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Hypoxia-Inducible Factor–Prolyl Hydroxylase Inhibitors for the Treatment of Anemia in CKD: Additional Pieces of the Jigsaw Puzzle

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The treatment of anemia in patients with chronic kidney disease (CKD) remains challenging 3 decades after the regulatory approval of recombinant human erythropoietin in 1989 and the subsequent approval of its derivatives, collectively known as erythropoiesis-stimulating agents (ESAs). In 2018, only 14.6% of patients in the United States were receiving ESAs at the time of end-stage kidney disease onset despite a mean Hb level in this population of 9.3 g/dl.[1] ESA hyporesponsiveness, the failure to achieve target Hb level despite escalating doses of ESA, is associated with adverse clinical outcomes and is an unmet need for anemia treatment in the CKD population, particularly among those receiving HD in whom it is best described. The confluence of barriers to effective and safe anemia treatment in patients with CKD has led to the exploration of therapeutic alternatives to ESAs. The elucidation of the hypoxia-inducible factor (HIF) pathway that regulates transcription of genes controlling EPO production as well as those regulating iron absorption and internal distribution led to the discovery of a new class of orally administered agents for the treatment of anemia that upregulate HIF by inhibiting the enzyme responsible for its degradation, prolyl hydroxylase. Six HIF prolyl hydroxylase inhibitors (HIF-PHIs) are currently in late-stage development programs worldwide (Table 1). Several of these agents have global development programs with sufficient statistical power to examine major cardiovascular events (MACE) versus comparator (ESA or placebo). The first 2 publications from these global studies appeared in *Kidney International Reports* earlier in 2021 and addressed the safety and efficacy of roxadustat in non–dialysis dependent (NDD)-CKD[2] and incident dialysis[3] patients. The NDD-CKD study demonstrated roxadustat to have superior efficacy and noninferior safety to placebo.[2] The incident dialysis patient study demonstrated roxadustat to have noninferior efficacy and superior safety (MACE) to ESA.[3] These 2 reports were accompanied by a commentary by Winkelmayer and Walther titled "Roxadustat for CKD Anemia—Starting the Jigsaw Puzzle, What Will the Finished Picture Show?"[4] The commentary recommended withholding judgment on HIF-PHIs in clinical practice until more detailed analyses are conducted regarding their use in special populations (such as those with ESA hyporesponsiveness), longer follow-up periods are examined to assess for off-target effects, and studies are reported with additional HIF-PHIs to assess the issue of class homogeneity. It is notable that data regarding the safety superiority of roxadustat in incident dialysis patients have been revised to a claim of noninferiority[5] since the publication of the commentary.[4] Three more pieces of the HIF-PHI "jigsaw puzzle" appear in this issue of *Kidney International Reports* that may allow incremental progress toward a "finished picture."

Charytan *et al.*[6] report the results of the 52-week SIERRAS study 741 dialysis-dependent (DD)-CKD patients previously treated with ESA randomized 1:1 to roxadustat or epoetin alfa.[7] The study was not powered to examine MACE. Although the least squares difference in Hb change was statistically higher for roxadustat versus epoetin alfa ($P < 0.001$; $P < 0.01$ regardless of rescue therapy with red blood cell transfusion and/or ESA [intention to treat analysis]), the authors concede that

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Table 1. Large-scale named phase 3 clinical trials of hypoxia-inducible factor–prolyl hydroxylase inhibitors

Study name	Population	Comparator	No. of Subjects	Primary analysis duration (weeks)
Roxadustat				
ALPS	NDD-CKD ESA- naive	Placebo	594	52–104
ANDES	NDD-CKD ESA-naive	Placebo	915	52
OLYMPUS	NDD-CKD ESA-naive	Placebo	2781	52
DOLOMITES	NDD-CKD ESA-naive	ESA	616	104
HIMALAYAS	DD-CKD ESA-naive and ESA-treated	Epoetin	1043	52
ROCKIES	DD-CKD ESA-naive and ESA-treated	Epoetin	2133	52
SIERRAS	DD-CKD ESA-treated	Epoetin	741	52
PYRENEES	DD-CKD ESA-treated	Epoetin or darbepoetin	838	52–104
Vadadustat				
INNO$_2$VATE	Incident DD-CKD Prevalent DD-CKD	Darbepoetin Darbepoetin	369 3554	52 52
PRO$_2$TECT	NDD-CKD ESA-naive NDD-CKD ESA-treated	Darbepoetin Darbepoetin	1751 1725	52 52
Daprodustat				
ASCEND-ID	Incident DD-CKD	Darbepoetin	330	52
ASCEND-TD	HD, daprodustat administered 3 times weekly	Epoetin or placebo	407	52
ASCEND-D	HD	Epoetin	2964	52
ASCEND-NHQ	NDD-CKD	Placebo	600	28
ASCEND-ND	NDD-CKD	Darbepoetin	6000	52
Molidustat				
MIYABI HD-C	HD ESA-naive	None	25	24
MIYABI HD-M	DD-CKD ESA-treated	Darbepoetin	229	52
MIYABI-PD	PD	None	51	36
MIYABI ND-C	NDD-CKD ESA-naive	Darbepoetin	162	36
MIYABI ND-M	NDD-CKD ESA-treated	Darbepoetin	164	36
Enarodustat				
SYMPHONY-HD	HD	Darbepoetin	173	24
SYMPHONY-ND	NDD-CKD ESA-naive and ESA-treated	Darbepoetin	216	24
Desidustat				
DREAM-D	DD-CKD ESA-treated	Epoetin	392	24
DREAM-ND	NDD-CKD	Darbepoetin	588	24

CKD, chronic kidney disease; DD, dialysis-dependent; ESA, erythropoiesis-stimulating agent; HD, hemodialysis; NDD, non–dialysis dependent; PD, peritoneal dialysis.

this is a comparison of the medications plus their dosing algorithms that may have favored roxadustat because the epoetin dosing algorithm was constrained by its package insert. Sixty-six percent of patients receiving roxadustat and 51% of patients receiving epoetin discontinued the study, although this could not be attributed to differences in treatment-emergent adverse events (TEAEs), which occurred in >90% of both populations. In contrast to some previous studies of roxadustat, there was no difference in the incidence of hyperkalemia between groups; patients in the roxadustat group experienced a decline in low-density lipoprotein cholesterol from baseline to week 48 ($P < 0.001$) versus epoetin alfa. The Hb response to roxadustat was comparable between patients with baseline high-sensitivity C-reactive protein (hs-CRP) less than versus greater than the upper limit of normal, whereas patients with baseline hs-CRP required larger increases in mean weekly epoetin doses versus those with baseline hs-CRP less than or equal to upper limit of normal. The protocol allowed i.v. iron if transferrin saturation (TSAT) <20% or serum ferritin <100 ng/ml despite attempts at oral iron supplementation. Mean monthly i.v. iron use (weeks 28–32) was 17 mg in the roxadustat group versus 37 mg in the epoetin group ($P < 0.009$). There was a greater fall in hepcidin levels among roxadustat-treated patients that did not reach statistical significance; the difference in the decrease in serum ferritin levels between the 2 arms also was nonsignificant. Reductions in TSAT were observed in both groups, which likely represent differential changes in total iron binding capacity (TIBC, increased transferrin from HIF-PHI) and serum iron (increased oral iron absorption from HIF-PHI).

Akizawa *et al.*[8] report the results of a phase 3, randomized, 24-week study of 3-times weekly roxadustat versus darbepoetin administered every 2 weeks in 334 Japanese patients with NDD-CKD previously treated with ESA. Roxadustat demonstrated noninferiority to darbepoetin in the primary efficacy endpoint, which was change in Hb from baseline to weeks 18 to 24. Medication dosage adjustments were made per

algorithm to maintain Hb within the 10 to 12 g/dl range. Transferrin and TIBC increased in roxadustat- but not in darbepoetin-treated patients. TSAT initially declined then stabilized among roxadustat-treated patients, most likely due to an increase in TIBC that was not accompanied by a proportional increase in serum iron. A decrease in hepcidin levels between weeks 0 and 4 was greater among roxadustat- than darbepoetin-treated patients. The Hb response to roxadustat was not influenced by high hs-CRP levels, whereas higher darbepoetin doses were required in in patients with high hs-CRP levels. In the safety analysis versus darbepoetin over 24 weeks, the incidence of TEAEs, serious TEAEs, and TEAEs leading to withdrawal of treatment was comparable across treatment arms. Ophthalmological exams with central grading by an independent expert panel revealed no clinically meaningful differences between roxadustat- and darbepoetin-treated patients. Patients receiving roxadustat were followed through 52 weeks and no significant changes in laboratory values, vital signs, or electrocardiograms were observed.

Akizawa *et al*.[8] report the results of the phase 3, randomized, 24-week SYMPHONY-ND study of daily enarodustat versus darbepoetin administered every 2 to 4 weeks in 216 Japanese patients with NDD-CKD who were ESA-naive or previously treated with ESA. Enarodustat demonstrated noninferiority to darbepoetin in the primary efficacy endpoint, which was mean Hb at weeks 20, 22, and 24. Medication adjustments were made per algorithm to maintain Hb within the 10 to 12 g/dl range. Eighty percent of patients in both treatment arms required 2 or fewer dosage adjustments. In enarodustat-treated patients, ferritin and hepcidin decreased; TSAT decreased and was related to increased TIBC and unchanged serum iron. In darbepoetin-treated patients, ferritin and hepcidin increased; TSAT was unchanged. There were no significant differences in TEAEs, serious TEAEs, or TEAEs leading to withdrawal of treatment between the 2 study arms. There were no clinically significant changes in laboratory tests, vascular endothelial growth factor levels, vital signs, electrocardiograms, chest X-ray, or fundoscopy among patients in either study arm.

The 3 articles just described confirm that the HIF-PHIs examined have noninferior efficacy to ESAs in NDD- and DD-CKD patients. Although these studies were not powered to examine MACE outcomes, they demonstrate comparable TEAEs to ESAs and no unexpected safety issues over 24 to 52 weeks. The incidence of hyperkalemia was not increased with HIF-PHI treatment in these reports. The lack of increase in vascular endothelial growth factor or acceleration of diabetic retinopathy allays some concerns regarding angiogenesis with HIF-PHIs. These agents improve iron utilization: DD-CKD patients demonstrated decreased i.v. iron requirements; NDD-CKD patients demonstrated decreased hepcidin and ferritin levels and increased TIBC levels. Perhaps as a result of decreases in hepcidin levels and improved iron mobilization, patients were equally responsive to HIF-PHIs irrespective of baseline hs-CRP level. Given their similar efficacy and safety to ESAs in these studies, where might HIF-PHIs fit into the anemia treatment landscape? Their oral route of administration offers a patient-friendly advantage in NDD-CKD and home dialysis populations. Their efficacy, irrespective of inflammatory status, makes HIF-PHIs an attractive option in ESA-hyporesponsive patients, but these agents have not been specifically tested in that population to date. Although some of the pieces of the jigsaw puzzle are now in place, the picture remains unfinished. Questions regarding long-term safety persist, especially in light of the report that vadadustat did not achieve MACE noninferiority to darbepoetin in NDD-CKD patients.[9] The issue of class homogeneity is clouded by the vadadustat report[9] and may not be elucidated until head-to-head studies of these agents are conducted. The differential pharmacokinetics and specificity for prolyl hydroxylase domain enzymes among the HIF-PHIs raises the possibility that these agents are not interchangeable. Because the cellular response to hypoxia may involve multiple processes beyond erythropoiesis including angiogenesis, a shift from aerobic to anerobic metabolism, and fibrosis, it remains to be demonstrated how many of these off-target effects emerge following long-term treatment with agents that simulate a hypoxic state. The uptake HIF-PHIs into clinical practice will ultimately be driven by prescriber confidence regarding their safety since efficacy noninferiority versus ESAs has been established. Cost considerations (relative to current therapy including supplemental iron) may be a barrier to HIF-PHI coverage by prescription drug plans in NDD-CKD patients and the incorporation of HIF-PHIs into dialysis organizations' formularies and treatment protocols for DD-CKD patients. The studies in this issue of *Kidney International Reports* add to our rapidly growing body of knowledge about a new class of agents for anemia of CKD, the treatment for which remains an unmet need in many patients. This information will inform

discussions with our patients regarding the agent best suited for their particular circumstances.

DISCLOSURE

JBW has served on advisory boards for AstraZeneca, Akebia, Otsuka, Vifor, and Rockwell Medical. He is on speakers bureaus for AstraZeneca and Akebia.

REFERENCES

1. U.S. Renal Data System. 2020 *USRDS Annual Data Report: Epidemiology of kidney disease in the United States* [Table 1.5]. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2020. https://adr.usrds.org/2020/end-stage-renal-disease/1-incidence-prevalence-patient-characteristics-and-treatment-modalities. Accessed June 22, 2021.
2. Coyne DW, Roger SD, Shin SK, et al. Roxadustat for CKD-related anemia in non-dialysis patients. *Kidney Int Rep*. 2021;6:624–635.
3. Provenzano R, Fishbane S, Szczech L, et al. Pooled analysis of roxadustat for anemia in patients with kidney function incident to dialysis. *Kidney Int Rep*. 2021;6:613–623.
4. Winkelmayer WC, Walther CP. Roxadustat for CKD anemia—starting the jigsaw puzzle, what will the finished picture show? *Kidney Int Rep*. 2021;6:559–561.
5. *Fibrogen Provides Additional Information on Roxadustat*. Accessed May 3, 2021. https://fibrogen.gcs-web.com/news-releases/news-release-details/fibrogen-provides-additional-information-roxadustat.
6. Charytan CM, Manllo-Karim R, Martin ER, et al. A randomized trial of roxadustat in anemia of kidney failure: SIERRAS study. *Kidney Int Rep*. 2021;6:1829–1839.
7. Akizawa T, Nangaku M, Yamaguchi T, et al. A phase 3 study of enarodustat in anemic patients with CKD not requiring dialysis, the SYMPHONY ND study. *Kidney Int Rep*. 2021;6:1840–1849.
8. Akizawa T, Iwasaki M, Otsuka T, et al. Phase 3 study of roxadustat to treat anemia in non-dialysis-dependent CKD. *Kidney Int Rep*. 2021;6:1810–1828.
9. Chertow GM, Pergola PE, Farag YMK, et al. Vadadustat in patients with anemia and non-dialysis-dependent CKD. *N Engl J Med*. 2021;387:1589–1600.