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Hypoxia-Inducible Factor Stabilizers: an Evolving Role in Post-Transplant Anemia

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In this edition of the journal, Kong *et al.*[1] report on a study of the hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), roxadustat, for the treatment of post-transplant anemia. After kidney transplantation, anemia is common, although the incidence varies in relation to clinical factors, including time after transplantation, allograft function, and other clinical characteristics. Failure to recognize anemia or undertreatment can be problematic in that it can lead to the need for blood transfusion with resulting allosensitization, although there is some controversy regarding antibody formation risk.

Anemia after kidney transplantation develops for a variety of reasons, thus treatment should be targeted to the underlying etiology. Clinical history, physical examination, and laboratory testing reveal a constellation of findings that help to identify the cause in most patients. For example, in a patient with iron deficiency anemia, appropriate iron supplementation should be administered. Among patients with diminished kidney function, relative erythropoietin deficiency may play an important role. In this setting, erythropoiesis stimulating agents can be employed as in other patients with nondialysis chronic kidney disease (CKD) anemia. However, the use of these agents has probably been somewhat limited by the need for parenteral administration and perhaps by safety concerns. In contrast to erythropoiesis stimulating agents, HIF-PHIs are administered orally and thereby have the potential to simplify treatment. These drugs work by stabilizing hypoxia-inducible factor, leading to erythropoietin production and improved iron availability. They have been extensively studied in nondialysis as well as dialysis CKD populations. The results were consistent in showing excellent efficacy for increasing hemoglobin concentrations. The safety picture was more complex, as has been recently reviewed.[2] There were inconsistencies found in cardiovascular safety, and other issues with residual concern. However, taken together, the accumulated phase 3 study results led to approvals of HIF-PHI drugs in several countries around the world. In the United States, only daprodustat and vadadustat have been approved, and only for patients treated with hemodialysis.

The study by Kong *et al.*[1] looked specifically at post-kidney transplantation patients, a population that was generally excluded from the large global studies. Patients were at least 6 months post transplant, which appropriately excluded anemia occurring in the perioperative period. Roxadustat, in comparison to usual treatment, was found to be effective and generally well tolerated. Although somewhat limited in generalizability, the study provides preliminary evidence to support consideration of roxadustat and other HIF-PHI drugs in the treatment of post-transplant anemia. Ideally, the study will stimulate interest in larger clinical trials to help more clearly define the balance between efficacy and safety of HIF-PHI treatment in post-transplant anemia.

The large, global, phase 3 studies of HIF-PHI drugs in nondialysis and dialysis CKD involved over 27,000 patients. This resulted in a wealth of information on the efficacy and safety of these drugs.[2] When considering treatment in the understudied kidney transplantation population, there are certain issues unique to these patients that should be considered (Figure 1). These patients differ from other nondialysis patients with CKD in material ways that will impact clinical treatment

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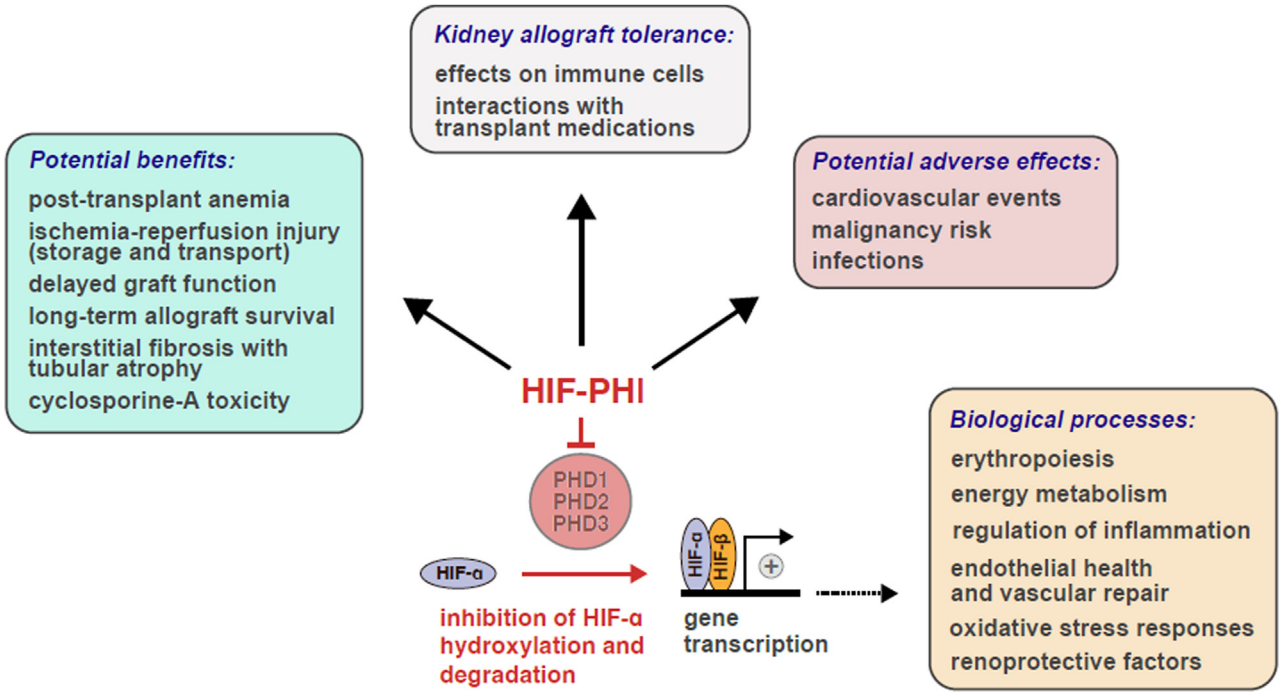

Figure 1. There are certain unknowns regarding HIF-PHI use in post-transplant anemia that include potentially adverse and beneficial effects of treatment. Under normal oxygen conditions, HIF-α is constitutively synthesized and rapidly degraded. 2-oxoglutarate-dependent PHD1, PHD2, and PHD3 dioxygenases initiate HIF-α degradation by hydroxylation. HIF-PHIs inhibit PHD activity reversibly, resulting in cellular HIF-α accumulation, its nuclear translocation, heterodimerization with HIF-β, and increased expression of HIF target genes. Depending on dosing and pharmacokinetics of individual HIF-PHI compounds, this may result in enhanced activity of several multiple biological processes. Some of the processes have been shown to be beneficial in experimental models of kidney diseases.[6] For example, daprodustat has recently been shown to be renoprotective in an animal model of cyclosporine-a toxicity.[S7] HIF, hypoxia-inducible factor; HIF-PHI, HIF-PHD inhibitor; PHD, prolyl-hydroxylase domain.

decisions, as outlined in the next section:

1. Perhaps most relevant is that cardiovascular disease is the leading cause of death among patients after kidney transplantation, with a rate much greater than in the general population.[3] This fact is highly relevant as a backdrop to concerns for increased cardiovascular events that surfaced in some of the roxadustat, vadadustat, and even to an extent in of the daprodustat nondialysis CKD studies. Locatelli and colleagues point to an increase in nondialysis major adverse cardiovascular events with roxadustat and daprodustat (in on-treatment analyses), and a failure to demonstrate noninferiority for major adverse cardiovascular events with vadadustat.[2] In our opinion, the cardiovascular safety analyses of HIF-PHIs led to distinctly heterogeneous results, but they generally indicated an acceptable cardiovascular safety profile, probably not much different than erythropoiesis stimulating agents; a recent meta-analysis describes this.[S1] However, because there is some residual uncertainty and questions remain with respect to the mechanisms of adverse cardiovascular events associated with the HIF-PHI agents (as well as traditional erythropoiesis stimulating agents), a careful risk benefit analysis should be an important part of the post-transplant anemia treatment decision.
2. Patients post transplantation are also at increased risk for malignancy. Several studies have found a 3-fold to 5-fold increase in malignancies, particularly skin cancer and lymphoma.[4] There has been some general concern about whether HIF stabilization by HIF-PHIs could increase cancer risk. This issue was raised because tumor cells, like any other cell, use the HIF pathway for metabolic and angiogenic adaptation to hypoxia and HIF activation in tumors had been associated with worse outcomes.[S2] For example, a classic HIF-dependent hypoxia response is the production of vascular endothelial growth factor, which has been shown to facilitate cancer progression by promoting tumor angiogenesis.[S2] HIF-PHIs in clinical development, however, have not been shown to stimulate significant increases in plasma vascular endothelial growth factor concentrations at the recommended clinical doses. Nonetheless, it is prudent to remain cautious about potential links to increased cancer risk.

Recently, a HIF-2 inhibitor, belzutifan, which generates effects opposite to those of HIF-PHIs, was approved for advanced sporadic clear cell renal cancer and tumors associated with von Hippel-Lindau disease, which are both characterized by high levels of HIF activation due to a genetic defect in the HIF degradation machinery.[S3,S4] In general, the large global HIF-PHI studies did not identify a significant relationship to risk for malignancy. One HIF-PHI, daprodustat, was associated with a small increase in cancer related death and tumor progression or recurrence compared to darbepoetin alfa.[5] It is unclear, whether this represents an artifact of study design, because the authors noted the probable role of the different dosing frequencies for daprodustat and darbepoetin alfa. *Post hoc* analyses to adjust for these differences showed attenuation of the cancer imbalance.[5] In our opinion, any relationship between HIF-PHI treatment and cancer development, recurrence or progression would have been difficult to evaluate from global phase 3 studies. Studies were not of long enough duration or adequate design to fully answer questions regarding the relationship between HIF-PHI use and malignancy risk. Considering that the transplant patient population is immunocompromised and at increased risk for malignancy, a cautious approach is certainly justified. We believe that high risk patients or those with existing cancer should be treated for anemia by other means.

3. The risk for infection is significant, especially in the first year after transplantation. With respect to HIF-PHIs, concern for infection risk came up in the roxadustat nondialysis studies. Specifically, there was a significantly increased rate of serious adverse events and death due to infection with roxadustat compared to placebo.[S5] In contrast, there was no increase in infection risk found in the roxadustat dialysis-dependent patient studies. It is unclear whether the increase in nondialysis infections with roxadustat reflects a true risk of treatment with this drug. Alternatively, the increased infection risk may have occurred due to bias arising from study design, because a much greater number of patients were followed-up, who were on roxadustat compared to placebo after starting dialysis (which would naturally lead to an imbalance in exposure to infection risk). We conclude that there was no clear demonstration of any true promotion of infection risk with roxadustat. Furthermore, an increased risk of infection was not demonstrated for other HIF-PHI compounds. Finally, it is reassuring that Kong *et al.*[1] found no increase in infection risk, specifically with roxadustat treatment in the post-transplant population.
4. Another important question is whether and to what extent HIF-PHIs might affect post-engraftment kidney function and long term graft survival, because the role of HIF in immune responses[S6] and cytoprotection is highly complex and context dependent.[6] Preclinical studies in animal models have suggested beneficial effects on graft injury and survival when organ donors were pretreated with a HIF-PHI.[7] This observation is in line with findings in human kidney transplant biopsies, indicating that low levels of HIF-1α expression in the post-engraftment period correlated with worse graft function compared to higher levels of HIF-1α expression.[8] In a study of patients with delayed graft function, up-regulation of HIF-1α after reperfusion was found to be a predictor of early recovery.[9] HIF-1α expression has also been demonstrated in renal allografts with clinical and subclinical acute rejection.[8] The authors suggested that this was either due to rejection induced renal hypoxia or cytokine production. Whether HIF activation in this setting is beneficial or generates adverse effects is unclear. Although cytoprotective effects of HIF-PHIs have been demonstrated in multiple experimental animal models of acute kidney injury and CKD,[6] potential beneficial effects of HIF-PHIs on graft survival in humans remain speculative. Currently, there is no clinical evidence to support benefit or to allay any concerns regarding harm. In the study by Kong *et al.*,[1] there was little difference in estimated glomerular filtration rate between the roxadustat compared to placebo over 12 weeks of follow-up. This is an area where further research is definitively needed.

In conclusion, the study of Kong *et al.*[1] focuses on a potentially important role for roxadustat and other HIF-PHIs in the treatment of post-transplant anemia. In geographic areas where the drugs are approved and available, treatment of post-transplant anemia can be considered. The oral route of administration and consistent efficacy are significant advantages that must be weighed against safety profiles that have not been well established among these patients. We suggest that patients in

whom HIF-PHIs may be employed for post-transplant anemia should be carefully selected, and that treatment duration should be limited as in the Kong *et al*.[1] study. With time, it is hoped that the ambiguous safety profile of HIF-PHIs that emerged from global phase 3 studies will give way to more precise knowledge on cardiovascular and other aspects of HIF-PHI safety in anemia treatment. This will help not just in post-transplant anemia, but in all aspects of HIF-PHI therapy.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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