A Review on Vadadustat: Hope in Treatment of Anemia Patients having chronic kidney disease

ABSTRACT

Vadadustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor, may offer an oral alternative to injectable erythropoiesis-stimulating agents (ESAs) to treat anemia in patients undergoing peritoneal dialysis. Current standard of care for anemia linked to chronic kidney disease (CKD) is the use of ESAs. Targeting the HIFs-the basic elements of RBC production-presents an oral alternative to the standard ESAs. Due to their low oxygen environment, HIF transcription factors are, by nature, constitutively activated at high altitude, which enhances iron mobilization and boosts production of endogenous erythropoietin (EPO). While clinical trials have demonstrated safety and efficacy for vadadustat, whether it will promote cancer is still a topic under investigation. In fact, research has suggested that activation of HIFs promotes tumor growth due to stimulation of angiogenesis through vascular endothelial growth factor (VEGF). The HIF system includes two subunits, α and β. Under low-oxygen conditions, the HIF-1α subunit accumulates and translocates to the cell nucleus, where it binds to HIF-β to form the heterodimer HIF-1αβ. This complex initiates the expression of sensitive hypoxic genes, including the EPO gene, whose production is increased under such conditions. Three isoforms of the HIF-α subunit exist: HIF-1α, HIF-2α, and HIF-3α, all of which can dimerize with HIF-β and activate the transcription of other genes besides EPO. In the intestine, duodenal cytochrome b (DCYTB) reduces ferric iron (Fe3+) to ferrous iron (Fe2+), which is then taken into enterocytes by the divalent metal transporter-1 (DMT1). HIF-2 controls both DCYTB and DMT1. Iron is exported from cells by ferroportin (FPN), and this export is repressed by hepcidin but stimulated by HIF. In blood, iron is transported in a complex with transferrin (TF) to the liver, RES cells, bone marrow, and other tissues. The increased erythropoietic activity in the marrow leads to the production of growth differentiation factor 15 (GDF15) and erythroferrone, which are known to inhibit hepcidin in liver cells. The inflammatory cytokine relates with increased hepcidin production in the liver, whose action is mediated by decreased ferroportin expression on the cell surface and lower blood iron levels. Vadadustat has HIF stabilized for the promotion of the secretion of EPO but does not seem to have an effect on the production of VEGF. It is also reported that increased activity of HIF results in an antitumor effect. Results from clinical trials support the use of vadadustat without genotoxicity, facilitating the treatment of anemia in patients with chronic kidney disease.

keywords: Vadadustat, Anaemia, Chronic kidney disease, Hypoxia-inducible factor, Erythropoiesis stimulating agents.

INTRODUCTION

1.1 Vadadustat

Vadadustat is an experimental oral inhibitor of hypoxia-inducible factor prolyl-hydroxylase, which stimulates the natural production of erythropoietin. Currently, erythropoiesis-stimulating agents are the first-line treatment for anemia associated with chronic kidney disease. All ESAs effectively treat anemia caused by CKD as they compensate for the deficit of EPO produced by failing kidneys. HIF-PHIs have been differentiated from ESAs by the fact that they activate the HIF pathway and result in downstream effects on the EPO gene transcription, expression of genes involved in erythropoiesis and iron metabolism. The conventional management of anemia in the CKD patient is intravenous ESA, either as monotherapy or with IV or oral iron supplementation. Although ESAs are highly effective for many patients with CKD, they do come with significant limitations. Many CKD patients have a diminished ability to produce EPO and absorb and mobilize iron. The production of Hb is largely dependent on the supply of iron, which is controlled by both the liver, the kidneys, and the bone marrow through synchronized signals. Normally, EPO stimulates erythroblasts to produce Erythroferrone, a protein that acts to inhibit the production of hepcidin in the liver.

“Hypoxia-inducible factor is a transcription factor that controls the expression of many low oxygen-regulated genes, including EPO, which is an important stimulator of erythropoiesis. HIF levels are controlled by oxygen-dependent degradation at the proteasome, a process mediated by a family of prolyl hydroxylases

that serve as oxygen sensors. HIF-prolyl hydroxylase inhibitors or HIF-PHIs are novel drugs that stabilize HIF and promote the expression of EPO and may correct anemia related to CKD. On the other hand, because initiation of HIF and its downstream genes results in a global response to hypoxia, there is, in theory, a potential risk for adverse events including neoplasia due to activation of the HIF pathway. The oxygen dependent hydroxylation of HIF-α is catalyzed by PHD1, PHD2, and PHD3 that function as oxygen sensors within the HIF pathway. PHDs are part of a large family of 2OG-dependent dioxygenases, with more than 60 members. Dioxygenases catalyze the hydroxylation reaction by using molecular oxygen, thereby linking oxygen, intermediary metabolism, and amino acid metabolism to a variety of cellular functions, including HIF regulation, hypoxia responses, collagen synthesis, epigenetic gene regulation, and fatty acid metabolism. Systemic activation of HIF reduces hepcidin production in the liver, thereby improving iron uptake and mobilization. The anemia of CKD is caused by a relative lack of renal production of EPO, together with functional or absolute iron deficiency and resistance to EPO signaling, often in the context of inflammation. Activation of HIF signaling by pharmacological agonists may provide a more physiologic and holistic treatment strategy for renal anemia than administration of recombinant EPO alone" [1,2].

While initial reports suggested a direct role for HIF-1 in suppressing the transcription of hepcidin, subsequent mouse models with global or liver-specific HIF activation showed that suppression of hepcidin depends upon EPO-induced stimulation of erythropoiesis.which would argue that HIF itself does not play a role in suppressing hepcidin transcription.

1.2 Anemia

Anemia is the most common disorder diagnosed in most patients with chronic kidney disease. It could significantly affect a patient's quality of life if left unappropriately managed. There are multiple reasons for anemia in this patient population. In addition to drugs and dietary restrictions, patients may develop anemia due to iron deficiency resulting from a decrease in the renal capability. This leads to lowering the amount of iron available for the bone marrow to produce various blood elements. Chronic patients with kidney diseases can hardly utilize their body's iron stores, and many of them, especially those who are hemodialysed, develop an increased need for additional iron therapy which has been primarily delivered by infusions.

"The erythropoietic system maintains the balance in the supply of red blood cells, therefore, ensuring an adequate tissue oxygenation4. In order to maintain this balance, senescent erythrocytes are replaced by new cells. Hypoxia is important in stimulating erythrocyte production through its interaction with the HIF (hypoxia-inducible factor) system. The HIF is a heterodimer, consisting of two subunits: alpha and beta. The production of HIF-alpha continues, but its degradation occurs in the absence of tissue hypoxia. On the opposite situation, alpha and beta subunits join and bind in the nucleus of the cell, a DNA sequence called hypoxia-responsive elements. Thus, the production of erythropoietin is stimulated" [3].

Erythropoietin, on the other hand, is a molecule of 165 amino acids and 4 chains of carbohydrates. Mainly produced in the interstitial cells of the renal cortex, the production of the liver significantly increases with reduction in glomerular filtration. The half-life of erythropoietin is 5 to 12 hours, and it acts like a true hormone that binds to the receptors of bone marrow cells to produce erythrocytes.

"Although reduction in erythropoietin production is one of the main causes of anemia in CKD, other causes include iron deficiency. It is assumed that iron loss varies between 1 and 3 gram per year in patients on hemodialysis. Also, in the absence of dialysis, depletion in iron is observed in most patients4. This might be related to frequent phlebotomies, blood loss in the hemodialysis apparatus, and impairment in its absorption. The initiation of treatment with erythropoietin analogs demonstrated how frequent iron deficiency is among CKD patients" [4].

"Iron deficiency is usually a functional deficiency and is often characterized by low TSI and normal or increased ferritin. Ferritin can be raised in the presence of inflammation, infection, liver disease, and malignancy. The systemic homeostasis of iron, being regulated and managed by hepcidin 9.10, is also produced in the liver. It mediates degradation of ferroportin in duodenal enterocytes, hepatocytes and macrophages, which mainly prevents proper absorption and usage of iron. Inflammatory cytokines can induce the transcription of hepcidin5.6, and its increase has been reported in patients with CKD5. Anemia in CKD therefore is a multi-factorial process with three major factors being deficiency of erythropoietin, reduction in the life span of erythrocytes of poorly defined etiology, and changes in homeostasis of iron" [5].

Anemia is associated with several symptoms that lead to reduced quality of life, such as fatigue, dyspnea, insomnia, and headache. It is also related to reduced cognitive capacity.In addition, as kidneys fail, patients may require erythropoietin - a stimulus to bone marrow to produce more blood. This hormone is naturally produced by the kidneys but becomes relatively limited in chronic disease of the kidneys.

Most patients will come to require erythropoietin or equivalent injectable products.The two main treatments for anemia are erythropoiesis-stimulating agents and iron replacement. However, despite these treatments, an important proportion of children remain anemic. Increasing the ESA dose to achieve higher hemoglobin levels has been associated with adverse outcomes in adults; this association has not been examined in children. Hemoglobin may be hard to keep within a narrow range using conservative ESA dosing. Careful administration of iron supplements may enhance ESA's efficacy, yet the commonly applied markers of iron storage in the clinical setting lack the sensitivity to identify which patients can benefit the most from supplemental iron. Other agents that target the HIF pathway, such as hypoxia-inducible factor stabilizers and prolyl hydroxylase inhibitors, and iron supplements delivered via dialysis are, therefore under investigation and may provide alternative management. Nonetheless, the effectiveness and safety of these treatments in children with CKD have not been reported yet.

For those with GFR < 30 ml/minute, it is fair to assume that anemia is secondary to renal failure. Nonetheless, it is important to rule out iron deficiency among others since the disease can be easily reversed. If anemia appears disproportionate to the level of kidney dysfunction, further investigation should be made. In such cases, an example-like hemoglobin at 9 g/dl with serum creatinine of 200 µmol/l should be investigated. Further.Type 2 diabetes and hypertension are the predominant causes of CKD in the developed world and increase the risk of developing cardiovascular disease, hyperlipidemia, mineral and bone disorders, and anemia. Anemia is characterized by a decrease in red blood cells and, consequently, hemoglobin (Hb), and typical symptoms and signs include paleness, fatigue, and breathlessness.

At least two factors determine the lag between CKD onset and development of anemia. First, EPO, the hormone that promotes red blood cell production, is produced in smaller quantities in CKD patients than in non-CKD patients. Second, hepcidin, a hormone that suppresses dietary iron absorption when levels are elevated, is elevated in greater concentrations in CKD patients. Iron is one constituent of hemoglobin; it serves as a critical component in the oxygen transport process.Anemia in patients with CKD is a known contributor to a lower quality of life and increased risk of clinical outcomes that are unfavorable.

1.3 Chronic Kidney Disease (CKD)

Chronic kidney disease is a degenerative and incurable illness with high morbidity and mortality rates and also the most common cause of morbidity in adults, especially those with diabetes and hypertension. As such, nonpharmacological interventions, for instance, dietary and lifestyle changes, and renal disease-specific pharmacological treatments, targeting chronic kidney disease can help preserve renal function that otherwise may otherwise improve the outcomes.

A plant-based diet low in protein and salt may reduce glomerular hyperfiltration and halt or slow the progression of renal deterioration and even contribute to alterations in acid-base balance and in the gut microbiome that are favorable.

Alteration in intrarenal hemodynamics through pharmacological therapies (e.g., renin-angiotensin-aldosterone pathway regulators and SGLT2 [SLC5A2] inhibitors) may preserve renal function through a reduction in intraglomerular pressure that is independent of control of BP and glycemia; other pharmacological therapies are novel active moieties: nonpharmacologic steroidal mineralocorticoid receptor antagonists which may protect the kidney through anti-inflammatory or anti-fibrotic mechanisms.

Some glomerular and cystic kidney diseases may benefit from disease-specific treatment. Considering the sheer number of comorbidities, the morbidity and mortality associated with them, and the role of non-traditional risk factors in CKD, managing the cardiovascular risk of CKD, minimizing infection risk, and preventing acute renal failure are some important interventions for these patients. If renal replacement therapy is unavoidable, then stepwise switching to dialysis may be considered. It has also been suggested that this may preserve residual renal function for longer. KSP and SC share similarities but are different from one another. More research is needed, along with the development of new treatment strategies in dietary and pharmacological interventions, to achieve optimal kidney-sparing treatment in these patients, increasing their life expectancy, and achieving better HRQOLID anemia is a frequent complication present in CKD. Both absolute and functional ID are encountered in CKD patients.

Absolute iron deficiency is defined as substantially depleted or depleted iron stores. Functional iron deficiency refers to sufficient storage but insufficient availability of iron to be absorbed into erythroid precursors, primarily because of increased hepcidin levels. Anemia in patients with CKD has been tied to increased morbidity and mortality. The association of mortality with anemia may be related to the severity of anemia. All patients with CKD should be assessed for anemia when first evaluated. The concept of iron deficiency in CKD is much less similar to that in patients with normal renal function. In the case of CKD patients, absolute iron deficiency is characterized by TSAT ≤20% and a serum ferritin concentration ≤100 ng/ml in predialysis and peritoneal dialysis patients and ≤200 ng/ml in hemodialysis patients.

Iron-restricted erythropoiesis, or functional iron deficiency, is characterized by TSAT ≤20% and elevated ferritin. Iron supplementation is provided to all CKD patients who have anemia. Furthermore, the overwhelming majority of patients do not attain optimal responses to ESAs. To overcome these barriers, HIF-PHIs have been created as oral agents in the treatment of anemia in CKD.They mimic the body's exposure to moderate hypoxia, thereby stimulating endogenous erythropoietin production. Some of these agents are already approved for clinical use in specific countries. Clinical trial data show noninferiority compared with ESAs and superiority to placebo for the correction of anemia.

HIF prolyl hydroxylase domain inhibitors could offer patients with inflammation another advantage: enhancing iron use and mobilization as well as reducing LDL cholesterol levels. Overall, non-inferiority was also established for major cardiovascular events except in one molecule in the population of non-dialysis. Such a finding is rather an unexpected given that, based on their mechanism of action, these drugs have low levels of erythropoietin. More data and longer follow-up are needed to clarify safety issues and further explore the diversity of signaling pathways activated by HIF that may have positive or negative effects and distinguish HIF-PHIs from ESAs.

2. MECHANISM OF ACTION OF VADADUSTAT

2.1 HIF-PH Inhibition

“The HIF system elicits an adaptive response to tissue hypoxia in order to prevent cell damage by optimizing oxygen delivery and reducing tissue oxygen utilization which causes the production of EPO, primarily by interstitial perinephric cells of the kidney and by cells in the liver. EPO binds to its receptor on the surface of erythroid progenitor cells in the bone marrow, thus enhancing the survival, maturation, and proliferation of red blood cells. The activity of the HIF system varies according to tissue oxygenation” [6].

“The HIF system consists of subunits α and β. HIF-1α accumulates and translocates to the nucleus of a cell where it binds to HIF-β and leads to the synthesis of the heterodimer HIF-1αβ. The heterodimer HIF-1αβ leads to the expression of various hypoxia-inducible genes, such as the gene for EPO, thereby enhancing its rate of production. There are three isoforms of the subunit HIF-α: HIF-1α, HIF-2α, and HIF-3α, which all can dimerize with HIF-β and stimulate the expression of many genes other than the EPO gene. Thus, the dimer composed of the HIF-α and HIF-β subunits controls the expression of transferrin receptors, VEGF, and endothelin-1 receptors” [7].

In addition, it has been postulated that the HIF system is somehow involved in the control of cell metabolism and activity, including immune cells, and affects the total cholesterol and LDL fraction. The HIF system is nearly ubiquitous: the transcription factor HIF-1α is induced in virtually all cell types whereas HIF-2α is expressed in a more tissue-restricted manner.

“mRNA expression of HIF-2α is mainly detected in the brain, heart, lung, kidney, pancreas, and intestine. HIF-3α tissue expression was observed in the heart, lungs, and kidneys. Normoxic tissue oxygenation leads to the degradation of HIF-1α through its hydroxylation via prolyl hydroxylase (PH) with the von Hippel-Lindau protein (pVHL) thereby preventing dimerization between HIF-1α and HIF-β at a lower level of gene expression that encodes EPO. Under hypoxia, PH is inhibited and HIF-1α does not undergo degradation, and there is possibility of combination to produce the heterodimer HIF-1αβ, which activates the gene in charge of EPO synthesis. Inhibition of PH corresponds to the site of action for a class of drugs HIF-PHIs, used to treat anemia in patients with CKD” [8].

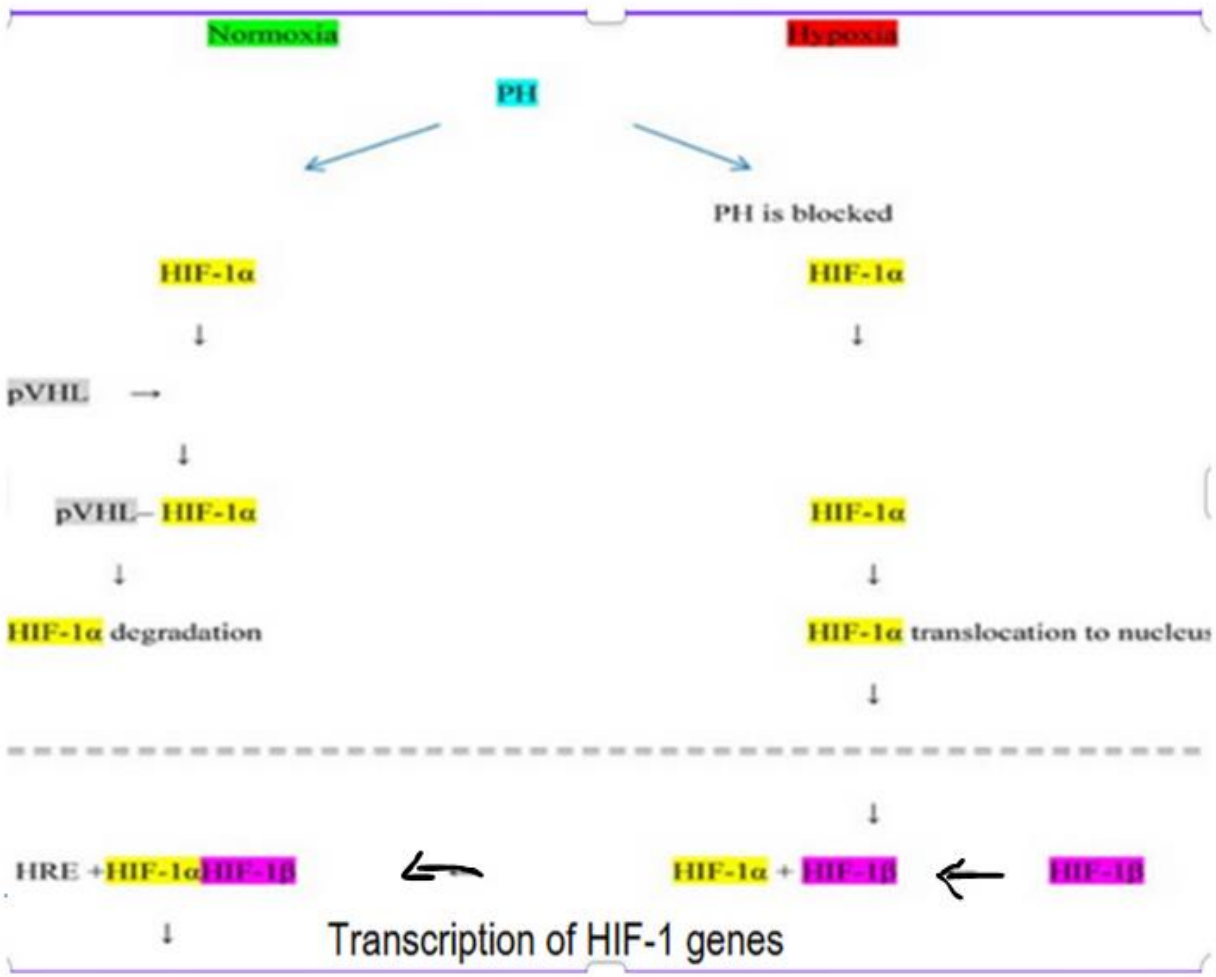

Figure 1. Hypoxia-inducible factor (HIF) system. PH—prolyl hydroxylase, pVHL—von Hippel−Lindau protein, HRE—hypoxia-responsive element, EPO—erythropoietin, VEGF—vascular endothelial growth factor.

2.2 The PHD/HIF Oxygen-Sensing Pathway

“HIF-α is rapidly degraded under normoxic conditions through the hydroxylation of certain proline residues. Hydroxylated HIF-α is tagged for proteasomal degradation by the von Hippel-Lindau (VHL) tumor HIFs are basic pleiotropic helix-loop-helix transcription factors that belong to the PAS (PER/aryl hydrocarbon receptor nuclear translocator [ARNT]/single minded) family of transcription factors. They consist of two subunits, an oxygen-sensitive α-subunit and a constitutively expressed β-subunit, which is often referred to as the ARNT. The HIF-α subunit is continuously synthesized but is rapidly degraded in the presence of molecular oxygen. Three HIF-α-subunits have been identified, HIF-1α, HIF-2α (also known as EPAS1), and HIF-3α. Under hypoxic conditions, HIF-α no longer gets degraded, but translocates to the nucleus, forms a heterodimer with HIF-β, and activates gene transcription.HIF-1 and HIF-2, the most intensively studied HIF transcription factors, control a very wide range of hypoxia responses, such as angiogenesis, anaerobic glucose metabolism, mitochondrial biogenesis, and many others, thus ensuring oxygen delivery and adaptation of cells to hypoxia. The list of genes directly HIF-regulated is vast and several hundred high stringency HIF binding sites have been identified in the genome. Although HIF-1 and HIF-2 share many transcriptional targets, some genes are not co-regulated. For example, the glucose metabolism through

glycolysis is under the control of HIF-1, whereas EPO production and some iron genes are under the regulation of HIF- suppressor protein, which acts as the substrate recognition" [9,10].

"Under hypoxic conditions, HIF-prolyl hydroxylation is decreased, HIF-α is no longer degraded and translocates to the nucleus where it heterodimerizes with HIF-β and initiates gene transcription.Any decrease in HIF-proline hydroxylation or inactivation of VHL function decreases HIF degradation and leads to greater expression of HIF target gene. For example, patients carrying particular inactivating VHL mutations are susceptible to CNS hemangioblastomas, clear cell renal cancer, and pheochromocytomas, cancers that are described by upregulated HIF-regulated gene expression. In addition, particular mutations that compromise the ability of cells to faithfully hydroxylate HIF-α lead to abnormal regulation of HIF activity and predispose to polycythemia" [11].

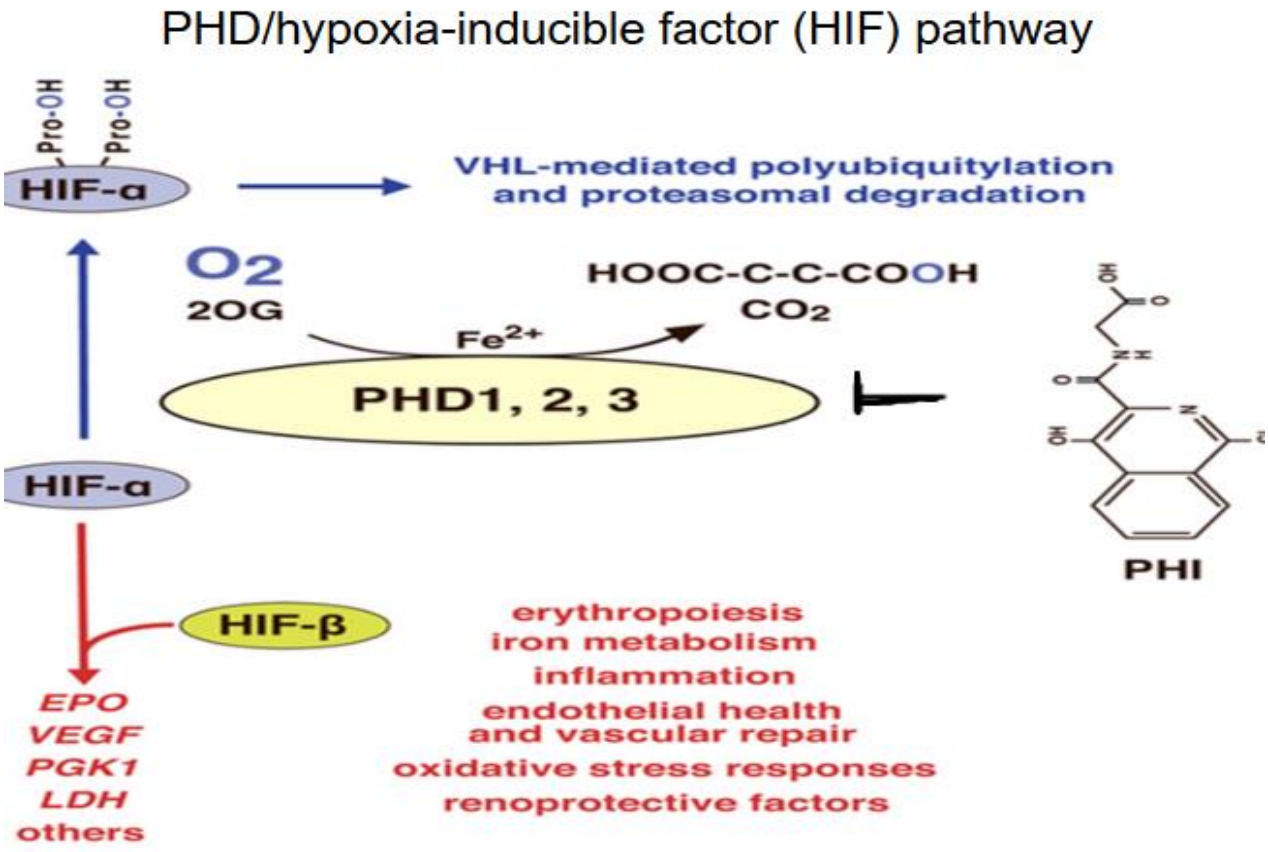

Figure-2 Schematic overview of the PHD/hypoxia-inducible factor (HIF) pathway**.**

"Although the oxygen-sensitive α-subunit of HIF is ubiquitously expressed and continuously produced, it is degraded rapidly in normoxic conditions. On the contrary, in hypoxia, the levels of cellular HIF-α accumulate and HIF-α moves to the nucleus, where it dimerizes with HIF-β. HIF-α degradation is orchestrated by the pVHL-E3-ubiquitin ligase complex, but this is only possible in the presence of oxygen- and iron-dependent PHD dioxygenases (PHD1-3) that hydroxylate prolyl residues of HIF-α. Decarboxylation of 2-oxoglurate (2OG produces hydroxylated HIF-α, succinate and CO2. Inhibition of PHD or von Hippel-Lindau leads to increased transcription of HIF-regulated genes such as VEGF, EPO, PGK1, LDH, and other genes implicated in hypoxia response regulation, including cellular metabolism, mitochondrial function, inflammation, vascular function, oxidative stress, and other responses. Here is the structure of a HIF-PHD inhibitor (PHI), which has been found to hold promise in potently inducing endogenous EPO in dialysis patients. HIF-α is hydroxylated in an oxygen-dependent reaction by PHD1, PHD2, and PHD3" [12].

“PHDs represent a large family of 2OG-dependent dioxygenases comprising over 60 members. Since these dioxygenases catalyze the hydroxylation requiring the use of molecular oxygen, they constitute a point of intersection between oxygen, intermediary, and amino acid metabolism and a variety of cellular processes including HIF regulation/hypoxia responses, collagen synthesis, epigenetic gene regulation, and fatty acid metabolism.Other small molecules, including reactive oxygen species, nitric oxide, and the Krebs cycle intermediates succinate and fumarate, have inhibitory effects on PHD catalytic activity and stabilize and activate HIFα, leading to associated transcriptional programs. The latter is clinically relevant in patients with deficiency of fumarate hydratase, who are at risk of developing the hereditary leiomyomatosis renal cell cancer syndrome associated with increased HIF activity within affected tissues. Structural analogues of 2OG that inhibit the access of 2OG and HIFα to the catalytic center of the PHD and thus reversibly inhibit HIFα hydroxylation are now under clinical development for treatment of renal anemia and other indications” [13].

2.3 The PHD/HIF Axis in Erythropoiesis and Iron Metabolism

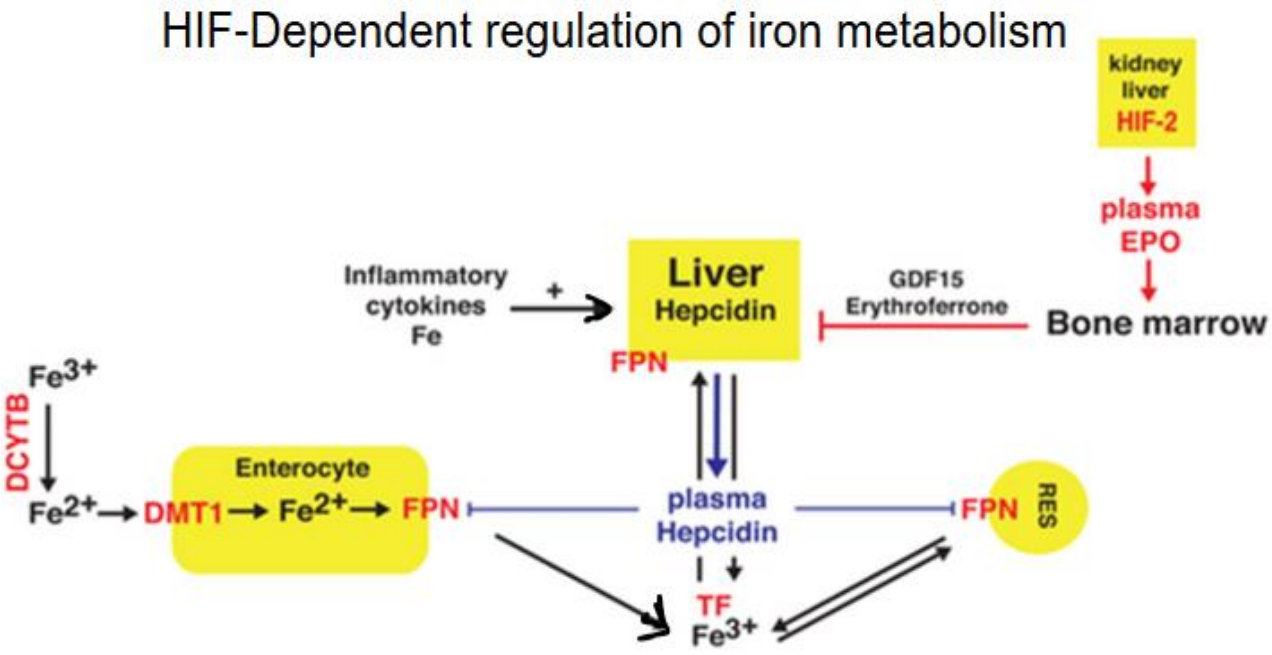

Figure 3: Schematic overview of HIF-Dependent regulation of iron metabolism.

“HIF-dependent regulation of iron metabolism. Overview Schematic overview of HIF-regulated genes in iron metabolism shown in red. In the intestine, duodenal cytochrome b (DCYTB) reduces ferric iron (Fe3+) to Fe2+, which enters via the enterocytes.DCYTB and DMT1 are both bonafide HIF-2-regulated genes. There is a release of iron into the circulation via ferroportin (FPN) that is hepcidin-regulated but also HIF-inducible. In blood, iron is transported in complex with transferrin (TF) to the liver, cells of the reticulo-endothelial system (RES), bone marrow, and other organs. It has been demonstrated that increased erythropoietic activity in the bone marrow produces growth differentiation factor 15 (GDF15) and erythroferrone that suppress hepcidin in hepatocytes. Inflammatory cytokines stimulate hepcidin production in the liver and lead to reduced ferroportin surface expression and hypoferremia.The small 25-amino-acid peptide produced by hepatocytes, hepcidin, targets FPN for degradation” [14].

“Its production increases with iron and inflammatory cytokines, including interleukin 6. As hepcidin decreases the expression of FPN on the cell surface, high plasma hepcidin levels have led to reduced intestinal iron uptake and impaired release of iron from internal stores. Plasma hepcidin levels are generally increased in more advanced stages of CKD and enhance the pathogenesis of renal anemia by causing functional iron-deficiency, due to increased hepcidin levels. This involves systemic activation of HIF, suppressing hepcidin production in the liver and thus enhancing iron uptake and mobilization. The first studies implicated HIF-1 directly in the suppression of hepcidin transcription; however, more detailed analysis of mouse models with either global or liver-specific HIF activation suggests that suppression of hepcidin is EPO-mediated stimulation of erythropoiesis.HIF does not have a direct repressor role on hepcidin transcription in the liver.The interaction between HIF and iron metabolism is a bi-directional one” [15].

“The 5′ UTR of the gene encoding HIF-2α bears an iron response element that interacts with IRPs. In analogy to the inhibition of ferritin translation, IRP binding to the HIF2A 5′ UTR will block HIF-2α translation and therefore diminish the level of HIF-2α protein in the cell in response to low intracellular iron. From this mechanism, one would anticipate that renal EPO production would be only mildly suppressed in iron deficiency anemia compared with other forms of anemia that are associated with either maintenance or even elevation of plasma iron. Hypoxia and the PHD/HIF pathway play an important role in regulating iron metabolism; in addition, it promotes erythropoiesis through direct effects on the bone marrow, including stimulating the expression of the EPO receptor and enhancing the synthesis of hemoglobin, as well as modulating the maintenance and lineage differentiation of stem cells and their maturation” [16].

Anemia associated with CKD results from relative deficiency of renal EPO production, combined functional and/or absolute iron deficiency and resistance to EPO signaling, a condition often seen in the context of inflammation. Pharmacologic activation of HIF signaling may offer a more holistic and physiologic therapeutic option for treating renal anemia than therapy with recombinant preparations of EPO.

3. PROGRESS IN CLINICAL RESEARCH

In clinical trials of a 20-week, phase 2b multicenter, randomized, double-blind, placebo-controlled study to assess the oral, once-daily vadadustat ability to correct anemia in patients with NDD-CKD. A total of 1,929 patients at NDD-CKD stage 3a/b, 4, and 5 stages from 61 centers were stratified by ESA therapy use and Hb level. Group 1: ESA treatment naïve and Hb ≤10.5 g/dl; group 2: previously treated with ESA and Hb ≤10.5 g/dl; group 3: actively treated with ESA, Hb ≥9.5 g/dl to ≤12.0 g/dl.

Patients in each group received double blinded randomization 2:1 for vadadustat versus placebo, stratified by CKD stage and the presence or absence of diabetes mellitus.Two hundred ten patients were included in the safety analyses: those patients who received the study drug were treated with either vadadustat (n = 138) or placebo (n = 72). For all efficacy analyses, the modified intent-to-treat population of 208 patients was used, those patients who had a baseline and ≥1 postbaseline measurement of Hb and red blood cells.

The former group included 136 patients randomized to vadadustat and 72 to placebo. The per-protocol population was defined a priori as the primary population for use in analysis of the primary endpoint and consisted of all modified intent-to-treat patients who completed the study, had efficacy data through week 20, were ≥80% compliant with study medication, and did not have a major protocol deviation.

A total of 160 patients qualified for the per-protocol population. of the 210 patients who were treated with the study medication, 81% (n = 112) in the vadadustat group and 88% (n = 63) in the placebo group completed treatment through to week 20 of the study. In terms of demographic and disease-related characteristics,Hb, hemoglobin; ITT, intent-to-treat population, i.e. all randomized patients who received ≥1 dose of study medication; TSAT, transferrin saturation; uACR, urine albumin-to-creatinine ratio. Values are n (%) or mean ± SD. If a subject had >1 reason checked for etiology of CKD, all reasons were counted. The most important endpoint of the investigation was the percentage of patients reaching or maintaining a mean Hb ≥11.0 g/dl at the end of the last 2 weeks of treatment or showing an increase in Hb ≥1.2 g/dl above the per dose average.

Vadadustat treatment raised and maintained Hb levels in the patients with anemia secondary to CKD. In the per-protocol population, 54.9% of patients treated with vadadustat achieved the primary endpoint compared with 10.3% of patients treated with the placebo ($P < 0.0001$). At an estimated odds ratio, patients receiving vadadustat were approximately 11.5 times more likely than patients receiving a placebo to attain a successful Hb response ($P = 0.0001$) Success: Hb average of weeks 19 and 20 ≥11.0 g/dl or Hb average of weeks 19 and 20 ≥1.2 g/dl higher than predose mean. For a missing value, a single value was used P-value for vadadustat versus placebo is from a logistic regression analysis,

Vadadustat dose-robustly increased and maintained Hb levels in patients throughout the 20-week study. By week 2, mean Hb levels in the vadadustat group had increased substantially from baseline; Hb levels plateaued between weeks 6 to 8 and were maintained throughout the 20 weeks of treatment Hb response versus time in each of the 3 study groups based on ESA treatment status is shown in Hb excursions ≥13 g/dl occurred in only 4.3% (6 of 138) of patients in the vadadustat group. Post hoc analysis of Hb values for all weeks between 8 and 20: for vadadustat 71.2% and for placebo 42.7% were between 10 and <12 g/dl; and for vadadustat 8.9% were between 12.0 and 12.9 g/dl, 1% were ≥13.0 g/dl, while none for the placebo group were≥12.0 g/dl.

Fewer vadadustat-treated patients required ESA rescue therapy compared with placebo (4.4% vs 16.7%, P = 0.045). Of the 6 vadadustat-treated patients who received ESA during the study, 4 did not meet the protocol-prespecified criteria for ESA rescue; of the remaining 2, 1 was in the previously treated group, and 1 in the actively treated group. Out of the 12 placebo patients treated with ESA rescue, 2 did not meet protocol-specified criteria; of the remaining 10, 1 was in the treatment naïve group, 3 were in the previously treated group, and 6 were in the actively treated group. No patient receiving vadadustat and 1 placebo-treated patient required transfusion rescue at any time during the trial.

Baseline increase in mean absolute reticulocyte count occurred in the vadadustat group at week 2 (+0.022 × 10 6 /µl) compared with a slight decrease in the placebo group (–0.005 × 10 6 /µl; P = 0.0001). The mean reticulocyte count in the vadadustat group continued to decrease and reached plateau during weeks 6 to 8 at a level significantly above that of the placebo group, reflecting the new Hb baseline.Markedly lower hepcidin and ferritin levels and significantly higher total ironbinding capacity were noted in the vadadustat group, compared with the placebo group, at each postbaseline evaluation. Serum iron and transferrin saturation did not differ between the 2 treatment groups over the course of the study.

At the end of 20 weeks, 45.8% of patients in the vadadustat group were also receiving iron supplementation, whereas 52.8% of those in the placebo group were receiving iron supplementation at this point. Furthermore, 2.9% of the patients (4 of 136) receiving vadadustat, but none in the placebo group received i.v. iron.Initial drug dosage at treatment initiation was 450 mg once daily; mean drug dosage at Week 19: 450 mg once daily. For the majority of patients: 89%, 120 of 135 who received vadadustat, a stable Hb level was achieved and maintained with ≤2 dose adjustments over the 20-week treatment period, and no dose adjustment was required in 24% of patients (33 of 135).

Patients who were ≥80% compliant with the allocated treatment had 92.8% (128/138) in the vadadustat group versus 94.4% (68/72) in the placebo group.A higher percentage of the vadadustat-treated patients experienced ≥1 adverse event (AE) compared to the placebo-treated patients (74.6% vs 73.6. The incidence of ≥1 drug-related AE was reported in 25.4% of the vadadustat-treated patients (35 of 138) and in 11.1% of placebo-treated patients (8 of 72). In both treatment arms, most of the AEs reported were mild or moderate in intensity. Commonly reported drug-related AEs in the vadadustat group were diarrhea (4.3%), nausea (4.3%), whereas most commonly reported drug-related AE in the placebo group was diarrhoea (2.8%). 10 patients treated with vadadustat (7.2%) and three patients treated with placebo (4.2%) discontinued the study due to AEs.Not listed in the table below is one of the 14 vadadustat-treated patients who were reported to have had a renal-related SAE- one of whom was Subject 1490001, previously study group treated. The patient was hospitalized for Goodpasture syndrome worsening that occurred following 1 dose of study medication; other than hospitalization for worsening Goodpasture syndrome, no other renalrelated adverse events were reported.

There were no trends observed (either increases or decreases) in the systolic values of blood pressure or diastolic values of blood pressure over time, and the distribution in the systolic values of blood pressure among patients receiving vadadustat was comparable to that in patients receiving placebo. Hypertension was an AE in 8.0% of patients treated with vadadustat (11 of 138) and in 2.8% of patients treated with placebo (2 of 72), and all patients had a pre-existing history of hypertension. One of the 11 patients on vadadustat who experienced an AE of hypertension during the study had furosemide discontinued about 1 month prior to the event. Otherwise, no participant experienced withdrawal or dose reduction of antihypertensive drugs before development of the AE of hypertension; no participant stopped vadadustat due to hypertension.

Out Of these, 33 patients treated with vadadustat experienced ≥1 SAE (23.9%), compared with 11 placebo-treated patients (15.3%); the higher proportion of SAEs was mainly due to a higher proportion of renal-related SAEs in the vadadustat arm (10.1%) than in the placebo arm (2.8%). The proportion of patients who received a baseline requirement for initiation of dialysis, an inorganic marker of the seriousness of renal SAEs, was similar between the vadadustat (11 of 138, 8.0%) and placebo (7 of 72, 9.7%) treatment groups. The incidences of investigation-reported renal-related SAEs were not related to the study drug, according to the investigator.The clinical studies mentioned above have proven vadadustat as a worthwhile option as an induction treatment for patients with anemia who have chronic kidney disease.

4. CONCLUSION

Anemia is an inadequacy in the number or quality of red blood cells (RBCs) or a reduction in the amount of hemoglobin, which is the oxygen-carrying protein in RBCs in the blood. It is associated with poorly oxygenated tissues and organs within the body, resulting in a variety of symptoms such as fatigue and weakness and paleness. ESAs or new HIF-PH inhibitors like vadadustat, which act through mimicking hypoxia by stabilizing the hypoxia-inducible factor pathway and activates erythropoiesis and EPO production, should be considered for achieving treatment goals. Vadadustat is an investigational oral hypoxia-inducible factor prolyl-hydroxylase inhibitor that stimulates endogenous erythropoietin formation. At present, erythropoiesis-stimulating agents (ESAs) are still the treatment mainstay for anaemia of chronic kidney disease (CKD). All ESAs function effectively to correct anemia in CKD by countering the EPO deficiency resulting from failing kidneys. In contrast, whereas ESAs function by antagonizing the activity of the HIF pathway, HIF-PHIs activate it, thereby stimulating the transcription of the EPO gene and upregulating the expression of genes participating in erythropoiesis and in iron metabolism. This unusual mechanism of action was believed to have an excellent anemic correction by promoting endogenous production of EPO and concomitantly boosting enteric iron absorption and mobilization of iron (in contrast to ESA).

In addition, the peak serum EPO level is reportedly a few folds less in HIF-PHIs as compared to ESA treatment. The vast majority of RCTs with HIF-PHIs established their non-inferiority as compared to ESAs. Vadadustat is a potent inhibitor of the catalytic activity of all three human PHD isozymes: PHD1, PHD2, and PHD3; all three endozymes have nanomolar inhibitory constant values and are similar. Vadadustat inhibits PHD with competition against the cellular endogenous cofactor 2-oxoglutarate and is not dependent on free iron concentration. In the human hepatocellular carcinoma cell line (Hep 3B) and human umbilical vein endothelial cells, PHD inhibition by vadadustat leads to time- and concentration-dependent stabilization of HIF-1α and HIF-2α. This results in synthesis and secretion of EPO in Hep 3B cells, whereas vascular endothelial growth factor is not measured at detectable levels. A single oral dose of vadadustat in rats potently increases circulating levels of EPO.

COMPETING INTERESTS

Authors have declared that no competing interest exist.

Disclaimer (Artificial intelligence)

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Details of the AI usage are given below:

1.

2.

3.

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