**in vivo** *36*: 1785-1789 (2022)
doi:10.21873/invivo.12892

# Treatment of Renal Anemia in Patients With Hemodialysis Using Hypoxia-inducible Factor (HIF) Stabilizer, Roxadustat: A Short-term Clinical Study

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**Abstract.** *Background/Aim: Renal anemia is a major complication in patients with chronic kidney disease (CKD) and hemodialysis, increasing morbidity and mortality. Roxadustat is a novel oral hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor (PHI), which is administrated for renal anemia. Different from erythropoiesis-stimulating agents (ESAs), Roxadustat could increase erythropoietin physiologically, improving the therapeutic effects. It has not been so long since Roxadustat was approved by the European Commission (EC). Thus, only a few studies have reported on the treatment of renal anemia using Roxadustat. Patients and Methods: In this study, we evaluated the efficacy of Roxadustat in patients undergoing hemodialysis (HD). Nine patients under HD (72±10 years old) were enrolled in this study. Patients received Roxadustat first time or changed from ESAs (5-10 mg, 3 times a week after HD). Observation period was 5.3±2.9 months. Results: Roxadustat treatment effectively increased and maintained hemoglobin levels. Levels of ferritin and C-reactive protein tended to decrease, but the difference was not statistically significant. No significant adverse effects were observed in all patients during the study. Conclusion: Roxadustat is effective and relatively tolerant for treating renal anemia in patients subjected to hemodialysis.*

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*Key Words:* Renal anemia, chronic kidney disease (CKD), hypoxia-inducible factor (HIF), prolyl hydroxylase inhibitor (PHI), erythropoiesis-stimulating agents (ESAs), endothelial dysfunction.



It is well known that chronic kidney disease (CKD) is increasing worldwide. Renal anemia is a common complication in CKD, which could increase the morbidity and mortality (1, 2). Anemic status increases oxidative stress and inflammation in the kidney, decreasing renal function in the patients with CKD (3, 4). Recommended renal anemia treatments are erythropoiesis-stimulating agents (ESAs), oral or intravenous iron, and red blood cell (RBC) transfusion. However, RBC transfusion could cause serious side effects such as infection and graft *versus* host disease (5, 6). Further, it is reported that excessive administration of iron can cause adverse cardiovascular events and mortality (7). Iron treatment also decreases phagocytic function, increasing the risk of infection (8). Thus, so far, recombinant erythropoiesis-stimulating agents (ESAs) are commonly used to increase levels of hemoglobin, reducing the need for red blood cell transfusions.

It has been reported that patients with renal anemia treated with ESAs may suffer from increased hypertension, stroke and adverse cardiovascular events , which may be due to the non-physiological increase in erythropoietin (9).

Hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor (PHI) is a new class of drug for renal anemia. The main mechanisms of this drug are as follows; stabilizes the transcription factor HIF, which regulates expression of genes increasing endogenous levels of erythropoietin and hemoglobin while decreasing hepcidin and ferritin levels (10, 11).

Roxadustat is a novel, orally administered HIF-PHI for the treatment of anemia in patients with CKD subjected or not to. Unlike other HIF-PHI, Roxadustat should be taken three times a week (12).

Few real-world data have been reported regarding treatment of renal anemia using roxadustat, because it has not been long since Roxadustat has been approved by the European Commission (EC). Thus, we tested the efficacy and safety of Roxadustat in Japanese hemodialysis patients.

Table I. *Clinical characteristics*.

| Patient number | Observation period (months) | Dosage of erythropoiesis stimulating agent (before therapy; /week) | Dosage of iron (on therapy; mg/day) |
|---|---|---|---|
| 1 | 3 | Epoetin alfa (9,000 IU/week)<br>Darbepoetin alfa (40 mg/week) | None |
| 2 | 3 | Darbepoetin alfa (20 mg/week) | None |
| 3 | 6 | Epoetin alfa (4,500 IU/week) | None |
| 4 | 10 | Epoetin alfa (9,000 IU/week) | None |
| 5 | 2 | None | None |
| 6 | 4 | Darbepoetin alfa (10 mg/week) | None |
| 7 | 10 | Epoetin alfa (9,000 IU/week) | Saccharated ferric oxide (40 mg/week) |
| 8 | 5 | Epoetin alfa (4,500 IU/week) | Saccharated ferric oxide (40 mg/week) |
| 9 | 5 | None | Ferric citrate hydrate (1,500 mg/day) |

## Patients and Methods

This study is a retrospective review of medical records. We have analyzed 154 patients who underwent outpatient HD three times a week at the outpatient dialysis clinic (Seiwadai Clinic, Nara, Japan), which is a facility of the Department of Nephrology, Osaka Medical and Pharmaceutical University (Osaka, Japan). All these patients were Japanese over 20 years of age. The inclusion criteria were hemoglobin >9.0 g/dl, serum ferritin ≥35 ng/ml, transferrin saturation ≥20%. The major exclusion criteria were history of cancer, proliferative diabetic retinopathy, or apparent thrombosis before the study. As a result of applying this criterion, 25 patients were excluded because they had a history of cancer, and 14 patients were excluded due to history of diabetic retinopathy. Nine patients with CKD under hemodialysis were enrolled in the study (Age: 72±10 years). Eligible patients were to receive roxadustat orally (20-100 mg) three times a week for 2-10 months. The safety or tolerability of roxadustat were evaluated using vital signs, laboratory findings, 12-lead electrocardiograms (ECGs), and adverse events. The dose was increased by 20 or 30 mg to achieve the target hemoglobin levels of 10.0-12.0 g/dl. Blood samples were collected at the start of HD and the beginning of the week. Serum iron, transferrin saturation, ferritin, and C-reactive protein were measured before and at the end of observation period of study. These were routine laboratory data, and no data were obtained directly from the patients for this study. At the time this study was conducted, Roxadustat was being administered to only a small number of carefully selected patients because of its early launch. The rest of the patients received ESAs as usual treatment, and their anemia was treated appropriately. We obtained a proper permission to access the medical records of the patients from the hospital committee. These patients were treated as per the stated protocol. All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Patients were informed in writing that routine laboratory data would be used for the study, and their consent was obtained. The patient consent form was approved by the Ethics Review Board.

*Data analysis*. Statistical significance of differences was determined by the interquartile range and Mann–Whitney *U*-test. All analyses were performed using StatView (SAS Institute, Cary, NC, USA). Statistical significance was defined as $p<0.05$.

## Results

Three male and six female patients were enrolled in the study. The age at onset was 72±years. Observation period was 5.3±2.9 months. The mean roxadustat dose was 60±17 mg at the start and 39±19 mg at the end of the study (Table I). ESAs were discontinued prior to roxadustat administration. All patients achieved the target hemoglobin levels after three weeks of treatment (Figure 1). However, the levels of ferritin, transferrin saturation, and C-reactive protein were not changed during the observation period (ferritin, before *vs*. on therapy: 155±136 mg/dl and 158±136 mg/dl, respectively, transferrin saturation, before *vs*. on therapy: 30±10% and 31±13%, respectively; C-reactive protein, before *vs*. on therapy: 0.4±0.6 mg/dl and 0.4±1.0 mg/dl, respectively) (Figure 2). During the observation period, adverse events such as nausea, vomiting, diarrhea, thrombosis, cerebral infarction, or convulsion were not recognized.

## Discussion

Since there has been little real-world data regarding Roxadustat, we examined efficacy and safety of roxadustat in Japanese patients with renal anemia under HD. Hemoglobin promptly reached target levels. However, in contrast to previous reports, there were no significant differences in other iron metabolic markers or C-reactive protein. There were no adverse events during the observation period.

It is reported that concomitant changes in ESAs, hepcidin and iron indices showed that erythropoiesis was regulated by a decrease in hepcidin and an increase in transferrin saturation, improving the iron supply to erythrocytes (11). In our study, there were no statistically significant differences, but the levels of ferritin tended to decrease after treatment with roxadustat.

Hepcidin is an important regulator of iron absorption remobilization, and its expression is usually reduced by erythropoiesis, anemia and hypoxia (13). Several reports

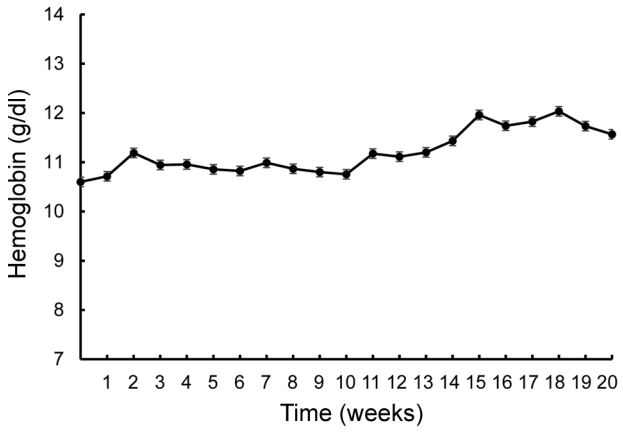


Figure 1. *Roxadustat increased hemoglobin and maintained the target levels.*

showed that HIF could sensor levels of iron and that HIF-PHI could suppress hepcidin, increasing iron absorption from the intestine or iron transport enzymes (14). Our previous reports indicated that angiotensin II and signal transducer and activator of transcription 3 (STAT3) are activated in the CKD state (15-17). Angiotensin II-induced inflammation increases STAT3, which binds to STAT3-responsive element in the hepcidin promoter (18). Furthermore, we previously reported that bone morphogenetic protein 4 (BMP4)/Smad1 axis plays a significant role in developing CKD; Smad1 transcriptionally regulates type IV collagen and smooth muscle α actin (19, 20). Interestingly, it is reported that Smad1 also binds to BMP-responsive element in the hepcidin promoter (18).

Renal anemia treatment with ESAs depends on supraphysiologic levels of recombinant erythropoietin to stimulate erythropoiesis (21, 22). High doses of ESAs in patients with CKD is associated with increased risk of hypertension and cardiovascular events including myocardial infarction, hospitalization for congestive heart failure and stroke (9). We have reported that glomerular endothelial dysfunction participates in developing CKD (15, 23). High doses of ESAs decrease nitric oxide in endothelial cells, inducing endothelial dysfunction (24).

In diabetic kidney disease (DKD), expression of sodium-glucose co-transporter 2 (SGLT2) is increased in proximal tubules, resulting in glucose processing overload and increased oxygen consumption (25, 26). Thus, glucose exposure is significantly increased in each residual nephron, inducing a metabolic burden that may lead to greater oxygen consumption. The vicious cycle of chronic ischemia and hypoxia in the kidney could cause tubulointerstitial fibrosis (27). It is reported that administration of HIF-PHI ameliorated tubulointerstitial fibrosis in an ischemia-reperfusion induced acute kidney injury mouse model (28).

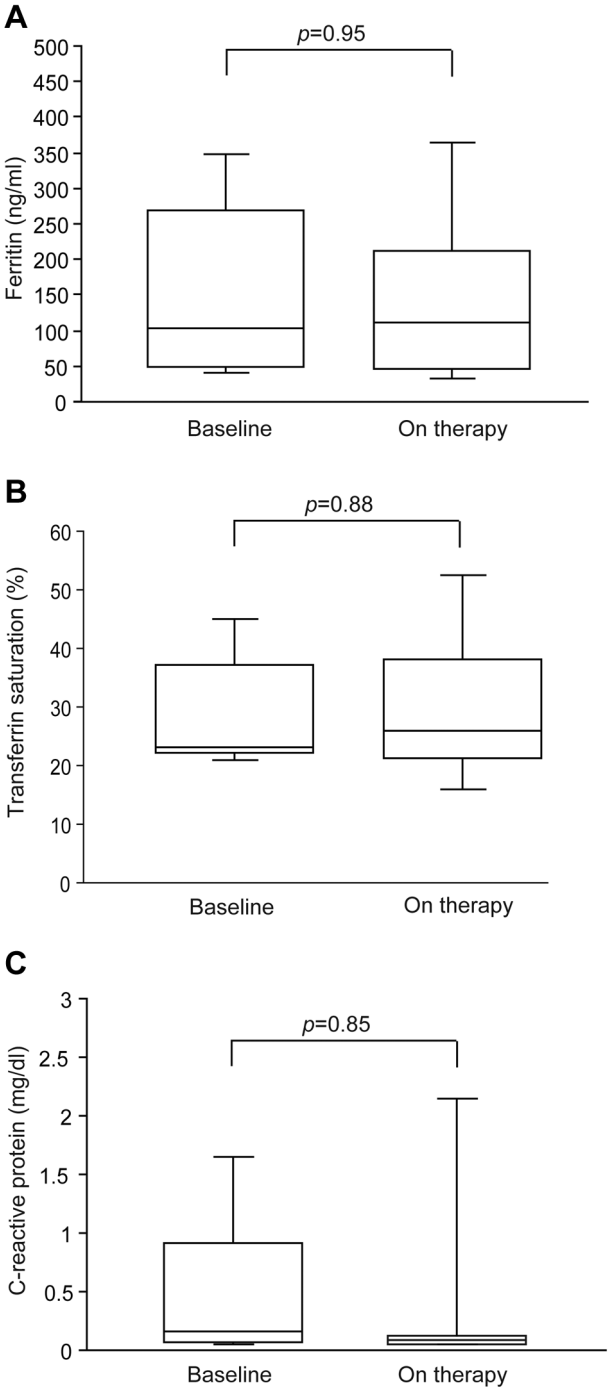


Figure 2. *Levels of ferritin, transferrin saturation and C-reactive protein did not change during observational period. (A) Ferritin. (B) Transferrin saturation. (C) C-reactive protein.*

Different from previous reports, the decrease in ferritin and TSAT, which implies an improvement in iron metabolism and inflammatory state was not clear in our study. However, this may be due to the short observation

period. Thus, this is considered to be a limitation of our study. Further, to report the effects of roxadustat as soon as possible, our study was based on only nine treated patients.

In summary, the results of our study suggest that oral roxadustat increased hemoglobin in the minimum required iron supplementation. Thus, administration of roxadustat may be useful to improve the prognosis of patients with renal anemia in CKD.

## Conflicts of Interest

In accordance with the ethical obligation of a researcher, the corresponding author reports that he received funding from Chugai, Kyowa Kirin, Sumitomo Pharma, Otsuka, Teijin Pharma, Torii, Boehringer Ingelheim, Eli Lilly, and Mochida that may have affected the research reported in the enclosed paper.

## Authors' Contributions

A.M. designed the study. A.M. wrote the manuscript, which was reviewed and edited by A.M. and Y.H. A.M. performed all analyses. Y.H. contributed to the discussion, reviewed, and edited the manuscript.

## Acknowledgements

This work was supported by JSPS KAKENHI Grant Number 17K09720.

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*Received May 4, 2022*
*Revised May 18, 2022*
*Accepted May 19, 2022*