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Roxadustat for Patients with Posttransplant Anemia: A Narrative Review

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Keywords
Roxadustat · Hypoxia-inducible factor · Renal transplantation · Anemia

Abstract
Background: Hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) are novel oral agents used for renal anemia treatment. Roxadustat, a first-in-class HIF-PHI used for treating anemia in chronic kidney disease patients, has been approved in China, Japan, South Korea, Chile, and Europe. Roxadustat is involved in HIF degradation, which can stimulate endogenous erythropoietin (EPO) production and improve iron utilization. Besides, roxadustat can promote dietary iron uptake and transport. In comparison with traditional erythropoiesis-stimulating agent treatment, it might reduce cardiovascular risk and mortality as it causes only a slight increase in the plasma EPO level. Phase II and III clinical trial reports have shown that roxadustat is effective for treating chronic kidney disease patients. The role of roxadustat in kidney transplant recipients (KTRs) needs to be examined as patients with chronic kidney disease are different from those receiving renal transplants. ***Summary:*** Clinical trials have demonstrated that roxadustat effectively increases and maintains hemoglobin levels in patients with dialysis-dependent and non-dialysis-dependent chronic kidney disease by stimulating endogenous EPO production and optimizing iron utilization. Roxadustat has recently been used effectively to treat patients with EPO-resistant anemia. It has also been used for treating patients with posttransplant anemia (PTA), which is a prognostic factor for mortality in KTRs with an iron deficiency and impaired glomerular filtration rate. Here, we examined the findings of four studies in a narrative review and discussed our perspectives regarding this field of study. ***Key Messages:*** Roxadustat significantly improves hemoglobin levels without affecting renal function in KTRs with PTA. It also enhances iron utilization by decreasing ferritin and hepcidin levels and increasing total iron binding capacity, transferrin, and serum iron levels. Roxadustat ameliorates anemia and inflammation, and might have reno-protective effects in KTRs.

Introduction

Posttransplant anemia (PTA) is defined as a hemoglobin (Hb) level <13 mg/dL in men and <12 mg/dL in women, and its prevalence varies from 20% to 70% [1–3]. Patients can be classified into two types based on the time of onset those with early PTA (within the first 6 months)

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and those with late PTA (>6 months posttransplant) [4–6]. Factors associated with PTA differ between the 2 types of patients. The occurrence of early PTA is reportedly associated with intraoperative factors, types of donors, and infections [2, 7]. In contrast, the occurrence of late PTA is associated with chronic allograft nephropathy, immunosuppression, inhibitors of the renin-angiotensin system, and second kidney transplants [2, 8]. PTA is significantly associated with cardiovascular disorders, graft loss, and mortality [9–11].

Erythropoiesis-stimulating agents (ESAs) have traditionally been used with iron supplements for treating PTA. The widespread use of ESAs reduces the risk of blood transfusion. Still, some studies found that treating patients with early PTA using ESAs resulted in no significant differences in postoperative Hb levels, kidney transplant functions [12], and renal prognosis [13]. ESAs might increase the risk of cardiovascular events, cerebrovascular events, and tumors. Moreover, long-term or high-dose ESA injections can induce the production of anti-erythropoietin (EPO) antibodies, which could result in pure red cell aplasia [14]. In addition, some patients may not respond to treatment due to the development of resistance to EPO [15].

Hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) are novel therapeutic agents used for anemia treatment in chronic kidney disease (CKD) patients. They stimulate the transcription of the *EPO* gene, which results in the production of endogenous EPO [16, 17]. In this review, we examined data from recently published clinical studies that investigated the use of roxadustat in PTA patients and discussed our perspectives regarding this field of study.

HIF, HIF-PHIs, and Roxadustat

Hypoxia-inducible factor (HIF) is a heterodimeric complex that consists of a hypoxia-regulated α subunit (HIF-1α, -2α, and -3α) bound to an oxygen-independent β subunit [18]. Under normoxic conditions, HIF-α is hydroxylated at specific proline residues by HIF-prolyl hydroxylase (HIF-PH). The ubiquitination of hydroxylated HIF-α by the von Hippel-Lindau-E3 ubiquitin ligase complex results in its proteasomal degradation [19]. Because HIF-PH requires molecular oxygen to hydroxylate HIF-α, hypoxia inhibits the hydroxylation and degradation of HIF-α. Intracellular HIF-α accumulation results in the formation of transcriptionally active HIF heterodimers with the β subunit that binds to the hypoxia-response element and induces the transcription of target genes [16]. HIFs control the genes involved in erythropoiesis and iron metabolism [19]. HIF-PHIs are novel therapeutic agents used to treat anemia in CKD patients. They are involved in HIF degradation, which can stimulate endogenous EPO production and improve iron utilization. Six compounds, namely roxadustat, daprodustat, vadadustat, enarodustat, molidustat, and desidustat, have been developed. These compounds competitively inhibit the binding of 2-oxoglutarate, an essential co-substrate of HIF-PH enzymes.

Roxadustat is a novel oral HIF-PHI. The results of phase II and III clinical trials showed increased levels of EPO and Hb, decreased levels of hepcidin, and helped reduce the rate of red blood cell transfusion in dialysis-dependent and non-dialysis-dependent CKD patients [20–22]. The presence of immunosuppressant agents and transplant-related medications, altered inflammatory milieu, and history of prolonged maintenance dialysis therapy in most KTRs differ from those of CKD patients [23]. Hence, it is not reasonable to extrapolate the efficacy and safety of the use of roxadustat for the treatment of KTRs according to CKD. It is necessary to evaluate the efficacy and safety of roxadustat during the treatment of KTRs with PTA. However, there are only a few studies on the use of roxadustat for the treatment of PTA.

Case Reports on the Use of Roxadustat for PTA Treatment

Till date, four case series have reported on PTA treatment with Roxadustat (Table 1). Naganuma et al. [24] reported on five KTRs for whom PTA was treated with roxadustat. These patients, treated as outpatients, received 150 or 250 mg of "epoetin beta pegol," an ESA, once every 3 months. Subsequently, they were treated with 100 mg roxadustat three times a week. Hb levels increased in all cases at 1 month, and ferritin and transferrin saturation levels decreased at the initial stage of roxadustat conversion. During 9 months, Hb levels tended to increase in patients administered iron orally. There was no notable effect on graft functions and complications. Li et al. [3] reported on 21 KTRs with PTA who were treated using roxadustat. The report demonstrates the same tendency of Hb levels to remain significantly higher after 10 weeks of roxadustat treatment. Therapeutic effects were observed at 2–4 weeks. In the study, patients were divided into EPO-nonresistant and EPO-resistant subgroups. In the EPO-resistant subgroup, 63.6% of patients exhibited the standard level of Hb, and 72.7% achieved a treatment response at 10 weeks, while 40% and 70% of the patients from the EPO-nonresistant group exhibited the standard Hb level and treatment response, respectively. These results demonstrate that roxadustat exhibits an excellent therapeutic effect in EPO-resistant and nonresistant patients. There was no significant change in

Table 1. Clinical characteristics of the four studies

Study	*N*	Age, years	Sex (male), %	Time after KT, m	Early (PTA/ late PTA)	Hb baseline	eGFR, mL/ min/1.73 m^2/ creatine, mg/dL	Ferritin	CRP	Previous ESA use or drug combination	Starting dose	The time of follow-up	Target Hb, g/dL	Adverse events	Summary
Naganuma et al. [24]	5	45.2±11.36	40	157.68±46.54	0/5	10.98±1.67	0.96–1.82 (Cr)	NR	0.02–0.26	Yes	100 mg, TIW	9 m	NR	NR	Conversion from ESA to roxadustat was effective in the treatment of five PTAs. Hb levels were increased, ferritin and TSAT levels decreased in the initial stage
Li et al. [3]	21	45.2±11.8	47.6	6.0±8.4	11/10	6.9±2.2	28.8±16.1 (eGFR)	333.5±322.4 μg/L	>8, 28.6%	Yes	70–120 mg, TIW	10 w	10–12	Fatigue (1)	Hb level was higher than baseline after 10 weeks of roxadustat treatment, and the therapeutic effect was shown from weeks 2–4. More than half part PTA reached standard Hb level and exhibited a response to treatment
Miki et al. [25]	31	55.1±10.9	35.5	98.4±117.6	8/23	9.8±0.86	1.78±0.72 (83.3±15.1 (eGFR)	128±105.44, ng/mL	NR	Yes	20–100 mg, TIW	20 w	11–13	Decreased Hb (3) Nausea (2) Myocardial Infarction (1)	Hb levels were increased at 4–12 weeks during the 25 weeks of roxadustat treatment. Ferritin and LDL cholesterol levels were reduced
Li et al. [26]	22	36.1±9.3	45.2	15.00±4.33, day	22/0	79.95±11.02	66.18±15.39 (eGFR)	128.42±90.17, ng/mL	NR	Iron	70 mg (body weight 40–60 kg) or 100 mg (body weight ≥60 kg), TIW	1 y	10–11.5	NR	Hb levels at month 3, the average change in Hb levels, TIBC, and levels of transferrin were higher in the roxadustat group. The levels of ferritin, hepcidin, and iFGF23 were lower

N, number; w, weeks; m, month; y, year; KT, kidney transplantation; PTA, posttransplant anemia; NR, no record; TIW, three times a week; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; TSAT, transferrin saturation; TIBC, total iron binding capacity; iFGF23, intact FGF23.

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ferritin levels in all KTRs after 10 weeks of roxadustat treatment. Miki et al. [25] conducted a study involving 31 KTRs. The average Hb level in 25 patients (6 patients dropped out) increased from 9.8 ± 0.78 g/dL before roxadustat administration to 12.1 ± 1.44 g/dL (p <0.001) after 12 weeks of treatment with roxadustat. The ferritin level in patients decreased from 107.6 ± 84.95 ng/mL before roxadustat administration to 51.7 ± 44.04 ng/mL (p = 0.022) after 8 weeks of treatment. The mean low-density lipoprotein (LDL) cholesterol level decreased from 114.1 ± 31.67 mg/dL before roxadustat administration to 78.7 ± 18.26 mg/dL (p = 0.0012) after 8 weeks of treatment. Complications after roxadustat administration included reduced Hb levels (3 patients), gastrointestinal symptoms (2 patients), and myocardial infarction (1 patient). Li et al. [26] conducted a retrospective study. A total of 57 KTRs were classified into three groups; 22, 13, and 22 cases were grouped into the roxadustat, ESA, and untreated groups, respectively. The findings of the study not only showed that the Hb level was increased in the roxadustat group but also showed that Hb levels at month 3 posttransplantation (128.00 ± 19.62 vs. 118.59 ± 11.60 g/L, p = 0.048) and the average change in Hb levels from week 2 to month 3 (48.05 ± 22.53 vs. 31.45 ± 12.96 g/L, p = 0.005) were significantly higher in the roxadustat group than in the untreated group. However, these indices were not significantly different between the roxadustat and ESA groups. Roxadustat can improve iron utilization by increasing the total iron binding capacity (TIBC) and transferrin levels and decreasing ferritin, hepcidin, and intact FGF23 (iFGF23) levels. The three groups exhibited no significant differences in creatinine and estimated glomerular filtration rate levels. No complications were reported after roxadustat treatment.

In summary, roxadustat can significantly improve Hb levels without affecting renal function in KTRs with PTA. Roxadustat also enhances iron utilization as it decreases ferritin and hepcidin levels and increases TIBC, transferrin, and serum iron levels. Furthermore, long-term treatment significantly reduced LDL cholesterol levels, which in turn might reduce the risk of cardiovascular events in KTRs with PTA (Fig. 1).

Discussion

The Treatment of PTA in KTRs and Use of HIF-PHIs, a New Class of Medicines

PTA occurs commonly in KTRs. The leading cause of early PTA is iron deficiency, and that of late PTA is impaired glomerular filtration rate [6]. PTA has been identified as a risk factor for cardiovascular disease, allogeneic graft dysfunction and loss, and mortality [6, 11]. Renal anemia treatment includes the use of ESAs, such as recombinant human EPO (rhuEPO), supplementing hematopoietic materials (such as iron, folic acid, or vitamin B12), intravenous blood transfusion, and new medications, such as HIF-PHIs. HIF-PHIs can inhibit the degradation of HIF α-subunits, thereby resulting in the increased expression of HIF-regulated genes, including EPO-related genes, and iron uptake and transport-related genes. Notably, the HIF-PHI-induced stimulation of EPO production in the kidney and liver may result in other erythropoiesis-promoting effects in the bone marrow [27]. In comparison with traditional ESA treatment, the increase in plasma EPO level is lower with HIF-PHI treatment. Thus, HIF-PHIs might reduce cardiovascular risk and mortality [28, 29]. Apart from this, a previous report has shown that HIF-PHIs decrease hepcidin production and increase the transcription of genes that promote dietary iron uptake and transport [30].

Roxadustat in PTA: Clinical Trials, Adverse Events, Timing, and Dosing

Roxadustat, the first oral small-molecule HIF-PHI approved by the Chinese Food and Drug Administration, has been used in dialysis-dependent and non-dialysis-dependent patients with CKD. A previous study showed that the effects of treatment with roxadustat were superior to those of traditional treatments, especially in patients exhibiting inflammation and iron utilization disorders [31]. Considering the efficacy of roxadustat, it has been administered to some KTRs. In all four studies, roxadustat significantly improved the Hb level without affecting renal function. Three studies [3, 24, 25] examined the efficacy and safety of roxadustat alone, and one [26] compared the efficacy of roxadustat with that of ESAs. The results showed that the therapeutic effect of roxadustat on early PTA at month 3 was no less than that of rhuEPO, and both roxadustat and rhuEPO could improve the rate at which Hb levels were restored. Roxadustat improved iron utilization by decreasing ferritin and hepcidin levels and increasing TIBC, transferrin, and serum iron levels.

The adverse events in the four trials include fatigue, decreased Hb levels, nausea, and myocardial infarction. The patient with myocardial infarction was 65 years old and consumed statins orally for hyperlipidemia. Her LDL cholesterol level of 100 mg/dL was within the recommended range. The Hb level increased from 9.8 g/dL to 14.2 g/dL at 16 weeks after roxadustat administration. Her serum iron level was 68 mg/dL and decreased to 13 mg/mL at 16 weeks, as oral iron supplementation was interrupted owing to severe gastrointestinal symptoms. A meta-analysis shows that the

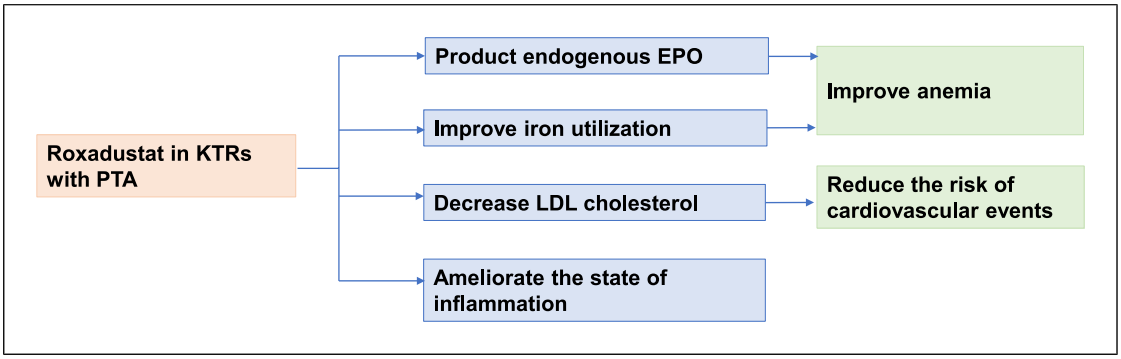

Fig. 1. Benefits of roxadustat in KTRs with PTA.

incidence of severe adverse events was significantly different between roxadustat and placebos or ESAs. The incidence of serious adverse events (infections, death, and renal, cardiac, vascular, and blood and lymphatic disorders) was especially higher in the roxadustat group than in the ESA group in dialysis-dependent patients [32]. In a pooled phase III analysis of efficacy and cardiovascular safety in CKD patients, roxadustat improved Hb levels in a manner similar to that observed for ESAs, while showing comparable cardiovascular and overall safety for anemic patients with dialysis-dependent CKD [33]. The number of adverse events associated with roxadustat was no higher than that of ESAs, but some severe adverse events should be a cause for concern.

The timing and dosing of roxadustat are very important in clinical settings. The dose administered three times per week during the start of four trials was between 20 mg and 100 mg. A dose of 70 mg (body weight between 40 and 60 kg), 100 mg (body weight ≥60 kg), or 120 mg (body weight ≥80 kg) of roxadustat was administered to CKD patients 3 times per week. It is recommended to start with small doses of roxadustat, especially in patients with low body weight. Roxadustat treatment begins to show effectiveness in 2–4 weeks, during which Hb levels increase significantly. Excessive Hb levels can lead to increased mortality and a high risk of cardiovascular events in KTRs and CKD patients [28, 34]. As iron availability increases and ferritin levels decrease, iron supplementation is recommended with roxadustat treatment.

The Possible Mechanism Underlying the Treatment of PTA with Roxadustat

The role of HIFs in ischemia-reperfusion injury (IRI) has been demonstrated in previous studies. In the transplanted kidney, IRI is one of the main factors adversely affecting the success of kidney transplantation [35]. Moreover, IRI generates reactive oxygen radicals and propagates a cascade of pro-inflammatory cellular events that are related to early PTA. Previous studies have shown that HIF-1α accumulation protects against acute tubular necrosis and is important to protect against ischemic kidney injury during ischemia and reperfusion [36, 37]. Bernhardt et al. [38] showed that the pretreatment of organ donors with FG-4497, which is a HIF-PHI, resulted in HIF accumulation and HIF target gene induction. It reduced the extent of acute renal injury and early mortality in acute models and improved the long-term survival of recipient animals in a model of chronic disease [38]. The above studies suggest that roxadustat might play a role in the treatment of early PTA via the reduction of IRI, and this needs to be explored further.

It is well known that there are differences in the effects of roxadustat between CKD patients and KTRs. KTRs always exhibit a state of low-level inflammation, even after receiving immunosuppressant treatment [39]. Studies have confirmed that HIF has an anti-inflammatory effect and promotes the regression of inflammation [40, 41]. Roxadustat can significantly reduce tumor necrosis factor-α, interleukin-1β, and interleukin-6 levels in a cisplatin-induced model of renal injury [42]. Therefore, roxadustat not only improves anemia but might ameliorate the state of inflammation in KTRs.

Limitations and Outlook

Certain limitations are associated with these reports. First, all the studies were not randomized controlled trials. Second, the number of patients was limited, and the follow-up duration was short. Third, the benefits and side effects of the use of roxadustat for the treatment of PTA have not been thoroughly investigated. Therefore, randomized controlled trials must be performed with larger sample sizes and longer follow-up durations. Some clinical trials are already ongoing (ChiCTR2200063657, ChiCTR2200057485).

The differences in dose, initiation, and time of administration between patients with early and late PTA receiving roxadustat treatment can be compared further. In conclusion, roxadustat is a promising drug, and its use against PTA needs to be explored further.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

X.T., F.L., and Q.L. wrote the manuscript; J.M. revised the manuscript.

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