Fellows First

HIF Stabilizers Get in Sync: Are ESAs Bye Bye Bye?

By Gonzalo Matzumura

Anemia is a well-known complication of chronic kidney disease (CKD), and treatment of anemia with erythropoietin (EPO)-stimulating agents (ESAs) is associated with improved quality of life and less need for transfusions (1–3). Since the introduction of ESAs three decades ago, gone are the days when large numbers of patients on dialysis were transfusion dependent—well, nearly (4). Up to 10% of people still do not respond adequately to ESAs, and hyporesponsiveness has been associated with increased mortality (5, 6). For years, ESAs have been the mainstay of treatment for anemia of CKD, but ESA hyporesponsiveness, concerns regarding increased cardiovascular events and mortality, and the desire for an orally active therapy have pushed the development of alternative agents to the forefront of clinical research (3, 4, 7).

The development of novel therapeutics to manage anemia in CKD requires knowledge of the physiology of oxygen sensing and homeostasis in the kidney, as well as the pathophysiology of anemia in CKD (8). When oxygen levels in the kidney drop, peritubular fibroblast-like cells in the juxtamedullary cortex sense this and activate a large number of genes to adapt to the hypoxia, including those to increase synthesis of EPO, which increases red blood cell production with the goal of re-establishing oxygen delivery back to the kidney (9).

The predominant mechanism by which these cells sense and adapt to hypoxia is the hypoxia-inducible factor (HIF) pathway, first described by Drs. Gregg Semenza and G. L. Wang in 1992 (10). Dr. Semenza was awarded the Nobel Prize in Physiology or Medicine along with Dr. William Kaelin and Dr. Peter Ratcliffe (a nephrologist!) in 2019 for their work on oxygen sensing. HIF is a transcription factor that under normal oxygenation is hydroxylated on its HIF-α subunit by prolyl-hydroxylase domain (PHD)-containing proteins. Subsequently, HIF-α undergoes ubiquitination by the von Hippel-Lindau E3 complex and is finally degraded in proteasomes. Under conditions of hypoxia, inhibition of hydroxylation of HIF-α allows it to persist and translocate to the nucleus where it dimerizes with HIF-β. In the nucleus, this heterodimer binds to hypoxia response elements, leading to transcription of oxygen homeostasis target genes, like vascular endothelial growth factor 1 (VEGF-1), EPO, and over 200 other gene products that regulate cell proliferation, metabolism, iron homeostasis, and cell growth (Figure 1) (11).

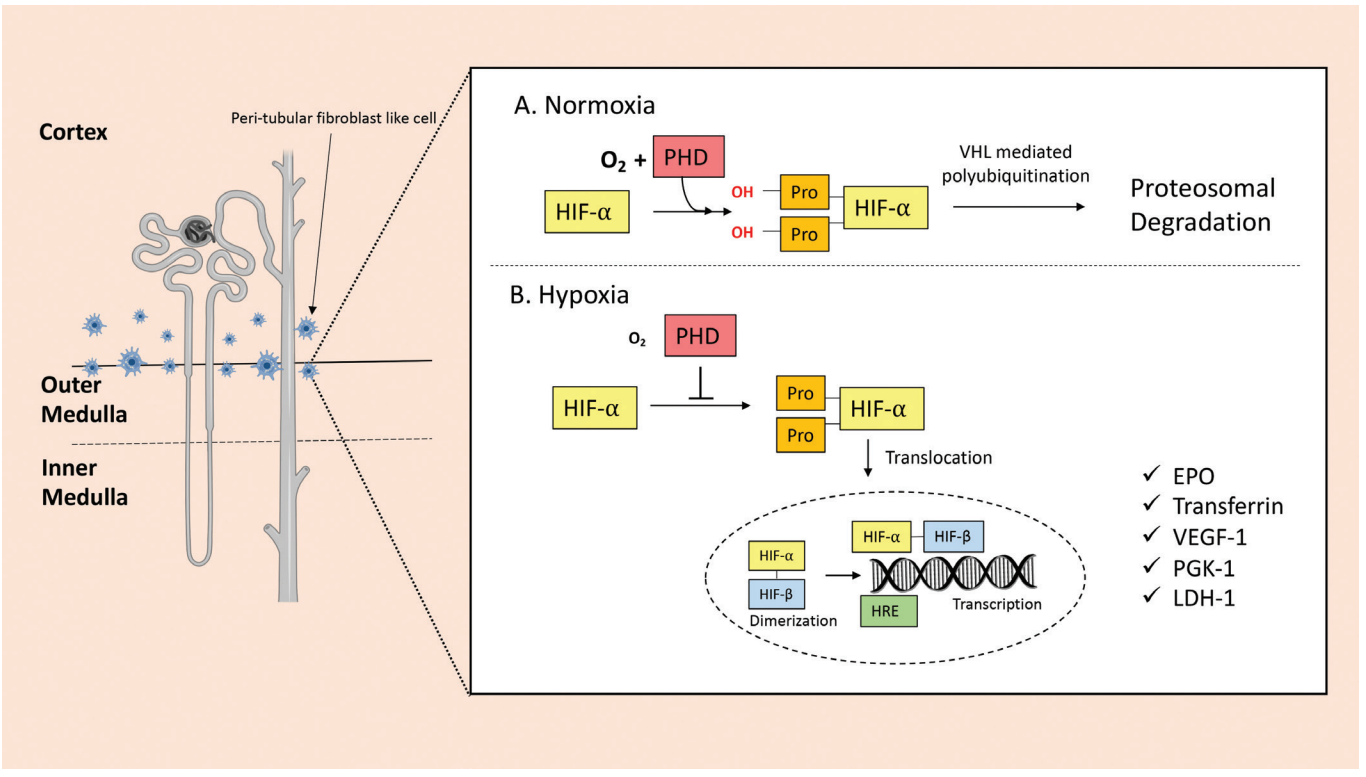
Over the past 15 years, HIF prolyl-hydroxylase inhibitors (HIF-PHIs), also known as HIF stabilizers, have been developed and studied for their efficacy and safety in patients with anemia in CKD (12). Stabilization of HIF by HIF-PHIs mimics a "pseudo-hypoxic" state, increasing endogenous EPO production in a fashion more closely resembling physiologic levels (as opposed to supraphysiologic peaks seen with exogenous ESA use) (13). One specific advantage of HIF-PHIs is their effect on iron homeostasis and iron store mobilization leading to a decrease in hepcidin, which improves anemia even in patients with elevated C-reactive protein (CRP) and ferritin who are traditionally thought to be hyporesponsive to ESAs (13).

Roxadustat is the first HIF-PHI to be approved for use anywhere globally and is currently undergoing US Food and Drug Administration (FDA) review in the United States. Data from a prior phase 3 clinical trial in China demonstrated it is non-inferior to darbepoetin alfa (DA) in patients with kidney failure receiving dialysis, and data from global phase 3 studies, including the Optimized Delivery of Mitomycin for Primary upper tract urothelial cancer (UTUC) Study (OLYMPUS), have found it is also effective in improving hemoglobin levels in patients with CKD not on dialysis when compared to placebo (14, 15). At ASN Kidney Week 2020 Reimagined, phase 3 clinical trials were presented on another HIF-PHI, vadadustat. Vadadustat was demonstrated to also be non-inferior to DA in achieving hemoglobin targets in patients with CKD not on dialysis (PRO2TECT [Efficacy and Safety Study to Evaluate Vadadustat for the Correction of Anemia in Subjects with Non-Dialysis-Dependent CKD (NDD-CKD)] trials) and in patients with kidney failure on dialysis (INNO2VATE [Efficacy and Safety Study to Evaluate Vadadustat for the Maintenance Treatment of Anemia in Subjects with Dialysis-Dependent CKD (DD-CKD)] trials) (16, 17). Other HIF-PHIs, including daprodustat, molidustat, and enarodustat, are in different stages of development, and a few have already been approved for use in other countries (13).

Due to the multiple downstream effects of HIF stabilization, concerns regarding nonspecific multiorgan effects beyond EPO production are being addressed during the development of HIF-PHIs (13). With regard to cardiovascular events, pooled safety data from trials of roxadustat showed that the risk of major adverse cardiovascular events (MACEs) was comparable to placebo in patients with CKD not on dialysis and non-inferior to epoetin alfa in patients with kidney failure receiving dialysis (18). This pooled study, recently published after first being presented at ASN Kidney Week 2019, showed a reduced risk of MACE in incident patients who had been on dialysis for less than 4 months (18, 19). Vadadustat, on the other hand, did not meet its primary safety endpoint of non-inferiority with regard to time to first MACE in patients with CKD not on dialysis (PRO2TECT trials) (16). However, in patients with kidney failure receiving dialysis, it was found to be non-inferior to DA in time to first MACE (INNO2VATE trials) (17). Regarding other adverse effects, increased VEGF-1 expression and other pro-angiogenic gene products by HIF-PHIs have led to concerns about the potential development of pulmonary hypertension, worsening retinopathy, and increased risk of malignancy (20). In a pooled analysis of roxadustat trials presented at ASN Kidney Week 2020 Reimagined, roxadustat, when compared to placebo and epoetin alfa, did not increase the risk of neoplasm-related adverse events during the treatment period; however, a relatively short follow-up limits the significance of this observation (21). We await the final peer-reviewed published data to decide on these effects.

Our progress in understanding oxygen homeostasis physiology and ongoing development of novel therapies, such as HIF-PHIs for anemia management in CKD, makes it an exciting time to start a career in nephrology. Whereas the prospect of "turning on" the HIF pathway master switch holds great promise for anemia and beyond, it will need to be carefully balanced with the ever-present risk of off-target effects. With the evidence accrued and different trials reaching completion with more efficacy and safety data to come, we just might be about to witness the rise to

Figure 1. Hypoxia inducible factor (HIF) pathway



HIF activity in peritubular fibroblast-like cells that produce erythropoietin under conditions of (A) normoxia and (B) hypoxia. HIF, hypoxia-inducible factor; PHD, prolyl-hydroxylase domain; VHL, von Hippel-Lindau; HRE, hypoxia response elements; EPO, erythropoietin; VEGF, vascular endothelial growth factor; PGK, phosphoglycerol kinase; LDH, lactate dehydrogenase.

stardom of HIF-PHIs. Will ESAs be bye bye bye? ■

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The author reports no conflict of interest.

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Play NephMadness 2021 During March, National Kidney Month

By Joel Topf, Anna Burgner, Timothy Yau, Pascale Khairallah, Samira S. Farouk, and Matthew A. Sparks

The 9th annual NephMadness is a social media and medical education campaign focused on all things kidney. You can participate in NephMadness during the entire month of March, National Kidney Month. NephMadness adopts the single elimination brackets that are a hallmark of the popular March Madness (the college basketball tournament held yearly in the United States), but with a nephrology twist. Instead of basketball teams, the bracket is populated with 32 nephrology concepts from eight different regions. This year's regions are: Liquid Biopsy, the return of Animal House, COVID-19, ICU Nephrology, Workforce, Anemia, Primary Care, and Artificial Kidney. Each region has four concepts; the full bracket is shown in the figure.

The winners of each competition are selected by a blue ribbon panel of nine individuals including patients, scientists, clinicians, and educators. Read more about the teams and perhaps get insight on which way they'll vote by reading their bios at AJKDblog. Participants play by filling out their own brackets and try to predict the winners chosen by the blue ribbon panel. The best NephMadness parties, urine microscopy pictures, players with the highest scores, and much more will win NephMadness swag, awarded by the *American Journal of Kidney Diseases* and the National Kidney Foundation. ■

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