



Beneficial effect of roxadustat on early posttransplant anemia and iron utilization in kidney transplant recipients: a retrospective comparative cohort study

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Background: Although posttransplant anemia (PTA) is a common complication after kidney transplant, it has not been thoroughly evaluated for appropriate treatment. Roxadustat can stimulate erythropoiesis by increasing erythropoietin (EPO) production and improving the utilization of iron. However, there are currently a few case reports describing its effect on PTA in kidney transplant recipients (KTRs). Our purpose was to evaluate the efficacy and safety of roxadustat in KTRs with PTA.

Methods: In this retrospective study, KTRs with early PTA were divided into a roxadustat group, erythropoiesis-stimulating agent (ESA) group, and untreated group (neither roxadustat nor ESA) according to the treatment prescribed by their physicians. We compared the levels of hemoglobin (Hb), creatinine, lipids, hepcidin, intact fibroblast growth factor 23 (iFGF23) and iron-related indices, at baseline and different time points posttransplant. Outcome was assessed at both month 3 and month 12 posttransplant. Adverse events during the treatment course were also recorded.

Results: A total of 57 KTRs were included (n=22 roxadustat group, n=13 ESA group, n=22 untreated group). There was no difference in age, sex, body mass index, dialysis method and duration, donor type among three groups at baseline. The mean Hb levels at month 3 posttransplant (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) in the roxadustat group were significantly higher than those in the untreated group. However, there was no significant difference in the above indices between the roxadustat and ESA groups. At month 3, the total iron binding capacity (TIBC) and levels of transferrin were significantly higher while levels of ferritin, hepcidin and iFGF23 were significantly lower in the roxadustat group than in other groups (P<0.05). No significant difference was found in creatinine or estimated glomerular filtration rate (eGFR) levels among the three groups at month 3. During the follow-up, no adverse events related to roxadustat were reported.

Conclusions: Administration of roxadustat in KTRs with early PTA could elevate Hb levels effectively and safely by enhancing endogenous EPO production and improving iron utilization. Further randomized studies with larger sample size are necessary to verify our results.

Keywords: Anemia; erythropoiesis-stimulating agents (ESAs); kidney transplant; roxadustat

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Introduction

After kidney transplantation, renal anemia caused by chronic renal failure may be temporarily aggravated by surgical blood loss, but hemoglobin (Hb) is expected to return to normal level with gradual improvement of the graft kidney's function (1). However, almost 90% of patients have reported anemia within the first month posttransplant, with the prevalence decreasing to 10–40% at 1 year despite normal graft function (2-4). Posttransplant anemia (PTA) can affect the prognosis of kidney transplant recipients (KTRs) because PTA is closely associated with increased all-cause mortality, graft failure, cardiovascular disease (congestive heart failure, left ventricular hypertrophy), decreased glomerular filtration rate (GFR), chronic fatigue and decreased exercise and cognitive ability (5,6).

In 2000, the American Transplantation Society defined PTA in adults and children >15 years old as Hb concentration <130 g/L in men and Hb <120 g/L in women (7). General risk factors associated with PTA include female sex, age, allograft dysfunction, use of renin-angiotensin system inhibitors (RASIs), use of mycophenolate mofetil (MMF), iron deficiency, folic acid, and vitamin B12 deficiency, erythropoietin (EPO) resistance, use of antiviral drugs and parvovirus B19 virus infection (3,8,9). Most researchers

suggested distinguishing early PTA from late PTA by the time point of 6 months posttransplant (10). The most common cause for early PTA and late PTA is iron deficiency and allograft dysfunction, respectively (11).

The optimum target Hb level for KTRs with stable graft function is unknown. Observational studies of KTRs given EPO have suggested that the mortality rate may be increased with Hb levels >125 g/L (12), which is consistent with studies in the chronic kidney disease (CKD) population. In the CHOIR and TREAT trials, the normalization of Hb in CKD patients, other than KTRs, was achieved through recombinant human (rhu) EPO treatment, but the risk of cardiovascular events was increased and progressive renal failure was not delayed (13,14). However, one prospective study has shown that Hb \geq 130 g/L can reduce the progression of chronic allograft nephropathy in KTRs (15). At present, it is unclear why the complete recovery of the Hb level to normal is helpful for protecting the transplanted kidney but not the native kidneys.

The main treatment of renal anemia includes the use of erythropoiesis-stimulating agents (ESAs), supplementing hematopoietic raw materials (e.g., iron, folic acid, or vitamin B12), intravenous blood transfusion, and the novel anti-anemia medication, roxadustat. ESAs such as rhuEPO and iron therapy are the cornerstones of renal anemia therapy, but their application in PTA has been limited, with only 5–30% of KTRs with anemia using ESAs (6,16). Long-term or high-dose injection of ESAs may lead to increased blood pressure, risk of thrombosis, stroke and tumor recurrence (17), and may induce the production of anti-EPO antibody and cause pure red cell aplasia (PRCA) (18). Moreover, inflammation or infection will interfere with the efficacy of both ESAs and iron supplementation (19).

Roxadustat is the first oral small molecule hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) in the world. It suppresses the activity of the prolyl hydroxylase domain protein under normoxia. Stable HIF- α translocates to the cell nucleus and forms a functional heterodimer with HIF- β , then combines with specific DNA sequences or hypoxia response elements (HREs) (20) to recruit transcriptional coactivators, which induces and activates the expression of target genes. It

Highlight box

Key findings

- Administration of roxadustat in KTRs with early PTA can effectively and safely elevate Hb levels.

What is known and what is new?

- PTA is a common complication yet underdiagnosed and undertreated after kidney transplant. HIF-PHIs has been verified as an effective drug for renal anemia in CKD patients without transplant history.
- Our findings demonstrated that roxadustat can increase Hb levels effectively and safely by enhancing endogenous EPO production moderately and improving iron utilization in KTRs with early PTA.

What is the implication, and what should change now?

- The application of roxadustat in KTRs with PTA was safe, and early initiation of roxadustat for early PTA could accelerate the recovery of Hb. Hence, early diagnosis, cause screening and timely treatment of early PTA is necessary for improving the prognosis of KTRs.

is a key transcriptional regulator of EPO induction and binds to human EPO gene enhancers required for EPO transcriptional activation (20–22). HIF-PHIs can also improve the absorption and utilization of iron by inhibiting the expression of hepcidin (23). Phase III clinical trials of roxadustat were first completed in China and it has been approved for marketing in China since 2018 (24,25). HIF-PHIs have emerged as an effective strategy for the treatment of anemia in patients with CKD, and a number of clinical studies of roxadustat in the CKD population have suggested it is superior to traditional EPO for correcting renal anemia, especially in patients with an inflammatory background and iron utilization disorder (24,26–28). Roxadustat may also have some advantages in slowing down the progress of kidney disease by relieving hypoxic-ischemic injury, and it has fewer adverse effects such as hypertension (29–31). However, it should be noted that the current phase III clinical study included dialysis-dependent and non-dialysis-dependent CKD patients, excluding KTRs. In view of the pathophysiological differences between KTRs and ordinary CKD patients, studies are needed to evaluate the efficacy and safety of roxadustat in KTRs with PTA. The current published studies regarding the therapeutic effect of roxadustat on KTRs with PTA were all case reports (32–34), which showed ideal effectiveness but lacked in the comparison with rhuEPO and the quantification of iron-related indices.

To date, there is no consensus on the timing and course of PTA intervention, and very few studies on the application of roxadustat in patients with anemia after renal transplantation. In this study, we focused on the application of roxadustat for early PTA to evaluate its efficacy and safety in KTRs. We present the following article in accordance with the STROBE reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5897/rc>).

Methods

Description of cohort

In this retrospective comparative cohort study, KTRs diagnosed with early-stage PTA were included. We defined early-stage PTA as anemia (Hb concentration <130 g/L in men, <120 g/L in women) occurring within 6 months after renal transplantation as described previously (10). Anemia was graded as mild (Hb level between 90 and 129 g/L in men and between 90 and 119 g/L in women), moderate (Hb level between 60 and 89 g/L for both sexes),

and severe (Hb level <60 g/L for both sexes) (35). Other inclusion criteria included age between 18 and 65 years, and first kidney transplantation and follow-up at West China Hospital. The exclusion criteria included acute rejection and infection within 4 weeks prior to qualification for study, ABO incompatibility transplantation, history of malignancy, history of auto-immune disease, history of delayed graft function, other types of anemia such as megaloblastic anemia, hemorrhagic anemia, thalassemia, aplastic anemia, or anemia caused by other systemic disease. We administered basiliximab intravenously as induction immunosuppressive therapy. Methylprednisolone at 500 mg/day was administered intravenously on the operation day and the following 2 days after transplantation. Prednisolone was then administered orally and tapered rapidly from 1 mg/kg/day to 5–10 mg/day within 7 days for long-term maintenance. Standard triple maintenance immunosuppressive therapy consisting of tacrolimus (Tac), MMF, and corticosteroids was administered to the KTRs. The dosage of Tac and MMF were adjusted to reach a stable plasma concentration between 2 and 4 weeks after transplantation. The enrolled KTRs were then classified into three groups (roxadustat group, ESA group, and untreated group (neither roxadustat nor ESA) according to the treatment prescribed by their physicians. When making the decision, the clinicians would consider the drug accessibility, patient's financial condition and preference on dosage form. Patients with higher Hb level may be more likely assigned to the untreated group. 20 adults without kidney transplantation were included in a healthy control group. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of West China Hospital, Sichuan University (Chengdu, China) (No. 2022219). Individual consent for this retrospective analysis was waived.

Treatment for PTA

The target Hb level in our study was 100–115 g/L. In the roxadustat group, the starting dose was 70 mg (body weight between 40 and 60 kg) or 100 mg (body weight \geq 60 kg) three times per week. In the ESA group rhuEPO at 75–100 IU/kg was administered once weekly initially. The doses of roxadustat and rhuEPO were thereafter adjusted by clinicians according to the changes in Hb levels and the drug instructions. In the untreated group, we monitored Hb levels and adopted expectant therapy. For KTRs with newly

occurred iron deficiency during the study, oral or intravenous iron supplementation was allowed in all three groups. Salvage blood transfusion was also allowed if Hb was <60 g/L. KTRs were seen in the transplant clinic weekly for the first month posttransplant, then every 2 weeks for next 2 months, then monthly for the half a year, and then every 3 months for the first year after transplantation.

Data collection and measurements

All patients were regularly followed for 1 year. Clinical information was obtained from electronic medical records, including demographics, historical data, transplantation details and medications. Routine examinations, including complete blood count, Hb, creatinine, EPO, ferritin, transferrin, total iron binding capacity (TIBC), and other parameters were measured in the central laboratory of West China Hospital using standard laboratory methods. Estimated GFR (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Fasting blood samples of KTRs were collected in the morning at week 2 and month 3 for measuring serum intact fibroblast growth factor 23 (iFGF23; Boster, Wuhan, China) and hepcidin (R&D system, USA) concentrations using enzyme-linked immunosorbent assay (ELISA) methods with available commercial kits.

Statistical analysis

The sample size was calculated using PASS 15.0 software. To detect a difference in Hb of 10 g/L at 3 months posttransplant in roxadustat group and untreated group with an estimated standard deviation (SD) in one of the groups of 10 g/L, a power of 80% ($\beta = 0.20$), and a statistical risk of 5% ($\alpha = 0.05$), a total of 34 KTRs (17 in each group) was required. Similarly, in order to detect the difference between ESA group and untreated group based on a ratio of 1:2, another 13 KTRs in ESA group were needed.

The data were analyzed using IBM SPSS Statistics 26.0 software. Normality test of continuous variables was performed with the Shapiro-Wilk test. Variables of normal distribution are displayed as mean \pm SD and were compared using independent samples *t*-test and analysis of variance (ANOVA). Asymmetric variables are reported as median (interquartile range) and comparisons were made using Mann-Whitney U test and Kruskal-Wallis test. Categorical variables were compared using the chi-square test or Fisher exact test. In the case of three quantitative samples,

ANOVA or Kruskal-Wallis would be used as appropriate. If adjustment for possible baseline incomparability is needed, ANOVA will be performed. A two-tailed P value <0.05 was considered statistically significant in all tests.

Results

Study population and treatment

Fifty-seven KTRs diagnosed with PTA who received their first kidney transplantation between June and December in 2020 at West China Hospital were retrospectively included in the study (*Table 1*). Among them, were 22 KTRs receiving roxadustat (roxadustat group), 13 KTRs receiving rhuEPO (ESA group) and the other 22 KTRs receiving neither roxadustat nor rhuEPO (untreated group). Both roxadustat and rhuEPO were initiated at around 2 weeks (15.00 ± 4.33 vs. 16.62 ± 4.35 days, $P > 0.05$) posttransplant and their treatment courses were similar [1.75 (1.00 – 3.00) vs. 2.00 (1.00 – 3.00) months, $P > 0.05$]. All KTRs received Tac, MMF and prednisone as maintenance immunosuppressive therapy after transplantation. There were no differences in the doses of MMF, the area under the curve (AUC) of mycophenolic acid (MPA), the doses of Tac or the mean trough Tac concentration among the three groups at month 3. No significant difference was observed in other treatment regimens such as iron supplement, treatment for secondary hyperparathyroidism (SHPT), or the use of angiotensin-receptor blockers and angiotensin-converting enzyme inhibitor among the three groups. None of the recipients in the three groups required intravenous blood transfusion.

Temporal changes in Hb levels and erythrocyte indices

The comparisons of laboratory parameters among the three groups at week 2 and month 3 after transplantation are shown in *Table 2*. Before administration of roxadustat, the levels of Hb were lower in the roxadustat group than in the untreated group (79.95 ± 11.02 vs. 86.59 ± 4.34 g/L, $P = 0.014$). However, at baseline all patients in the three groups were defined as having moderate anemia. The comparison of other red blood cell parameters including mean corpuscular volume (MCV), mean corpuscular Hb (MCH), mean corpuscular Hb concentration (MCHC) and red blood cell distribution width-coefficient of variation (RDW-CV) showed no difference among the three groups at baseline. At month 3, all the KTRs in the three groups had Hb levels significantly increased above baseline levels ($P < 0.05$). The

Table 1 Clinical characteristics of the three treatment groups of KTRs (n=57)

Characteristics	Roxadustat group (n=22)	Untreated group (n=22)	ESA group (n=13)	P value
Age (years)	36.05±9.27	33.05±10.27	37.08±12.57	0.585
Male sex	14 [64]	14 [64]	5 [38]	0.271
Body mass index (kg/m ²)	21.32±3.54	20.54±3.10	21.62±2.7	0.574
Dialysis time (months)	42 [12–69]	24 [12–36]	24 [12–36]	0.321
Dialysis method				0.354
Hemodialysis	19 [86]	22 [100]	12 [92]	
Peritoneal dialysis	2 [9]	0	1 [8]	
Non-dialysis	1 [5]	0	0	
HLA mismatch	4 [4–6]	4 [3–5]	4 [3–5]	0.198
Deceased donor	7 [32]	9 [41]	8 [62]	0.075
Immunosuppressive drugs at month 3				
Tac (mean daily dose, mg)	3.61±0.67	3.84±0.66	3.46±0.78	0.540
Tac (mean trough level, ng/mL)	6.51 [5.19–7.47]	6.49 [5.83–7.56]	6.50 [5.50–7.52]	0.646
Mycophenolate (mean daily dose, mg)	1,500 [1,312–1,500]	1,500 [1,062–1,500]	1,500 [1,000–1,500]	0.821
MPA AUC (mg·h/L)	66.30±22.57	61.48±22.30	62.09±17.15	0.770
Roxadustat or ESA treatment				
Initiation time post transplantation (days)	15.00±4.33	NA	16.62±4.35	NA
Duration (months)	1.75 [1.00–3.00]	NA	2.00 [1.00–3.00]	NA
Iron supplements	4 [18]	3 [14]	2 [15]	0.917
Duration of iron supplement (months)	1.44±0.52	1.17±0.29	1.25±0.35	0.282
SHPT treatment				
Calcitriol	2 [9]	1 [5]	1 [8]	1.000
Vitamin D	9 [41]	8 [36]	5 [38]	0.953
Cinacalcet	0	1 [5]	0	1.000
ARB and/or ACE inhibitor, n [%]	12 [55]	10 [45]	7 [54]	0.809

Normally distributed data presented as mean ± SD; non-normally distributed data presented as median [interquartile range]. The categorical variables were presented as n [%]. KTRs, kidney transplant recipients; ESA, erythropoiesis-stimulating agent; HLA, human leukocyte antigen; Tac, tacrolimus; MPA, mycophenolic acid; AUC, area under the curve; NA, not available; SHPT, secondary hyperparathyroidism; ARB, angiotensin-receptor blocker; ACE, angiotensin-converting enzyme; SD, standard deviation.

roxadustat group had significantly higher Hb levels than the untreated group (128.00±19.62 *vs.* 118.59±11.60 g/L, P=0.048). The mean change in Hb from week 2 to month 3 in the roxadustat group was significantly higher than in the untreated group (48.05±22.53 *vs.* 31.45±12.96 g/L, P=0.005) (Figure 1). However, no difference was found in HB level between the roxadustat and ESA groups at month 3. Anemia severity changed from week 2 to month 3 among the three

groups. At month 3, all three groups had significantly more KTRs with normal Hb levels compared with week 2. The rate of KTRs with normal Hb in the roxadustat (45%, n=10) and ESA (54%, n=7) groups was much higher than that in the untreated group (14%, n=3, P=0.010). All three groups had lower RDW levels compared with week 2, but no significant difference was observed in RDW levels among the three groups.

Table 2 Comparison of laboratory parameters among the three treatment groups at week 2 and month 3 (n=57)

Time	Parameters	Roxadustat group (n=22)	Untreated group (n=22)	ESA group (n=13)	P value
Week 2	Hb (g/L)	79.95±11.02	86.59±4.34 ^a	80.77±10.07	0.018*
	Anemia				0.570
	No anemia	0	0	0	
	Mild anemia	4 [18]	7 [32]	3 [23]	
	Moderate anemia	18 [82]	15 [68]	10 [77]	
	MCV (fL)	97.45 [91.35–102.05]	96.60 [95.18–100.85]	98.10 [95.30–101.10]	0.968
	MCH (pg)	31.20 [29.80–32.38]	31.10 [30.25–31.78]	30.50 [30.10–31.70]	0.565
	MCHC (g/L)	317.00 [301.25–328.00]	321.00 [308.25–323.75]	316.00 [307.00–319.00]	0.213
	RDW-CV (%)	14.40 [13.80–16.18]	14.30 [13.93–15.55]	14.50 [13.80–15.10]	0.928
	Creatinine (µmol/L)	134.00±46.37	128.27±48.36	139.15±48.50	0.811
	eGFR (mL/min/1.73 m ²)	59.50±19.45	66.21±25.83	54.62±23.47	0.339
	Cholesterol (mmol/L)	3.29±0.95	3.57±0.66	3.68±0.72	0.310
	Triglyceride (mmol/L)	1.86±1.11	1.71±0.81	1.42±0.69	0.389
	HDL-C (mmol/L)	1.00±0.28	1.13±0.24	1.16±0.29	0.146
	LDL-C (mmol/L)	1.58±0.60	1.77±0.45	1.94±0.69	0.163
	Pi (mmol/L)	1.11±0.51	0.95±0.51	1.10±0.63	0.584
	Ca (mmol/L)	2.31±0.12	2.30±0.11	2.32±0.14	0.865
	iFGF23 (pg/mL)	678.51 [177.02–1,295.00]	831.84 [647.56–1,079.25]	643.57 [403.09–1,801.27]	0.446
	Hepcidin (ng/mL)	32.13±18.82	31.65±19.75	31.19±22.53	0.991
	Serum iron (µmol/L)	8.52±2.95	8.23±2.39	8.31±2.56	0.934
Ferritin (ng/mL)	401.00 [258.00–510.50]	465.40 [352.45–514.00]	431.00 [269.00–611.00]	0.714	
Transferrin (g/L)	1.88±0.36	1.93±0.48	1.90±0.45	0.939	
TIBC (µmol/L)	36.77±5.14	36.40±8.27	39.7±9.05	0.535	
Normal transferrin	1 [5]	2 [9]	2 [15]	0.624	
Normal TIBC	2 [9]	3 [14]	2 [15]	0.883	
Month 3	Hb (g/L)	128.00±19.62 ^{#a}	118.05±11.60 [#]	121.46±14.12 [#]	0.114
	Anemia				0.010*
	No anemia	10 [45] ^{#a}	3 [14] [#]	7 [54] ^{#a}	
	Mild anemia	12 [55] ^{#a}	19 [86] [#]	5 [38] ^{#a}	
	Moderate anemia	0 [#]	0 [#]	1 [8] [#]	
	MCV (fL)	93.50 [90.90–95.90]	94.50 [89.85–97.33]	92.00 [90.80–94.90]	0.926
	MCH (pg)	30.15 [29.25–30.68] [#]	30.10 [28.63–31.28]	29.40 [28.90–31.10]	0.901
	MCHC (g/L)	321.50 [312.00–324.00]	319.00 [314.00–324.50]	313.00 [309.00–323.00]	0.519
	RDW-CV (%)	13.45 [12.83–14.10] [#]	13.40 [12.75–14.10] [#]	13.50 [13.00–14.10] [#]	0.669
	Creatinine (µmol/L)	118.00±35.67	110.82±25.02	118.85±25.27	0.630

Table 2 (continued)

Table 2 (continued)

Time	Parameters	Roxadustat group (n=22)	Untreated group (n=22)	ESA group (n=13)	P value
	eGFR (mL/min/1.73 m ²)	66.18±15.39	70.96±13.77	59.74±14.99 ^a	0.100
	Cholesterol (mmol/L)	4.44±1.01 [#]	4.55±0.74 [#]	4.41±1.01 [#]	0.885
	Triglyceride (mmol/L)	1.63±0.54	1.51±0.64	1.67±0.77	0.719
	HDL-C (mmol/L)	1.33±0.47 [#]	1.46±0.41 [#]	1.25±0.31	0.342
	LDL-C (mmol/L)	2.61±0.81 [#]	2.65±0.61 [#]	2.45±0.68	0.712
	Pi (mmol/L)	0.84±0.23 [#]	0.80±0.16	0.79±0.21 [#]	0.718
	Ca (mmol/L)	2.47±0.12 [#]	2.49±0.11 [#]	2.50±0.13 [#]	0.830
	iFGF23 (pg/mL)	31.34±27.20 ^{#a}	63.18±58.89 [#]	47.70±25.85 [#]	0.050
	Hepcidin (ng/mL)	13.26±8.71 ^{#ab}	22.23±14.28 [#]	21.30±14.54 [#]	0.047*
	Serum iron (μmol/L)	26.21±9.67 [#]	22.28±6.62 [#]	21.91±4.53 [#]	0.205
	Ferritin (ng/mL)	128.42±90.17 ^{#ab}	220.65±71.55 [#]	195.46±96.72 [#]	0.002*
	Transferrin (g/L)	2.77±0.57 ^{#ab}	2.35±0.61 [#]	2.32±0.43 [#]	0.027*
	TIBC (μmol/L)	55.15±10.08 ^{#ab}	41.89±8.71 [#]	47.44±10.95 [#]	0.000*
	Normal transferrin	12 [54] ^{#a}	5 [23]	3 [23]	0.051
	Normal TIBC	13 [59] ^{#a}	6 [27]	5 [38]	0.097

Normally distributed data presented as mean ± SD; non-normally distributed data presented as median [interquartile range]. The categorical variables were presented as n [%]. *P<0.05 compared among three groups; [#]P<0.05 compared with week 2; ^aP<0.05 compared with untreated group; ^bP<0.05 compared with ESA group. ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular Hb; MCHC, mean corpuscular Hb concentration; RDW-CV, red blood cell distribution width-coefficient of variation; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, high-density lipoprotein cholesterol; iFGF23, intact fibroblast growth factor 23; TIBC, total iron binding capacity; SD, standard deviation.

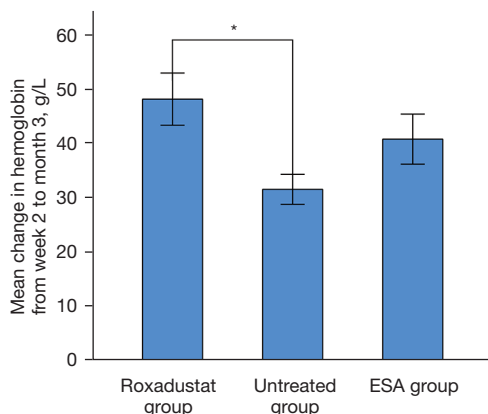


Figure 1 Mean change in Hb from week 2 to month 3. Error bars indicate standard errors. *P<0.05. ESA, erythropoiesis-stimulating agent; Hb, hemoglobin.

Mean [95% confidence interval (CI)] levels of Hb in the three groups during the 1-year follow-up are shown in *Figure 2*. At 1-year posttransplant, neither the mean change in Hb level from baseline nor the mean level of Hb was significantly different among the three groups.

Temporal changes in iron-related indices

The changes in iron metabolism parameters among three groups are shown in *Table 2*. The mean concentration of serum hepcidin in the healthy control (n=20) group with normal renal function was 17.95±14.10 ng/mL. At week 2, no significant difference was observed in serum hepcidin, serum iron, ferritin, and transferrin levels or TIBC among the three groups. At month 3, the levels of transferrin, and serum iron and the TIBC in three groups increased dramatically while the hepcidin and ferritin levels significantly decreased as compared with those at week 2. In the roxadustat group, the levels of transferrin and the TIBC

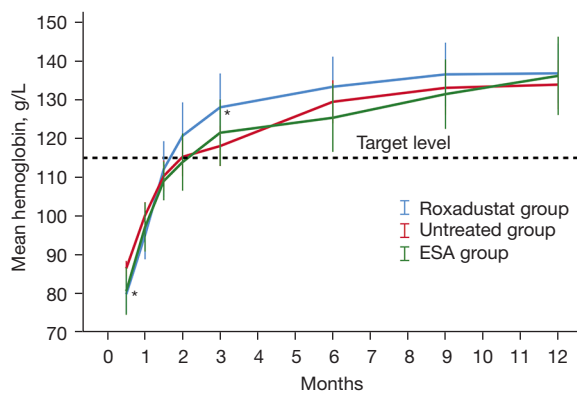


Figure 2 Mean (95% CI) levels of Hb over time after kidney transplantation. Blue line is for patients in the roxadustat group, red line is for patients in the untreated group, and green line is for patients in ESA group. The significant difference was only between the roxadustat and untreated groups at week 2 and month 3. * $P < 0.05$. ESA, erythropoiesis-stimulating agent; CI, confidence interval; Hb, hemoglobin.

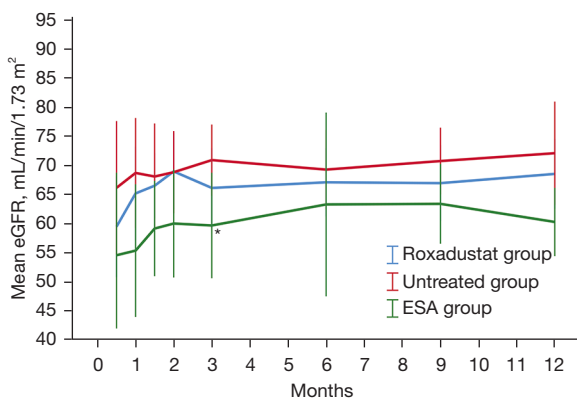


Figure 3 Mean (95% CI) levels of eGFR over time after kidney transplantation. Blue line is for patients in the roxadustat group, red line is for patients in the untreated group, and green line is for patients in the ESA group. The significant difference was only between the ESA and untreated groups at month 3. * $P < 0.05$. eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; CI, confidence interval.

were significantly higher while the ferritin and hepcidin levels were significantly lower than in both the untreated and ESA groups at month 3. However, the serum iron level in the roxadustat group was only slightly higher than that in the other two groups ($P > 0.05$). It is also worth noting that even though most KTRs in the three groups had TIBC and transferrin levels around the normal range, more KTRs

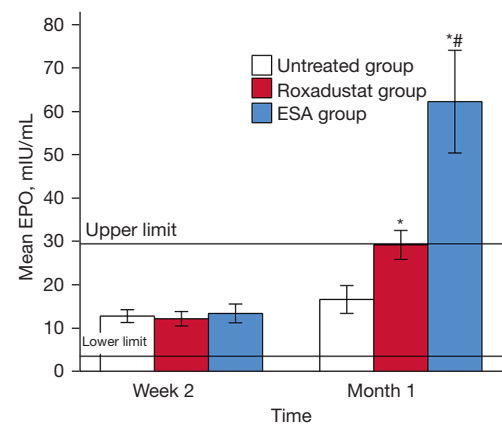


Figure 4 Mean levels of EPO at week 2 and month 1. Error bars indicate standard errors. * $P < 0.05$ compared with week 2. # $P < 0.05$ compared with roxadustat group at month 1. The upper limit of reference range in the central laboratory is 29.5 mIU/mL, the lower limit is 3.7 mIU/mL. EPO, erythropoietin; ESA, erythropoiesis-stimulating agent.

in the roxadustat group had normal transferrin ($P = 0.033$) and normal TIBC ($P = 0.030$) compared with KTRs in the untreated group.

Temporal changes in eGFR and iFGF23 levels

At both week 2 and month 3, no significant difference was found in serum creatinine levels or eGFR among the three groups (Table 2). During the 1-year follow-up, no significant difference was observed in eGFR among the three groups (Figure 3).

At week 2, the mean iFGF23 level was comparable among the three groups (Table 2). The ratio of patients who received treatment for SHPT such as calcitriol, vitamin D and cinacalcet was comparable among the three groups (Table 1). At month 3, the mean iFGF23 in the roxadustat group was significantly lower than that in the untreated group ($P = 0.017$). However, there was no significant difference in the levels of phosphorus and calcium among the three groups at month 3 (Table 2).

Comparison of EPO level

At baseline, the mean EPO level was comparable among the three groups. At month 1, the mean EPO level in the ESA and roxadustat groups was significantly higher than at week 2 (Figure 4). Even though the mean Hb levels in the ESA and roxadustat groups were not significantly different

at month 1 (*Figure 2*), the mean EPO level in the ESA group was dramatically higher than the upper limit of the EPO normal range, which was significantly higher than the EPO level (that was still within the normal range) in the roxadustat group (62.15 ± 42.50 vs. 29.26 ± 15.57 mIU/L, $P=0.018$) (*Figure 4*).

Safety

During the 1-year follow-up, patients did not voluntarily report any adverse events related to roxadustat or rhuEPO, nor did the physicians find any abnormal laboratory results significantly related to treatment. No change in blood pressure was observed after medication, nor was there need to increase the dose or type of antihypertensive drugs.

Discussion

In our study, the mean Hb levels at month 3 in the three groups were all significantly higher than those at week 2, which indicated that early PTA may resolve due to improved iron utilization with the gradual recovery of graft function and decreased uremia toxins. KTRs in the roxadustat group who had significantly lower mean Hb levels at week 2 posttransplant showed significantly higher mean Hb levels and normal Hb rate at month 3 when compared with the untreated group. The rate of KTRs with normal Hb in the roxadustat and ESA groups was much higher than that in the untreated group. The mean Hb level in the ESA group at month 3 was similar to that in the roxadustat group. These results indicated 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 of achieving normal Hb levels. However, there was no significant difference in the mean Hb level among the three groups at 1-year posttransplant, which might be due to the short intervention time of only 1–3 months for roxadustat and ESA (*Table 1*) and the natural recovery of Hb levels over time after transplant.

EPO levels at month 1 in both the roxadustat group and ESA group were significantly increased compared with those at week 2 (*Figure 4*). Moreover, the EPO level in the ESA group at month 1 was dramatically higher than the upper limit of the EPO normal range and significantly higher than that in the roxadustat group (*Figure 4*). Despite the high levels of EPO, the mean Hb levels in ESA group were similar to those in the roxadustat group at month 1 (*Figure 2*), which indicated that patients with rhuEPO

treatment require an EPO concentration much higher than physiological to only to reach the similar level of Hb in patients who receive roxadustat. Previous study has identified that a high level of EPO is associated with increased risk of hypertension (36). We also found that EPO levels in the ESA group varied greatly, with a maximum value of 170 mIU/L and a minimum value of 10.7 mIU/L. A possible reason was that the time interval between the weekly injection of rhuEPO and EPO measurement varied among patients. It is hypothesized that consistent, near-physiological EPO levels may be better than high intermittent levels once weekly (37).

Besides increasing the serum EPO level, roxadustat also improved the utilization of iron. Heparin is a key hormone involved in the regulation of iron homeostasis and intestinal iron absorption. It can bind to ferroportin (FPN), which is an iron exporter expressed on the surface of intestinal enterocytes, macrophages and hepatocytes (38,39), leading to the internalization and degradation of FPN and resulting in blocked cellular iron output (40). In addition, hepcidin inhibits the secretion of divalent metal transporter 1 (DMT1) and duodenal cytochrome B (DcytB), thus affecting intestinal iron absorption (41,42). In our study, we excluded patients with infection or malignancy to reduce the factors that may interfere with iron utilization and ensure the representation of ferritin on the status of systemic iron storage. At month 3, although TIBC, and the transferrin and serum iron levels were increased and the ferritin and hepcidin levels decreased in all three groups when compared with week 2, the TIBC and levels of transferrin were significantly higher and the levels of ferritin and hepcidin significantly lower in the roxadustat group than in the other two groups. These results showed that iron utilization was improved in the untreated group, which may be related to a decreased hepcidin level as graft function improved and the inflammatory microenvironment caused by uremia resolved. Furthermore, roxadustat effectively increased the utilization of serum iron by increasing the level of transferrin and lowering the level of hepcidin, and such an effect was not observed with rhuEPO. These findings are consistent with results observed in CKD patients (24,43,44). KTRs remain in a low-level inflammatory state despite immunosuppressive therapies (45). Inflammation promotes the secretion of hepcidin (46-51) and inhibits the proliferation and differentiation of erythroid precursors in bone marrow, especially erythroid burst forming units and erythroid colony forming units (52). Inflammation can also cause lipid peroxidation of the erythrocyte membrane

(53-55), shortening of the lifespan of RBCs. The pathways by which hypoxia/HIF affects hepcidin expression remain unclear. Hypoxia can repress the expression of the hepcidin gene (*bmp1*) through inhibition of bone morphogenetic protein (BMP)/small mothers against decapentaplegic (SMAD) signaling (56). Meanwhile, hypoxia can also promote the production of erythroferrone (ERFE) by erythroblasts in response to EPO, which can suppress hepcidin produced by the liver (57,58). In addition to lowering hepcidin levels, stable HIF-2 can promote DcytB, DMT1, and FPN expression at the gene level (42,59-61) while HIF-1 promotes transferrin expression (62). These expressions are important and involved in iron absorption and export, facilitating plasma transport of iron to tissues and intestinal absorption of dietary iron. Studies have confirmed that HIF has an anti-inflammatory effect and promotes regression of inflammation (63-65). In a model of renal injury induced by cisplatin, the induction of increased cytokines, such as tumor necrosis factor- α , interleukin (IL)-1 β and IL-6 was significantly reduced after treatment with roxadustat (66).

In patients with CKD, roxadustat reportedly reduces the levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) (24,29,30), but our results showed that no differences in the cholesterol and LDL-C levels among the three groups. The possible reason may be related to the immunosuppressive medications, particularly glucocorticoids and calcineurin inhibitors, which frequently cause secondary dyslipidemia (67). The relatively small dosage and short course of roxadustat might also have contributed to the result. In clinical trials among patients with CKD, roxadustat was used continuously for more than 1 year.

Our study also evaluated the effect of roxadustat on the iFGF23 level. FGF23 is mainly produced in bone cells and new evidence shows that erythroid progenitors in the bone marrow can also produce FGF23 (68). A proportion of synthesized iFGF23 can be cleaved onto the N-terminal fragment and C-terminal tail of FGF23 (cFGF23) intracellularly before secretion, which also regulates FGF23 signaling (69). Hormonal activity presumably only resides in iFGF23, while cFGF23 can competitively binds to the FGF receptor (70). High plasma levels of FGF23 are an independent risk factor for cardiovascular death of KTRs (71). Hypoxia and iron deficiency are both factors affecting the production of FGF23 (72-75). It has been reported that the HIF/EPO pathway activates coordinated control of FGF23 transcription and translation (76). Researchers found that

in patients with normal renal function and increased EPO secretion caused by HIF-2 α acquired mutation, cFGF23 was significantly increased, while iFGF23 and phosphate levels were normal and unchanged (70). However, our study showed that KTRs in the roxadustat group had significantly decreased iFGF23 levels and increased EPO levels. The possible explanation is that EPO might predominately increase cFGF23 instead of iFGF23, and iron deficiency was relieved by improved iron utilization with roxadustat, which may interfere with the production of iFGF23. Noonan *et al.* reported that a CKD mouse model treated with a HIF-PHI to restore proper iron utilization had a 70% reduction in circulating iFGF23 (77).

To our knowledge, our study is the first to compare the therapeutic effect of roxadustat and ESA on early PTA and explore their effects on hepcidin in KTRs. However, there are some limitations. Firstly, this was a nonrandomized cohort trial, which may create a selection bias. Secondly, the follow-up was only 1 year, so the effect of early correction of Hb and of short-term use of roxadustat on long-term graft survival remains unknown. Thirdly, our sample size was small and did not include KTRs without early PTA as disease controls to evaluate the effect of kidney transplantation itself on hepcidin level. Therefore, well-designed randomized control trials with a larger sample size and longer follow-up time should be performed to further assess the effect of roxadustat on PTA and long-term graft function.

Conclusions

In summary, administration of roxadustat in KTRs with early PTA could increase Hb levels effectively and safely by enhancing endogenous EPO production and improving iron utilization, and thus may provide a new therapeutic choice for anemia in these patients. Further randomized studies with larger sample size are necessary to verify our results.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5897/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5897/coif>). GC serves as an unpaid editorial board member of *Annals of Translational Medicine* from November 2021 to October 2023. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of West China Hospital, Sichuan University (Chengdu, China) (No. 2022219). Individual consent for this retrospective analysis was waived.

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