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Research Article

Roxadustat: A Narrative Review of Action and Safety Profile

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Abstract

Hypoxia-inducible factor prolyl hydroxylase inhibitors are a relatively new class of drugs that act by inhibiting the enzyme hypoxia-inducible factor-proline dioxygenase (HIF prolyl-hydroxylase or HIF-PHD). Of the many drugs being studied, Roxadustat (FG-4592) has been approved for use in some countries between 2019 and 2022 after multiple Phase III trials. This narrative review aims to summarize the mechanism of action, utility, evidence related to adverse effects, and implications of the approval of Roxadustat in Anesthesiology. We utilized the Pubmed and Cochrane Library Database for this review. We searched for the keyword Roxadustat between January 1st 2018 and December 30th 2021. The HIF-PHD breaks down the HIF under conditions of normoxia. When inhibited due to a drug or hypoxia, the HIF is stabilized, and as a result, the body initiates transcription of multiple proteins that are responsible for a variety of adaptive mechanisms, including Epopeitin production, which has led to the approval of the use of Roxadustat in Chronic Kidney Disease Anemia. Although there are promising findings in Phase 3 trials and other prior studies regarding its efficacy and safety when comparing Roxadustat to ESAs, significant but rare safety concerns, including thromboembolic events and pulmonary hypertension associated with its use at current recommended clinical doses, have been reported. Long-term studies are essential to unmasking any other potential adverse effects, and strict vigilance must be maintained if used in the interim.

Keywords: Anemia; Anesthesiology; Chronic; Hypoxia-Inducible Factor-Proline Dioxygenases; Hypoxia; MeSH; Prolyl-Hydroxylase Inhibitors; Renal Insufficiency.

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Abbreviations

- CKD: Chronic kidney disease
- ESRD: End Stage Renal Disease
- KDRA: Kidney Disease Related Anemia
- EGFR: Estimated glomerular filtration rate
- ESAs: Erythropoiesis-stimulating agents
- PHIs: Prolyl Hydroxylase Inhibitors
- HIF: Hypoxia-inducible factor
- NDD-CKD: Non-dialysis-dependent chronic kidney disease
- EPO: Erythropoietin
- TIBC: Total iron binding capacity
- TrSat: Transferrin saturation
- HIF: Hypoxia Inducible Factor
- PAH: Pulmonary arterial hypertension
- RDS: Respiratory Distress Syndrome
- Hypoxia Inducible Factor Prolyl Hydroxylase enzyme (HIF-PHE)
- TSH: Thyroid stimulating hormone
- FDA: Food and Drug Administration
- CRDAC: Cardiovascular and Renal Drugs Advisory Committee

Introduction

The 2019 Nobel Prize for medicine was awarded to three scientists, Gregg L Semenza, M.D., Ph.D., William G. Kaelin, Jr., M.D., and Peter J. Ratcliffe, for the discovery of Hypoxia Inducible Factor (HIF) and further elucidation of its role in oxygen homeostasis. This protein is responsible for switching genes on in hypoxic conditions and responsible for specific adaptive mechanisms to hypoxia. This discovery is allowing scientists to better understand the impact of oxygen levels in anemia, hematological and solid malignancies, retinopathy of prematurity, organ ischemia, coronary artery disease, and other conditions. Drugs targeting the HIF pathway are being studied as an alternative option for the management of Chronic Kidney Disease Anemia (CKDA) and anemia in cancers by tricking the body into thinking that hypoxic conditions exist and initiating adaptive pathways, including the production of more hemoglobin and red blood cells. A class of drugs, the Hypoxia Inducible Factor Prolyl Hydroxylase Inhibitors (HIF PHI), have gained traction with the first-in-class approval of Roxadustat (FG-4592, ASP1517, 47 N-[(4-hydroxy-1-methyl-7-phenoxy-3-isoquinolinyl) carbonyl]-glycine, AZD9941 or Au Rui Zhuo® in China), an analog of 2-oxoglutarate, in China. This narrative review aims to describe and summarize the physiology of the HIF pathway, mechanism of action of Roxadustat, current status,

drug trials, and future directions of HIF-PHIs and its implications in the field of Anesthesia.

Methods

We utilized the Pubmed and Cochrane Library Database. We searched for the keyword Roxadustat between the dates January 1st, 2018, and December 30th, 2021. The Cochrane Database search resulted in 109 articles, and the PubMed search resulted in 180 articles. Supplemental articles were used to elaborate on the HIF pathway that was outside of this primary search.

The hypoxia-inducible factor pathway physiology

HIF is a heterodimeric transcription factor which acts as the central regulator of cellular adaptative mechanisms in oxygen-depleted states. It consists of an oxygen-sensitive Alpha subunit- HIF-1α or HIF-2α and a constitutively expressed HIF-1β subunit. Hypoxia-inducible factor-proline dioxygenase or Prolyl hydroxylases (PHD) are oxygen-sensitive enzymes that regulate the HIF pathway. In the presence of normal oxygen levels, the HIFα subunit undergoes hydroxylation of its proline residues by PHD, enabling it to interact and bind to the Von Hippel-Lindau (VHL) protein. This interaction enables the ubiquitination and degradation of the HIFα. During hypoxic states, the PHDs are inactivated, leading to the dimerization of the HIFα and HIFβ subunits. HIFβ is also known as the Aryl Hydrocarbon Receptor Nuclear Translocator (ARNT). Interaction with the Beta subunit causes the dimerized HIF unit to translocate to the nucleus and activate the Hypoxia Response Elements (HRE). Activation of HREs within the promoter region leads to increased EPO production and oxygen homeostasis [1].

EPO is primarily produced by the fibroblast cells in the renal cortex and medulla. In humans, HIF-2α is activated in response to hypoxia, instead of activation of HIF-1α. Thus, HIF-2α is the primary driver of erythropoiesis in humans [2]

Mechanism of action of hif-phis

HIF-PHD inhibitors slow down the degradation of the HIF Alpha Units. This deceives the body into detecting a hypoxic state and enables many pathways that help adapt to hypoxic conditions. Targeting the HIF-PHD enzyme improves endogenous EPO production, and thereby decreases transfusion dependence among anemic patients. Several agents, many of which can be administered orally, have the potential to mitigate the inconvenience of intravenous administration that Erythropoiesis-Stimulating Agents (ESAs) pose and their serious side effects. Roxadustat is a reversible inhibitor of PHD2α, which is responsible for the breakdown of HIF in the absence of hypoxia. By inhibiting PHD2α, it transiently stabilizes the HIF. Blocking the PHD enzyme also has the potential to exert other beneficial effects mediated by HIF. For example, stabilization of HIF has been found to reduce blood pressure, improve glucose utilization, decrease circulating hepcidin, improve iron availability, and improve lipid profile [3].

Current status of roxadustat

Roxadustat is the only approved oral medication for Chronic Kidney Disease Anemia. It is undergoing Phase III studies for use in Dialysis Dependent (DD) and Non-Dialysis- Dependent (NDD) CKDA, many of which have been completed between 2019-2022. It has shown efficacy and tolerability in thirty-five Phase 1 and 2 clinical studies, details of which we have not listed as it is beyond the scope of this narrative review.

It was approved in China for the treatment of anemia in dialysis-dependent CKD patients in December 2018, and in non-dialysis dependent CKD patients in August 2019 [4,5] The Japan new drug application submitted by Astellas Pharma Inc. also passed through. Roxadustat was approved in Japan for use in CKDA for patients on dialysis. During the FDA Cardiovascular and Renal Drugs Advisory Committee (CRDAC) meeting on July 15th, 2021, Roxadustat was discussed. There was a 12 to 2 vote against the approval of Roxadustat use in adult dialysis-dependent CKD patients and a 13 to 1 vote against the approval for use in adult non-dialysis-dependent CKD patients due to a need for additional clinical trials on safety to gain a stronger understanding of the drug's benefit-risk profile [6] The drug is therefore not in use in the United States. Roxadustat was approved in the European Union to treat symptomatic anemia associated with CKD in 2021 [7].

Pharmacokinetics of roxadustat

One of the earlier studies from 2013 evaluated the drug's pharmacokinetics in Caucasian and Japanese subjects. In healthy subjects who received one-time oral doses of Roxadustat 0.3, 1, 2, 3, or 4.0 mg/kg, the mean peak drug concentrations (C_{max}) were 1, 5, 11, 17, and 26 μg/mL, respectively. The mean half-life values were 12, 12, 14, 10, and 12 h without evidence for drug accumulation. In a second randomized, double-blind, placebo-controlled study, oral doses of roxadustat 40, 100, 160, or 200 mg were used; roxadustat mean C_{max} of 4, 8, 14, and 15 μg/mL was reached, respectively, within a median time of 2-3 h. Mean elimination time was 7-9hrs across multiple groups with confirmation of the absence of drug accumulations with multiple dosing. The pharmacokinetics did not change significantly with fasting conditions, moderate liver impairment (N=8 per group) or when taken concomitantly with Spherical carbon adsorbent. However, a study exploring the effects of Sevelamer carbonate and calcium acetate on the pharmacokinetics of Roxadustat found that concomitant administration of Roxadustat with either of these substances reduced exposure to Roxadustat in healthy individuals; Roxadustat maximum plasma concentration decreased by 26% when administered 1 hour before receiving sevelamer carbonate and decreased by 19% when administered 1 hour before receiving calcium acetate.

A recent literature review looking at 57 studies relating to pharmacokinetics and pharmacodynamics of Roxadustat proposed a hypothetical sequence of clinical effects. The study used models based on sigmoidal hill equations and suggested that Roxadustat has a primary effect on increasing EPO levels within a few hours after administration with the half-maximum EPO concentration-effect inferred at 10-36 μg/mL, the Hill coefficient at 3.3, and the effect bisection time at 10-17 h, corresponding to EPO half-life. The following effects on hemoglobin levels were observed several weeks after the administration of Roxadustat as hemoglobin synthesis depends on the erythrocyte cell lifespan and is not quickly influenced by fluctuating EPO levels [8].

The drug was also tested for interactions with Omeprazole [9], Lanthanum Carbonate [10] used for hyperphosphatemia and Warfarin [11] in open-label phase 1 studies in healthy subjects. There were minimal or clinically insignificant effects on the pharmacokinetics of Roxadustat when co-administered with these drugs. Furthermore, a review looking at phase 1, open-label, and cross-over studies suggests an interaction between Roxadustat and statins. It was found that Roxadustat inhibits organic anion transporting polypeptide 1B1, which

	Study	Origin	Population Included	Study Design	Number Of Patients	Endpoint	Hemoglobin (Hb) Results	Safety Results
Pyrenees	EudraCT number 2013-001497-16	Europe	Patients > 18 years of age on dialysis for at least 4 months who had been previously treated with stable doses of ESA for 8 weeks. Starting Hb values of all patients were within 9.5-12.0 g/dL	Phase 3 randomized, open-label, active-controlled study	836 Rox: 415 ESA: 421	Efficacy and Safety of Roxadustat compared with ESA among anemic ESRD patients on dialysis.	Roxadustat was non-inferior to ESA in changes of Hb. Hb change from baseline of Roxadustat and ESA was 0.477 and 0.205 respectively (p<0.001). LSM difference of 0.235 (95% CI 0.132, 0.339)	Rates of TEAE (treatment emergent adverse events) was similar among Roxadustat and ESA group at 86.7% and 86% of patients
Sierras	NCT02273726	USA	Patients > 18 years on dialysis for >3 months who had been previously taking an ESA for at least 8 weeks. Starting Hb values of all selected patients were within 9.0-12.0 g/dL.	Phase 3 randomized, open-label, epoetin alfa-controlled study	741 Rox: 370 EpoA:371	Efficacy and Safety of Roxadustat compared with epoetin alfa among anemic ESRD patients on dialysis.	Mean changes in hemoglobin averaged over weeks 28 to 52 were 0.39 (0.93) and −0.09 (0.84) g/dl in Roxadustat and epoetin alfa groups (least squares mean [LSM] difference: 0.48 [95% CI: 0.37, 0.59]; P < 0.001)	Rates of TEAE were similar among Roxadustat and Epoetin alfa group. At least 1 TEAE was experienced by 91.6% and 91.4% of patients in the Roxadustat and epoetin alfa groups.
Rockies	NCT02174731	International	Patients >18 years of age on dialysis for at least 30 days prior to randomization with a baseline Hb of 10 g/dL if not on ESA or 12 g/d L if ESA-treated.	Phase 3, randomized, open-label active-controlled study.	2133 Rox 1068 EpoA:1065	Efficacy and Safety of Roxadustat compared with epoetin alfa among anemic ESRD patients on dialysis.	Roxadustat group had higher adjusted least squares mean (LSM) increase in Hb from baseline over weeks 28-52 at 0.77 g/lL vs .68 g/dl for epoetin alfa. LSM difference, 0.09 g/dl [95% CI, 0.01 to 0.18], P=0.036 for superiority	Rates of TEAE were similar among Roxadustat and Epoetin alfa group. At least 1 TEAE was experienced by 85% of Roxadustat group and 84.5% of epoetin alfa group.
Himalayas	NCT02052310	Unites States, Europe, South America, and Asia	Patients >18 years of age on dialysis for >2 weeks and <4 months prior to randomization. Selected patients had mean Hb level of 10 g/dl and had not received ESA for more than 3 weeks within the 12-week period prior to study	Phase 3 randomized, open-label, active-controlled study	1043 Rox 522 EpoA:521	Efficacy and Safety of Roxadustat compared with epoetin alfa among anemic ESRD patients on dialysis.	Average changes in Hb were similar in Roxadustat (1.27 g/dl) and epoetin alfa groups (1.21 g/l) with LSM difference of 0.18 [95% CI: 0.08, 0.29]	Rates of TEAE were similar among Roxadustat and Epoetin alfa group. At least 1 TEAE was experienced by 85% of both the Roxadustat and epoetin alfa group.
Olympus	NCT02174627	United States	Patients ≥18 years not on dialysis who had eGFR <60 ml/min corresponding to CKD stage 3-5. Mean baseline Hb of <10 g/dl	Phase 3, randomized, double-blind, placebo-controlled study.	2781 Rox: 1371 Plac: 1357	Efficacy and Safety of Roxadustat compared with placebo among CKD patients.	LSM change in Hb from baseline over weeks 28-52 was significantly greater with Roxadustat than placebo group. LSM +1.75 g/dl [95% CI, 1.68 to 1.81] versus +0.40 g/dl [95% CI, 0.33 to 0.47] in Roxadustat and placebo group respectively	The proportions of TEAEs were similar among the Roxadustat and placebo groups with 89.8% and 88.3% respectively

Alps	NCT01887600	Europe	Patients ≥ 18 years previously diagnosed with CKD 3-5 not on dialysis with mean baseline Hb <10g/dl who had not received ESA within 12 weeks prior to study.	Phase 3, randomized, double-blind, placebo-controlled study	594 Rox: 391 Plac: 203	Efficacy and Safety of Roxadustat compared with placebo among CKD patients.	LSM change from Hb baseline over weeks 28-52 was significantly greater with Roxadustat than placebo group. LSM +1.992 (95% CI 1.82–2.16) for Roxadustat group and 0.300 (95% CI 0.09–0.51)	The proportions of TEAEs was similar among the Roxadustat and placebo group with 87.7% and 86.7% respectively
Andes	NCT01750190	United States, South America, Australia, New Zealand, and Asia	Patients ≥18 years not on dialysis who had eGFR <60 ml/min corresponding to CKD stage 3-5. Mean baseline Hb of <10 g/dl	Phase 3, randomized, double-blind, placebo-controlled study	922 Rox: 616 Plac: 306	Efficacy and Safety of Roxadustat compared with placebo among CKD patients.	Mean hemoglobin changes from weeks 28 to 52 waws significantly higher in Roxadustat versus placebo group. LSM difference was 1.85 g/dl (95% CI 1.74–1.97; P < 0.0001)	The incidence of TEAEs was comparable in Roxadustat (87.6%) and placebo group (85.9%).
Dolomites	NCT02021318	Europe	Patients ≥18 years not on dialysis who had eGFR <60 ml/min corresponding to CKD stage 3-5. Mean baseline Hb of <10.5 g/dl	Phase 3 randomized, open-label, active-controlled study	616 Rox: 323 DarbA: 293	Efficacy and Safety of Roxadustat compared with Darbepoetin alfa among CKD patients.	Mean Hb changes from weeks 28-36 weeks were similar between the Roxadustat and Darbepoetin alfa group. LSM difference 0.015 (95%CI –0.131, 0.162)	Incidence of TEAEs was comparable in Roxadustat (91.6%) and Darbepoetin alfa group (92.5%).

Table 1: Summary of findings of completed Phase III trials evaluating Roxadustat.

can affect statin concentrations. Roxadustat, when given in conjunction with different statins, resulted in increases in maximum plasma concentrations and area under the plasma concentration-time curve (AUC) of the statins; 1.75-fold increase for simvastatin, 2.93-fold increase for rosuvastatin, and 1.96-fold increases for atorvastatin [12]. Additionally, increased statin maximum plasma concentration and AUC were not attenuated by separating Roxadustat and statin dosing time. No significant difference was observed for terminal elimination half-life when these medications were given together [12].

Phase 3 data

Data from phase 3 clinical trials in patients with anemia and dialysis-dependent CKD (PYRENEES, SIERRAS, ROCKIES, HIMALAYAS) and non-dialysis CKD (OLYMPUS, ALPS, ANDES, DOLOMITES) were promising. Findings of the main Phase 3 trials have been summarized in Table 1.

The OLYMPUS, ALPS, and ANDES study compared Roxadustat to placebo, whereas the DOLOMITE compared Roxadustat to Darbepoetin Alfa in NDD CKD patients. HIMALAYAS compared Roxadustat to Epoetin Alfa in incident dialysis patients. ROCKIES AND SIERRAS did include both incident and prevalent dialysis patients. These studies found the safety profile of Roxadustat comparable to that of ESAs.

Pooled data from approximately 4700 patients worldwide were analyzed, and no clinically meaningful difference in risk of Major Adverse Cardiovascular Events (MACE) between Roxadustat and placebo was reported [13] It was also reported that on a pooled analysis of the data from three of the NDD CKD studies, there was a slower reduction in estimated glomerular filtration rate (e-GFR) decline among the Roxadustat group at 12 months compared to placebo as well as a statistically significant increase in quality of life endpoints from baseline to week 12 [14-16] Of note, it was found that the positive effects of Roxadustat were independent of baseline C-reactive protein, an inflammatory marker. In the SIERRAS trial, epoetin alfa dose requirements increased by 57% over 52 weeks in the epoetin alfa arm for maintenance, while the dose requirement of Roxadustat remained stable [17].

Proposed uses of the drug

Use in anemia

Anemia is one of the most common co-morbidities seen as a result of Chronic Kidney Disease (CKD). Approximately 40% of patients with CKD will have a low hemoglobin level (defined as <13 g/dL in males and <12 g/dL in females) [18] Hemoglobin levels less than 10 g/dL frequently warrant medical intervention either in the form of Erythropoietin Stimulating Agents (ESA) or transfusion support. ESAs have been associated with increased adverse events, including strokes and venous thromboembolism [19]. Additionally, they are only available in the intravenous or subcutaneous injectable form leading to long-term patient discomfort and injection-related risks. Roxadustat is a medication that can significantly impact anemic patients through a different mechanism of inhibiting Hypoxia Inducible Factor- Prolyl Hydroxylase enzyme (HIF-PHD).

A recent meta-analysis by Zheng et al. in 2021 looked at multiple randomized controlled trials comparing the efficacy of Roxadustat to ESAs in anemic CKD patients up till early 2021. A total of 9 trials were analyzed, totaling over 2700 patients. A statistically significant increase in hemoglobin level of 0.9 g/dL was observed among the CKD patients receiving Roxadustat compared to those receiving ESAs. [20] Other authors had similar conclusions after performing an independent systematic review and meta-analysis [21, 22].

Other beneficial effects of hif pathway activation

1. Anti-depressant: A study demonstrated that FG-4592 effectively reverses depression-like behavior and memory impairment caused by chronic mild unpredictable stress. Brain-derived neurotrophic factor (BDNF) and postsynaptic density protein 95 (PSD95) expression increased when the HIF signaling pathway was activated, eventually leading to increased hippocampal neurogenesis and synaptic plasticity that elicit anti-depressant effects. The observed beneficial effects are probably attributable to activation of the HIF-1 pathway and increased expression of memory-related proteins, such as BDNF, PSD95, and Homer1 [23].

2. Retinopathy of Prematurity: A study looking at the transcriptome of mice cured of oxygen-induced retinopathy (ROP model) by Roxadustat determined that direct HIF stabilization in the retina with induction of aerobic glycolysis and indirect stabilization of HIF-1 in the liver with increased serum angiokines conferred protection from ROP. This gene expression analysis was determined by RNA sequencing [24].

3. Hyperoxia-Induced Lung Injury: Oxygen therapy used for premature infants with Respiratory Distress Syndrome (RDS) often leads to lung injury such as bronchopulmonary dysplasia caused by inhibited angiogenesis. The complete mechanism of this lung injury is not entirely understood, but it is accepted that HIF plays a role. A study explored the effects of Roxadustat on pulmonary angiogenesis in newborn mice. It was concluded that Roxadustat increased pulmonary angiogenesis in the hyperoxia-exposed group; it was hypothesized that the stabilization of HIF-1α by Roxadustat led to upregulation of proangiogenic transcription factors [25].

4. Organ transplantation: A study looking at the effect of a single dose of HIF-PHI and FG-449 given to the donor animal and graft function in a Fisher-Lewis rat model of allogenic kidney transplantation showed promising results. It was found that the induction of HIF target genes by the accumulation of HIF decreased Acute Kidney Injury (as measured by Creatinine On Day 10), decreased early mortality in the acute model (where recipients were followed for up to 10 days), and improved long term survival of the recipient animals in the chronic model (where recipients were followed up to 24 weeks) [26].

5. SARS-CoV2: A recent study exploring the role of HIF signaling in the SARS-CoV2 infection pathway highlighted how HIF-PHDs like Roxadustat could hinder the infection process. Through both in vivo and in vitro models, the study demonstrated that Roxadustat reduced ACE2 expression, a key surface receptor involved in the viral entry of SARS-CoV2, through a HIF-1α pathway [27].

Implications in anesthesia

The field of modern Anesthesiology rests upon different ways to prevent oxygen depletion in the cells of essential organs by ensuring adequate oxygenation and preventing hypoxia. Intubation and ventilation have greatly improved the safety of surgery. On the other hand, inducible ischemia has also been found to improve the future capability of the organs to resist damage from hypoxia [28].

HIFs are thought to be the reason for remote ischemic preconditioning, where treatment of a limb for short periods of ischemia results in attenuated myocardial infarct sizes. Randomized controlled studies evaluating morbidity and survival outcomes in coronary artery bypass surgery showed no clinically significant difference with remote ischemic preconditioning compared to a control group in cardiac surgery [29,30] In a randomized, single-blind, and controlled pilot study done on 120 high-risk patients, significantly less acute kidney injury outcome was noted after cardiac surgery with an absolute risk reduction of 0.27 and a significantly reduced relative risk of 0.43 due to preconditioning [31] The Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent) study showed that preconditioning reduced procedural symptoms, ST-segment changes, and cardiac troponin I release after elective PCI with a reduction in Major Adverse Cardiac and Cerebral Events (MACCE) rate at six months. They later confirmed that MACCE numbers were lower than the control group even after six months. Further interdisciplinary studies are required to look at the use of Roxadustat in CKD patients undergoing surgical procedures and to compare them to ESAs. In the future, once the safety of Roxadustat has been evaluated more thoroughly in the general CKD population, it should be expanded to Kidney transplant patients, given the preexisting positive evidence.

Adverse events and concerns

Multiple Phase 3 safety trials in Chinese and Japanese CKD patients showed that Roxadustat was well tolerated. The most common side effects were nasopharyngitis, back pain, diarrhea, and vomiting.

In a Phase 2 study in dialysis-dependent patients who were earlier on epoetin alfa (NCT01147666), cardiovascular safety events such as death, myocardial infarction, stroke, and heart failure requiring hospitalization, unstable angina requiring hospitalization or thromboembolism in patients receiving 19 weeks' therapy occurred in 12% of the Roxadustat group compared with 17% of epoetin alfa group. According to the study team, three deaths in the Roxadustat group were not considered to be treatment-related. In another Phase 2 Study from China (NCT01596855), treatment-emergent adverse events were seen in 43% (32/74) of Roxadustat and 18% (4/22) of epoetin alfa recipients. The most common ones included decreased appetite and muscle spasms. Other Phase2b studies in different patient groups such as newly initiated dialysis (NCT01414075) and non-dialysis dependent CKD, had similar findings (NCT00761657). According to the studies, hyperkalemia and hypertension requiring a change in anti-hypertensive medications were other common adverse effects.

One case of severe pulmonary hypertension was reported in a trial patient on Roxadustat for two years. After a Pulmonary Embolus was ruled out, a right heart catheterization confirmed precapillary irreversible Pulmonary Arterial Hypertension (PAH) with a mean PAP of 48mmHg, a PVR of 12.3 WU, and normal LV function. It was proposed that stabilizing the oxygen-dependent subunit HIF2 Alpha upregulates Notch3 and Transforming Growth Factor Beta, which, in turn, causes a conversion of pericytes into myofibroblasts vascular smooth muscle cells associated with remodeling in PAH. There was an increase in endothelial to mesenchymal transition with upregulation of SNAI1/2 genes in the lung [32] The transcription proteins coded by these genes have been thought to contribute to epithelial/endothelial to mesenchymal transition.[31] The authors of the case report proposed that although they could not comment on causality, this gene upregulation might have contributed to pulmonary hypertension in their patient.

We found one case report of rhabdomyolysis in an anemic CKD stage 5 54-year-old male patient after being administered

Roxadustat. The patient, in this case, was switched to Roxadustat from his EPO 12000 u once-weekly subcutaneous injection since his hemoglobin levels did not increase above 9.6 g/dL. Within one month, the patient's hemoglobin increased to 11.3 g/dL. However, two months afterward, the patient had myalgias and lower extremity weakness along with high levels of serum myoglobin and creatine kinase. These rhabdomyolysis symptoms improved after discontinuing the Roxadustat, but his hemoglobin levels again decreased [33].

We found another report that showed Roxadustat might have an impact on TSH. In this case, an 85-year-old Male patient with Hypothyroidism due to chronic thyroiditis well controlled on levothyroxine and anemia secondary to CKD on a regular hemodialysis regimen was switched from darbepoetin alpha (40 ug/week) to Roxadustat (100mg 3 times per week). One month after making this switch, the patient's TSH decreased from 2.78 to 0.038 mIU/mL, free T3 decreased from 2.5 to 2.0 ng/dL, and free T4 decreased from 1 to 0.7 despite being on the same levothyroxine dose. TSH and thyroid hormone levels returned to the normal range after stopping Roxadustat. One proposed reason for this rapid suppression of TSH is that Roxadustat has structural similarities to the T3 hormone, resulting in negative feedback on the pituitary gland [34].

Another major concern is the association of HIF upregulation with certain high-grade tumors. Increased levels of HIF-α have been shown to extend a poorer prognosis in certain solid cancers. The effect of HIF-PHIs on the incidence and prognosis of malignancies needs to be further studied over a longer duration.

Conclusion

Roxadustat, an oral HIF PHI, was developed primarily for the treatment of CKD-associated anemia in both dialysis-dependent and non-dialysis-dependent adults. However, based on its mechanism of action involving inhibition of HIF prolyl hydroxylases and thus stabilization of HIF, its use is being explored in a broader context across other medical subspecialties. Despite promising data in studies, including Phase 3 trials regarding its efficacy and positive effects, significant safety concerns, including thromboembolic events and pulmonary hypertension associated with its use at current recommended clinical doses, have been raised. Thus, while this medication has been approved for CKD anemia in Japan, Chile, China and South Korea, US FDA approval was withheld in 2021, citing the need for an additional clinical study to determine if its benefits outweigh its risks. For anesthesiologists and intensivists, the knowledge and maintenance of oxygen homeostasis and adaptations that occur in response to hypoxia is crucial to patient care. It is crucial to stay abreast and garner more information regarding the safety and efficacy of HIF PHIs like Roxadustat, not only in the prevention of anemia and its consequent adverse effects in CKD patients presenting for surgery but also to determine and potentially explore an even broader scope of its applicability in oxygen homeostasis in perioperative and critical care management of patients.

Details of author contributions

The authors' responsibilities were as follows: TS conceived of the presented article. TS and SJK contributed to the design and wrote the initial drafts of the manuscript. PD, OD, and TS edited and contributed to the final drafts of the manuscript, and all authors read and approved the final manuscript.

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