HIF-PHIs for Anemia Management in CKD
Potential and Uncertainty ASCEND

Wendy McCallum and Daniel E. Weiner

The introduction of recombinant human erythropoietin in 1989 was a watershed moment in the care of people with advanced CKD, dramatically decreasing transfusion requirements and potentially improving quality of life, particularly among individuals with severe anemia (1), while reducing complications such as transfusion-associated infections and iron overload. Although the optimal management of anemia remains controversial and practice patterns of erythropoiesis-stimulating agent (ESA) dosing have changed significantly over the past two decades, in part reflecting potential safety concerns with ESAs, the importance of disordered iron homeostasis is increasingly accepted. The novel class of hypoxia-inducible factor prolyl-4-hydroxylase inhibitors (HIF-PHIs) garnered attention for being more physiologic than ESAs by mediating both the erythropoietin pathway as well as the iron metabolism pathway, with an additional hope that these would represent safer alternatives for anemia management in CKD. In this perspective, we discuss the results of the Anemia Studies in Chronic Kidney Disease: Erythropoiesis via a Novel Prolyl Hydroxylase Inhibitor Daprodustat-Non-Dialysis (ASCEND-ND) trial as well as other HIF-PHI trials within the historical and current context of anemia management in CKD.

Although the pendulum of anemia management has swung from aggressive use of ESAs to attempts to normalize hemoglobin levels in the 2000s to more conservative anemia management, most notably following a 2011 Food and Drug Administration (FDA) black box warning regarding risks associated with ESAs, many questions remain in the optimal management of anemia. The Trial to Reduce Cardiovascular Events with Aranesp Therapy, which compared hemoglobin normalization with darbepoetin with that of placebo in individuals with diabetes and advanced CKD not receiving dialysis, revealed no difference in most outcomes between randomization groups, although there was a greater risk of the secondary outcome of stroke and a lower risk of fatigue among those randomized to darbepoetin (2). This lack of cardiovascular benefit in the treatment arm, viewed in the context of prior trials that suggested potential harm with hemoglobin normalization, subsequently launched a decade of low hemoglobin targets, with US dialysis facilities penalized for ESA use that resulted in hemoglobin levels exceeding 12 g/dl.

One unanswered question is whether it was the high target hemoglobin versus how one achieves that high target hemoglobin that is associated with potential harm. Safety concerns regarding the use of high doses of ESAs to target high hemoglobin levels are supported by studies that suggest increased mortality with use of ESAs to treat anemia of malignancy, potentially due to increased thrombotic events among ESA recipients, the cause of which remains uncertain (3). Acknowledging differences in iron administration between oncology and nephrology practices, the oncology space tended to use higher ESA doses than the kidney space, paralleling ESA doses in patients with kidney disease and ESA resistance. Given the challenges of chronic inflammation and disordered iron metabolism among patients with ESA resistance balanced against cardiovascular concerns observed with high doses of ESAs, HIF-PHIs have been a highly anticipated class of medications.

HIF-PHIs treat anemia by stabilizing hypoxia-inducible factor (HIF), thereby stimulating endogenous erythropoietin production. Additionally, HIF-PHIs also affect the iron metabolism pathway via effects on hepcidin and iron transport proteins. In contrast to ESAs, which increase iron utilization through erythropoiesis, the HIF-PHIs activate HIF transcription factors that promote both endogenous erythropoietin production, even in states of normoxia, as well as transcription of several iron metabolism and transport genes. Many of the clinical efficacy studies of HIF-PHIs showed a decrease in ferritin levels as well as decreases in hepcidin, a key regulator of iron metabolism that blocks iron absorption and iron recycling. Accordingly, it is hypothesized that HIF-PHIs may represent a “more physiologic” and, therefore, a safer treatment for anemia than traditional ESAs in people with CKD. However, there also have been safety concerns with HIF-PHIs given the extensive role that the HIF transcription factors play in multiple biologic pathways involving responses to hypoxia, particularly the concern for angiogenesis or thrombotic events. Of note, HIF-PHIs are an oral anemia therapy, a potentially attractive option particularly for the nondialysis CKD population and the home dialysis population, with potential opportunity to improve adherence and access to anemia management agents.
Table 1. Findings from prior randomized trials of hypoxia-inducible factor prolyl-4-hydroxylase inhibitors among patients with anemia and CKD

<table>
<thead>
<tr>
<th>Name</th>
<th>N</th>
<th>Manufacturer</th>
<th>Dose</th>
<th>Control</th>
<th>Goal Hemoglobin, g/dl</th>
<th>Study Design</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CKD, nondialysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roxadustat, OLYMPUS (7)</td>
<td>2781</td>
<td>FibroGen</td>
<td>Starting 70 mg TIW, titrated to a maximum of 3 mg/kg (or 300 mg) TIW</td>
<td>Placebo</td>
<td>11±1</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>Roxadustat superior to placebo in raising Hgb</td>
</tr>
<tr>
<td>Vadadustat, PRO2TECT (8)</td>
<td>3476</td>
<td>Akebia</td>
<td>Starting 300 mg once daily, titrated to 150–600 mg daily</td>
<td>Darbepoetin alfa</td>
<td>10–11 or 10–12a</td>
<td>Randomized, open-label, active-control noninferiority trial</td>
<td>Vadadustat noninferior to darbepoetin alfa in raising Hgb but not in cardiovascular safety</td>
</tr>
<tr>
<td>Daprodustat, ASCEND-ND (4)</td>
<td>3872</td>
<td>GlaxoSmithKline</td>
<td>Starting 1–4 mg daily, titrated to 1–24 mg daily</td>
<td>Darbepoetin alfa</td>
<td>10–11</td>
<td>Randomized, open-label, active-control noninferiority trial</td>
<td>Daprodustat noninferior to darbepoetin alfa in raising Hgb and in cardiovascular safety</td>
</tr>
<tr>
<td><strong>Dialysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roxadustat, HIMALAYAS (9)</td>
<td>1043</td>
<td>FibroGen</td>
<td>70 or 100 mg TIW</td>
<td>Epoetin alfa</td>
<td>≥11</td>
<td>Randomized, open-label, active-control trial</td>
<td>Roxadustat noninferior to epoetin alfa among patients on incident dialysis</td>
</tr>
<tr>
<td>Vadadustat, INNO2VATE (10)</td>
<td>3923</td>
<td>Akebia</td>
<td>Starting 300 mg once daily, titrated to 150–600 mg daily</td>
<td>Darbepoetin alfa</td>
<td>10–11 or 10–12a</td>
<td>Randomized, open-label, active-control noninferiority trial</td>
<td>Vadadustat noninferior to darbepoetin alfa in raising Hgb and in cardiovascular safety</td>
</tr>
<tr>
<td>Daprodustat, ASCEND-D (11)</td>
<td>2964</td>
<td>GlaxoSmithKline</td>
<td>Starting 4–12 mg once daily, titrated to 1–24 mg daily</td>
<td>Epoetin alfa or darbepoetin alfa</td>
<td>10–11</td>
<td>Randomized, open-label, active-control noninferiority trial</td>
<td>Daprodustat noninferior to ESAs in raising Hgb and in cardiovascular safety</td>
</tr>
</tbody>
</table>

TIW, three times a week; Hgb, hemoglobin; ASCEND, Anemia Studies in Chronic Kidney Disease; Erythropoiesis via a Novel Prolyl Hydroxylase Inhibitor Daprodustat; ND, non-dialysis; D, dialysis; ESA, erythropoiesis-stimulating agent.

*Goal of 10–11 g/dl in the United States and 10–12 g/dl elsewhere.
The ASCEND-ND trial compared use of the HIF-PHI daprodustat versus ESA for treatment of anemia (4), enrolling 3872 individuals with CKD stages 3–5 and anemia who were not currently receiving dialysis or anticipated to start dialysis within 90 days. Anemia was defined by a hemoglobin of 8–10 g/dl (not receiving ESA) or 8–12 g/dl (receiving ESA). The median eGFR was 18 ml/min per 1.73 m², and median hemoglobin was 9.9 g/dl, with 49% prescribed oral iron. Participants were randomized in a one-to-one fashion to either oral daprodustat or subcutaneous darbepoetin alfa in an open-label manner to a target hemoglobin of 10–11 g/dl. With 378 primary major adverse cardiac events in the daprodustat arm (20%) and 371 events in the darbepoetin alfa arm (19%), the trial met its noninferiority margin of 1.25 (hazard ratio [HR], 1.03; 95% confidence interval [95% CI], 0.89 to 1.19). Although there were significantly lower hepcidin, transferrin saturation, and total iron binding capacity levels in the daprodustat arm, intravenous iron use was similar in both arms. The need for rescue therapy, defined as hemoglobin level <9 g/dl or transfusion of >2 units of packed red cells, was met in 2% of participants in the daprodustat group and 3% in the darbepoetin group, and the proportion of participants receiving at least one transfusion was similar in both arms (13% in the daprodustat arm versus 14% in the darbepoetin arm). In terms of safety, there were no differences in the rates of thrombosis or proliferative retinopathy; notably, there were more cancer-related death or tumor progression events (HR, 1.47; 95% CI, 1.03 to 2.10) and more esophageal or gastric erosion events (HR, 1.70; 95% CI, 1.16 to 2.49) in the daprodustat arm.

The results of ASCEND-ND showed noninferiority in the management of anemia as compared with darbepoetin alfa. However, despite improved iron profiles with daprodustat, there was no difference in iron repletion requirements or red blood cell transfusion events (4). Given that HIF-PHI s have demonstrated anti-inflammatory effects in ischemic disease models, they may be a promising agent for patients in heightened inflammation states and erythropoietin hyporesponsive anemia; however, the noninferiority design of this and several other trials precludes any conclusions on this question. Table 1 summarizes major HIF-PHI trials.

The ASCEND-ND trial somewhat allayed existing concerns for substantially increased cardiovascular risks with this class of agents relative to traditional ESAs, contrasting somewhat with the PROTECT trial of vadadustat, which did not meet the prespecified noninferiority criteria for cardiovascular safety in people with nondialysis CKD. The absence of an increased cardiovascular risk in ASCEND-ND is an important finding given that the FDA in July 2021 voted against approval of the HIF-PHI roxadustat on the basis of concerns that it did not meet cardiovascular safety noninferiority standards and similarly declined to grant marketing approval to vadadustat in March 2022. The analyses behind the roxadustat decision are complicated as roxadustat did meet safety noninferiority margins in an intention-to-treat analysis but not in an on-drug analysis, possibly due to significantly higher rates of study dropout in the placebo arm (5–7). The FDA’s determination on daprodustat remains uncertain.

Despite the reassuring cardiovascular risk profile in ASCEND-ND, concerns do linger regarding potential off-target harms, including both cardiovascular and cancer risks with HIF-PHI s; this is particularly true given the relatively short median follow-up of 1.6 years in PROTECT and 1.9 years in ASCEND-ND, trial durations too brief to fully examine cancer risks. In ASCEND-ND, there were 72 events of either cancer-related death or tumor progression or recurrence among those randomized to the daprodustat arm in comparison with 49 such events among those randomized to darbepoetin. Longer phase 4 trials or registry data are needed to address these concerns. Longer-term follow-up data from Japan and China, where HIF-PHI agents have been approved for use, are highly anticipated.

Anemia is highly prevalent among individuals with CKD and is strongly associated with quality-of-life domains. Current treatment options have numerous limitations, including parental or subcutaneous administration and potential prothrombotic risks. Almost universally, patients place a high value on less fatigue and fewer symptoms versus longevity, and the HIF-PHI s, because of their pleotropic effects of stimulating endogenous erythropoietin production and effects on iron metabolism, offer an oral alternative to ESAs with risks that overall appear similar to currently used medications.

No treatment is perfect, and no medication is without adverse effects. Although important limitations exist that require longer-term evaluation, HIF-PHI s represent potentially useful items in our anemia armamentarium with an overall current safety profile that seems, in sum, no better than the existing ESAs. The ideal remains preventing progression of kidney disease to a stage where anemia is common as, even with the better understanding of the physiology that led to the development of the HIF-PHI s, we still have not figured out how to optimally replicate what the body does so well when the kidneys are working.

Disclosures
D.E. Weiner reports research funding from Bayer (site Principal Investigator [PI]), CSL Behring (site PI), and Goldfinch Bio (site PI; all compensation paid to Tufts Medical Center); serves as a member of the American Society of Nephrology (ASN) Quality and Policy Committees, an ASN representative to Kidney Care Partners, Editor-in-Chief of Kidney Medicine, a member of the scientific advisory board of the National Kidney Foundation (NKF), and Coeditor-in-Chief of NKF’s Primer on Kidney Diseases, 8th Edition; and reports other interests or relationships as a member of the data monitoring committee of the Feasibility of Hemodialysis with GARNET™ in Chronic Hemodialysis Patients with a Bloodstream Infection trial (Avania Contract Research Organization [CRO]), a member of the safety and clinical events committee for A Prospective, Multi-Center, Open-Label Assessment of Efficacy and Safety of Quanta SC+ for Home Hemodialysis trial (Avania CRO), and chair of the adjudications committee of VALOR Trial (George Institute, CRO, sponsored by Tricida). D.E. Weiner was a member of the adjudications committee for trials of roxadustat (Fibrogen) through December 2019 managed via ICON plc, a contract research organization. He has no ongoing or additional relationship with Fibrogen. He is the Medical Director of Clinical Research for Dialysis Clinic, Inc., a not-for-profit kidney care provider in the United States, with salary support paid to his institution. The remaining author has nothing to disclose.
Funding
This work was supported by National Center for Advancing Translational Sciences grant KL2 TR002545-04 (to W. McCallum).

Acknowledgments
The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or CJASN. Responsibility for the information and views expressed herein lies entirely with the author(s).

Author Contributions
W. McCallum and D.E. Weiner conceptualized the study, wrote the original draft, and reviewed and edited the manuscript.

References

Published online ahead of print. Publication date available at www.cjasn.org.