase of 1.9 ± 1.2 g/dL in hemoglobin, a mean reduction of 56.14 ± 63.40 ng/mL in hepcidin, and a decrease of 40.6 mg/dL from baseline in cholesterol, while patients in the placebo group suffered a mean decrease of 0.4 ± 0.8 g/dL in hemoglobin, a mean reduction of 15.10 ± 48.06 ng/mL in hepcidin, and a decrease of 7.7 mg/dL from baseline in cholesterol. During the open-label period, the hemoglobin was well maintained by Roxadustat. And, patients initially treated by placebo were witnessed to have an improvement in lipid metabolism as well (shown in Table 2).

In dialysis patients, Roxadustat has also been confirmed to improve anemia unaffected by inflammation, enhance iron utilization, and reduce cholesterol [31, 36–39]. Whether it can replace ESAs to be the first-line therapy in dialysis patients has been explored in several clinical trials with no consensus reached. Chen et al. [39] enrolled 305 DD patients with stable use of ESA and randomized them to either Roxadustat or epoetin alfa in a phase III study in 2015~2016. During the study period of 27 weeks, the 2 treatment shows no difference in anemia correcting (Δ Hb: Roxadustat vs. epoetin alfa 0.7 ± 1.1 vs. 0.5 ± 1.0 g/dL, $p > 0.05$, hemoglobin response: 92.5 vs. 92.5%), partially aligned with Provenzano et al.'s [37] findings in a phase II study in 2010~2012. However, in the

Table 2. Roxadustat's effects in NDD patients [32–35, 40]

Study	No	Drugs	Follow-up time	Protocol	Primary endpoint	Response rate	Other benefits
Akizawa et al. [32] (Japan, mean eGFR: 16.3 mL/min/1.73 m)	83	Roxadustat versus placebo	24 wk	Placebo, 50, 70, and 100 mg TIW for 18 weeks; if Hb 10~12 g/L, Roxadustat switched to TIW or QW; if not, continue TIW	Rate of rise of Hb within the first 6 wk	14.8 versus 81.5 versus 100 versus 100%	1. Hepcidin reduction 2. Increase in TIBC 3. Reduction in cholesterol
Besarab et al. [34] (US, CKD stage 3–4)	116	Roxadustat versus placebo	6 wk	Four dose cohorts Roxadustat BIW (0.7, 1.0, 1.5, and 2.0 mg/kg) versus placebo BIW versus Roxadustat TIW (0.7, 1.0, 1.5, and 2.0 mg/kg) versus placebo TIW for 4 weeks	1. Mean Hb change (Δ Hb) from baseline 2. Proportion of Hb responders (Δ Hb $\geq$ 1.0 g/dL)	Δ Hb: Roxadustat group: 0.8 $\pm$ 0.9~2.2 $\pm$ 0.8 g/dL, placebo: -0.1 g/dL Response rate: Roxadustat group: 30~100%, placebo: 13%	1. Hepcidin reduction 2. Increase in TIBC
Provenzano et al. [33] (USA, CKD stage 3~4)	145	Roxadustat	16~24 wk	Randomization into 6 cohorts with varying Roxadustat starting doses and frequencies followed by hemoglobin maintenance with Roxadustat 1–3 times weekly A: TIW, 16 W, (60, 100, and 140 mg based on patient's weight) B: TIW to BIW (maintenance), 16 W, (60, 100, and 140 mg based on patient's weight) C: TIW, 24 wk, 50, mg D: TIW, 24 wk, 100 mg E: BIW to QW, 24 wk, (70, 100, and 150 mg based on patient's weight) F: TIW to BIW to QW, 24 wk, 70 mg	The proportion of patients achieving hemoglobin increase of $\geq$ 1.0 g/dL from baseline and hemoglobin of $\geq$ 11.0 g/dL by 17 (16 weeks of treatment)	Overall: 91.6% A, B, C, D, E, F: 82.6, 100, 91.3, 95.8, 95.8, 84%	1. Hepcin reduction 2. Not influenced by inflammatory status 3. Cholesterol reduction
Chen et al. [40] (eGFR: 10~60 mL/min/1.73 m ²)	91	Roxadustat versus placebo	8-wk treatment	Randomization into 3 cohorts: Placebo versus low dose (1.1~1.75 mg/kg, TIW) versus high dose (1.5~2.25 mg/kg, TIW)	1. The maximum Hb change from baseline 2. The proportion of subjects who were Hb responders (defined as an Hb increase of $\geq$ 1.0 g/dL from baseline at any time) 3. The proportion of subjects who achieved an Hb level of $\geq$ 11.0 g/dL	Placebo versus low dose versus high dose 1. 0.65 versus 1.82 versus 2.59 g/dL 2. 25.9 versus 88.5 versus 93.1% 3. 6.7 versus 50 versus 71%	1. Hepcin reduction 2. Increase in TIBC 3. Improvement in lipid metabolism
Chen et al. [35]	154	Roxadustat versus placebo	8 wk (Roxadustat vs. placebo) + 18 wk Roxadustat	Randomization into 3 cohorts: Placebo versus low dose (70 mg, TIW) versus high dose (100 mg, TIW)	The mean change from baseline in the hemoglobin level during weeks 7–9	Placebo versus Roxadustat: 0.4 $\pm$ 0.8 versus 1.9 $\pm$ 1.2 g/dL	1. Hepcin reduction 2. Increase in iron utilization 3. Improvement in lipid metabolism

TIBC, total iron-binding capacity.

subgroups of patients with high-level CRP, Roxadustat resulted in a greater Δ Hb of 0.9 ± 1.0 g/dL than epoetin alfa (0.3 ± 1.1 g/dL). In addition, compared with epoetin alfa, patients treated with Roxadustat had an increase in TIBC level (difference, 10.7 ± 1.3 μ mol/L; 95% CI: 8.1–13.3) and

a decrease in hepcidin level (Roxadustat vs. epoetin alfa: 30.2 vs. 2.3 ng/mL), indicating an improvement in iron utilization. Moreover, Roxadustat enhanced lipid metabolism, causing a greater decrease in total cholesterol than epoetin alfa (difference, -22 mg per deciliter; 95% CI: -29

Table 3. Roxadustat's effects in DD patients [37–40, 51]

Study	No.	Drugs	Follow-up time	Protocol	Primary endpoint	Response rate	Other benefits
Akizawa et al. [38] (Japan)	53 PD	Roxadustat	24 wk	ESA naïve ^a patients: 50 or 70 mg TIW ESA-dependant patients: 70 or 100 mg TIW	At weeks 18~24: Maintenance rate of Hb within 10–12 g/dL Average Hb levels at weeks 18–24	At weeks 18~24: ESA naïve: 92.3%, Hb 11.05±0.62 g/L ESA dependant: 74.4%, Hb 10.93±0.61 g/L	Reduction of hepcidin
Besarab et al. [51]	48 HD + 12 PD	Roxadustat	12 wk	Roxadustat (TIW initial dose: 1.0–1.7 mg/kg per dose, adjustment every 4 weeks based on Hb) to 4 groups: HD with oral iron, HD with IV iron, PD with IV iron and HD without iron	The maximum Hb change from baseline during the last 10 weeks of the dosing period	ΔHbmax: HD with oral iron: 3.5±0.2; HD with IV iron: 3.5±0.4; PD with oral iron: 3.5±0.2; HD without iron: 2.8±0.2 Δhepcidin: HD without iron: –63.4±13.3; HD + PD with oral iron: –48.2±18.2; HD with IV iron: –12.6±31.6	1. Hepcidin reduction 2. TIBC increase 3. Not influenced by inflammatory status
Provenzano et al. [37]	Part 1: 42	Roxadustat versus epoetin alfa	Part 1: 6 wk	Roxadustat (1.0, 1.5, 1.8, or 2.0 mg/kg) TIW versus epoetin alfa, IV, TIW	Hb level response (end-of-treatment Hb level change of –0.5 g/dL or greater from baseline)	Roxadustat versus epoetin alfa: 79 versus 33%	1. Hepcidin reduction 2. Cholesterol reduction 3. Not influenced by inflammation status
Provenzano et al. [37]	Part 2: 83	Roxadustat versus epoetin alfa	Part 2: 19 wk	Roxadustat (from different cohorts) versus epoetin alfa, IV, TIW	Hb level response (mean Hb level ≥11.0 g/dL during the last 4 treatment weeks)	Roxadustat versus epoetin alfa: 51 versus 36%	1. Hepcidin reduction 2. Cholesterol reduction 3. Not influenced by inflammation status
Chen et al. [40]	87	Roxadustat versus epoetin alfa	6 wk	Roxadustat (1.1~1.8, 1.5~2.3, and 1.7~2.3 mg/kg) TIW versus epoetin alfa	Successful dose conversion# percentage	Roxadustat (1.1~1.8, 1.5~2.3, and 1.7~2.3 mg/kg) TIW versus epoetin alfa: 59.1 versus 88.9 versus 100 versus 50%	1. Hepcidin reduction 2. Increase in TIBC 3. Cholesterol reduction
Chen et al. [39]	305	Roxadustat versus epoetin alfa	26 wk	Roxadustat (100, 120 mg) TIW versus epoetin alfa	Mean change in hemoglobin level from baseline to the average level during week 23 through 27	Roxadustat versus epoetin alfa: 0.7±1.1 versus 0.5±1.0 g/dL	1. Hepcidin reduction 2. TIBC improvement 3. Cholesterol reduction 4. Not influenced by inflammatory status

TIBC, total iron-binding capacity; ESA, erythropoietin-stimulating agent. ^a Patients not receiving ESA before.

to –16). The study concluded that oral Roxadustat was noninferior to parenteral epoetin alfa in patients undergoing dialysis. In another phase II Chinese study in 2011~2012, 87 DD patients with stable doses of ESA were randomized to either different regimens of Roxadustat or continuation of epoetin alfa. After 6 weeks, 59.1, 88.9, and 100% of the low-, medium- and high-dose Roxadustat-treated subjects maintained their hemoglobin levels versus only 50% of the epoetin alfa ones, which concluded a superiority of Roxadustat over epoetin alfa [40]. Although the results varied among different studies, Roxadustat was shown to be at least no inferior to epoetin alfa and could

be a good alternative of ESA in anemia correction in DD patients (shown in Table 3).

With regard to the safety issues, Roxadustat has demonstrated its safety with only 0~14.2% drug-related serious adverse events recorded, which mainly comprised vascular access complications, infections, and cardiac disorders. The main adverse events reported are diarrhea, nausea, nasopharyngitis, hyperkalemia, and hypertension (shown in Table 4). In general, Roxadustat is quite effective in renal anemia correction unaffected by inflammation and could be a good alternative of anemia correction in CKD patients.

Table 4. Side effects of Roxadustat [32–35, 37–40, 51]

Study	Patients using Roxadustat	AE, %	SAE, %	Frequent adverse events
Tadao et al. [32] (Japan)	80	78.8	13.8	Gastrointestinal disorders: diarrhea (27.5%) and nausea (10%) Infections: nasopharyngitis (26.3%) Declining kidney function (6.3%) Musculoskeletal and connective tissue disorders: muscle spasm (1.3%) Respiratory, thoracic, and mediastinal disorders: cough (1.3%)
Tadao et al. [38] (Japan)	56	87.5	14.3	Gastrointestinal disorders: diarrhea (7.1%), vomiting (7.1%) Infections: nasopharyngitis (25%), catheter site infection (7.1%) Musculoskeletal and connective tissue disorders: back pain (8.9%) Skin and subcutaneous tissue disorders: pruritis (5.4%)
Besarab et al. [51]	60	50	10	Hypertension (10%, the most frequent), all the other AE were ≤5%
Besarab et al. [34]	88	59.1	5	Gastrointestinal disorders: diarrhea (9.1%) Neurologic disorders: headache (6.8%), dizziness (2.3%), insomnia (2.3%) Electrolytes disorder: hyperkalemia (4.5%) Others: fatigue (4.5%), back pain (4.5%), peripheral edema (3.4%), seasonal allergy (1.1%), UTI (1.1%)
Provenzano et al. [37]	106	63.9	24.1	Frequent SAE Gastrointestinal disorders: Gastrointestinal hemorrhage (0.9%) Cardiac disorders: cardiac failure (1.9%), ACS (1.9%) Infections: gastroenteritis (1.9%) Metabolism and nutrition disorders: hyperkalemia (0.9%) Neurologic disorders: stroke (1.9%) Vascular disorders: AV fistula thrombosis (0.9%) Hypersensitivity (0.9%)
Provenzano et al. [33]	145	80	24.1	Gastrointestinal disorders: nausea (9.7%), diarrhea (8.3%) Cardiac disorders: cardiac failure (3.4%) Infections: sinusitis (5.5%), UTI (9.7%), nasopharyngitis (9%) Metabolism and nutrition disorders: hyponatremia (2.1%) Neurologic disorders: dizziness (6.2%), headache (5.5%) Skin and subcutaneous tissue disorders (0.9%) Vascular disorders: hypertension (7.6%), peripheral edema (12.4%) Renal disorders: renal failure (4.9%)
Chen et al. [40]	135	50	5.93	Gastrointestinal disorders: decreased appetite (4%), nausea (3%), diarrhea (2%) Infections: nasopharyngitis (1%), upper respiratory tract infection (4%) Metabolism and nutrition disorders: hyperkalemia (4%) Neurologic disorders: dizziness (3%) Vascular disorders: hypertension (5%) Renal disorders: renal failure (3%)
Chen et al. [39]	204	47.1	14.2	Gastrointestinal disorders: vomiting (5.9%), liver function perturbation (5.4%) Infections: upper respiratory tract infection (18.1%) Cardiovascular disorders: hypertension (12.3%), chest discomfort (6.4%), hypotension (4.9%) Metabolism disorder: hyperkalemia (7.4%) Neurologic disorders: dizziness (4.9%)
Chen et al. [35]	101	37	9	Gastrointestinal disorders: gastrointestinal hemorrhage (1%) Infections: upper respiratory tract infection (5%), pyrexia (2%) Metabolism and nutrition disorders: hyperkalemia (16%), metabolic acidosis (12%), gout (1%) Neurologic disorders: dizziness (1%) cardiovascular disorders: hypertension (6%), peripheral edema (7%) Renal disorders: ESRD (1%), chronic glomerulonephritis (1%)

Daprodustat

Daprodustat was developed in 2007 by GSK. It inhibits all 3 PHDs with a preference for PHD1 and PHD3. The clinical trials on renal anemia correction were started in

2008 and showed that Daprodustat was also effective in improving anemia and enhancing iron utilization in CKD patients, whereas its effects on lipid metabolism was only reported in DD patients [41–45]. Holdstock et al. [42] enrolled 156 CKD patients in a phase II study in 2013~2014,

including 73 NDD and 83 DD, and randomized them to either Daprodustat or control (placebo for NDD, EPO for DD). By the end of 4 weeks, the observed Δ Hb in different Daprodustat dose groups ranged from -0.12 ± 0.51 to 0.95 ± 0.66 g/dL in NDD and -1.06 ± 0.83 to -0.08 ± 0.63 g/dL in DD, versus -0.23 ± 0.51 g/dL in placebo and -0.25 ± 0.81 g/dL in EPO. Besides, the study also showed a decrease in hepcidin and an increase in TIBC in patients with Daprodustat. In Akizawa et al.'s [45] phase II study in 2012~2013 with 86 DD patients enrolled, a mean hemoglobin change of $-0.28 \sim 0.97$ g/dL was witnessed in Daprodustat groups as compared to -1.41 g/dL in placebo, aligning with previous findings [41–44]. Moreover, the study also demonstrated a modest decrease in lipid parameters in DD patients treated with Daprodustat. The main serious drug-related adverse events reported varied from 1.3 to 18%, which mainly comprised cardiac disorders [41–45]. Given that the published studies on Daprodustat are relatively small and short, prolonged and enlarged clinical trials are needed for further assessment of the long-term effects and safety issues of Daprodustat in CKD patients.

Molidustat

Molidustat was a predominantly HIF-2 α -stabilizing prolyl hydroxylase inhibitor developed by Akebia. Like Roxadustat and Daprodustat, Molidustat was shown by the Dialogue studies to be effective in treating renal anemia. The Dialogue studies consisted in 3 separate trials: Dialogue 1 phase II study conducted in 2014~2015 was to compare Molidustat with placebo in NDD patients not receiving ESA, while Dialogue 2 and 4 phase II study carried out in 2013~2015 centered on comparison between ESA and Molidustat in NDD and DD patients, respectively. In Dialogue 1, Molidustat was revealed to be associated with a mean increase in hemoglobin levels by 1.4–2.0 g/dL after 16 weeks of administration. Dialogue 2 and 4 illustrated that compared with EPO, Molidustat maintained hemoglobin level with an estimated difference of up to 0.6 g/dL in NDD and -0.1 to 0.4 g/dL in DD patients [46]. To further observe its long-term effect, the Dialogue studies were extended to 52 weeks with NDD patients initially treated with placebo all switching to Molidustat. By the end of the study, hemoglobin was well maintained in both ESA and Molidustat groups with similar proportions of adverse events. Thus, the study concluded that Molidustat could be a good alternative of ESA in CKD patients. Besides, in NDD patients, a decrease in hepcidin

and an augmentation of TIBC were observed in the Molidustat group, implicating an enhanced iron utilization while no similar changes were witnessed in DD patients [47].

In brief, Molidustat was effective in treating renal anemia and may be a good alternative of ESA in CKD patients. Yet, unlike Roxadustat, its effects on iron utilization were only observed in NDD patients. More clinical trials with more DD patients enrolled should be done to further explore the issues.

Vadadustat

Vadadustat was developed by Bayer Healthcare in 2008. Similar to the 3 drugs mentioned above, published phase II studies [48–50] also showed that Vadadustat improved renal anemia and enhanced iron utilization in a dose-dependent manner in CKD patients. However, the clinical trials were relatively small with a comparatively short follow-up time. Besides, in DD patients, only comparisons of different regimens of Vadadustat were performed with no control group included. Therefore, more studies should be done in the field to confirm Vadadustat's effects.

Among the 4 HIF-PHIs, Roxadustat was the first HIF-PHIs tested in clinical studies to prove its efficacy of renal anemia correction in both NDD and DD patients. In addition, it could also improve lipid metabolism and iron utilization in all CKD patients. Besides, the lower frequency of Roxadustat administration may enhance patients' compliance. Daprodustat has a similar effect as Roxadustat while its lipid metabolism improvement was only reported in DD patients. The other 2 HIF-PHIs are more recently developed with less data which should await more clinical trials for further assessment. All 4 HIF-PHIs were well tolerated in published studies with low rate of serious adverse events.

Conclusion

HIF-PHI is a novel class of therapeutic agents in treating renal anemia. Its main effects comprised boosting EPO production, enhancing iron utilization, and suppressing hepcidin production. Compared with ESA, it is unaffected by inflammation and may ameliorate lipid metabolism. Besides, the oral form may improve patients' compliance with treatment. Viewing its success in CKD patients, ongoing clinical trials have been ex-

tended to treat MDS and chemotherapy-induced anemia. As the drug is newly developed, prolonged and enlarged clinical trials are needed for further assessment of the long-term effects and safety issues of HIF-PHI in CKD patients before its widely application in the market.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

C.N. designed the research; H.X.F. contributed to reference collection and drafting the manuscript; X.J.Y. and C.N. provided substantial guidance and revised the manuscript. All authors read and approved the final manuscript.

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