in vivo *37*: 825-829 (2023)
doi:10.21873/invivo.13148

Enarodustat Treatment for Renal Anemia in Patients With Non-dialysis Chronic Kidney Disease

AKIRA MIMA

Department of Nephrology, Osaka Medical and Pharmaceutical University, Osaka, Japan

Abstract. *Background/Aim: Renal anemia is a major complication in patients with chronic kidney disease (CKD), leading to morbidity and mortality. Hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitors (PHI), also called HIF stabilizers, increase endogenous erythropoietin production and are expected to be novel orally administrated agents for renal anemia in CKD. Enarodustat is being developed as an oral HIF-PHI. It was recently approved in Japan and clinical development is ongoing in the USA and South Korea. Therefore, there are only a few real-world data regarding treatment of renal anemia using enarodustat. This study evaluated the efficacy of enarodustat in patients with non-dialysis CKD. Patients and Methods: Nine patients (78±11 years old, male=6, female=3) were enrolled in this study. Patients received enarodustat as first-line therapy or changed from erythropoiesis stimulating agents (2-6 mg). The observation period was 4.8±2.0 months. Results: Levels of hemoglobin were effectively increased and maintained with enarodustat administration. C-reactive protein and serum ferritin were significantly decreased, but no change in renal function was observed. Furthermore, no serious adverse effects were recognized in all patients during the study. Conclusion: Enarodustat is an effective and relatively well-tolerated agent for the treatment of renal anemia in patients with non-dialysis CKD.*

Correspondence to: Akira Mima, MD, Ph.D., Department of Nephrology, Osaka Medical and Pharmaceutical University, Osaka, 569-8686, Japan. Tel: +81 726831221, Fax: +81 726813723, e-mail: akira.mima@ompu.ac.jp

Key Words: Renal anemia, chronic kidney disease (CKD), diabetic kidney disease (DKD), hypoxia-inducible factor (HIF), prolyl hydroxylase inhibitor (PHI), inflammation, ferritin.

Chronic kidney disease (CKD) is increasing global disease burden (1, 2). Renal anemia is a common and important complication of CKD that is mainly due to the decrease in erythropoietin production by the kidneys (3, 4). Despite significant advances, limited progress has been made regarding the prevention and treatment of renal anemia (5). Inflammation and oxidative stress, which could be increased by renal anemia, play a significant role in developing CKD (6). In addition, many patients with renal anemia should receive intravenous iron supplementation. However, there is concern that this iron supplementation may increase the risk of atherosclerosis, and cardiovascular-related side effects (7). Iron administration also decreases phagocytic function, increasing the risk of infection (8). Another recommended treatment for renal anemia is red blood cell (RBC) transfusion. However, RBC transfusion could cause serious adverse effects such as infection and graft *versus* host diseases, which could induce acute kidney injury and exacerbate CKD (9-11). Therefore, erythropoietin (EPO) replacement therapies, such as recombinant human EPO (rhEPO), and erythropoietin-stimulating agents (ESAs), are widely used to manage renal anemia, improving quality of life and reducing the risk of renal anemia-related adverse effects and the need for blood transfusion (12, 13). However, according to the literature, rhEPO and ESAs may increase the risk of thrombotic complications and vascular events due to non-physiological EPO concentrations (5).

The hypoxia-inducible factor (HIF)-prolyl hydroxylase domain (PHD) pathway can increase the transcriptional activity of several genes involved in hematopoiesis, rheumatoid arthritis, psoriasis, or glucose metabolism (14). HIF-PHD inhibitors (HIF-PHIs) are a new type of treatment for renal anemia; they activate HIF transcription factors, increasing endogenous EPO production while also decreasing hepcidin and ferritin levels (15).

Furthermore, HIF-PHIs can increase the transcriptional activity of vascular endothelial growth factor (VEGF) and pyruvate kinase M2, which may induce a reno-protective action. Thus, HIF-PHIs may be advantageous for non-dialysis CKD (5).

Enarodustat (ENALOY®, Japan Tobacco and Torii Pharmaceutical, Tokyo, Japan) was developed as an orally active inhibitor of the HIF-PHD enzymes for the treatment

Table I. *Clinical characteristics of the study.*

Patient number	Observation period (months)	Disease causing chronic kidney disease	Dosage of erythropoiesis stimulating agent (before therapy; /month)	Dosage of iron (on therapy; mg/day or month)
1	2	Diabetic nephropathy	None	None
2	7	Nephrosclerosis	None	None
3	3	Nephrosclerosis	None	None
4	3	Nephrosclerosis	Darbepoetin alfa (60 mg/month)	None
5	4	IgG4-related tubulointerstitial nephritis	Darbepoetin alfa (120 mg/month)	Saccharated ferric oxide (80 mg/month) Ferric Citrate Hydrate (500 mg/day)
6	7	ANCA-associated glomerulonephritis	Darbepoetin alfa (120 mg/month)	Ferric Citrate Hydrate (500 mg/day)
7	7	Nephrosclerosis	None	None
8	4	Diabetic nephropathy	None	None
9	6	Diabetic nephropathy	None	None

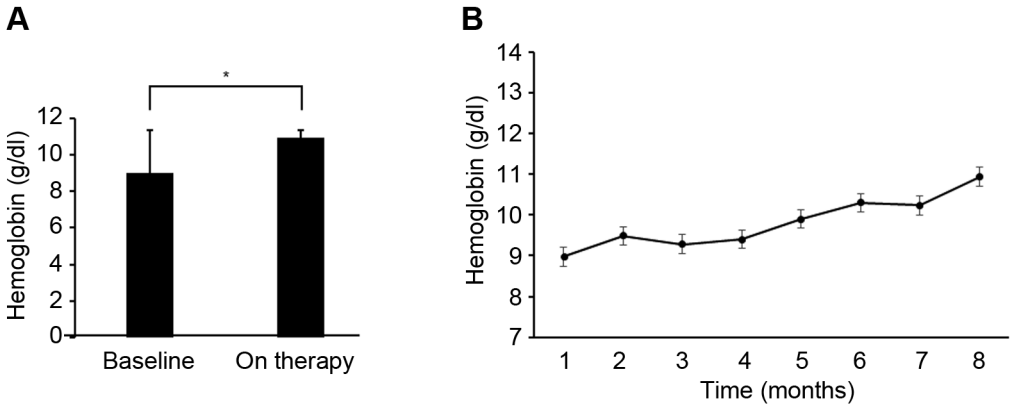

Figure 1. *The effect of enarodustat on the levels of hemoglobin in patients with chronic kidney disease. (A) Changes in the levels of hemoglobin by enarodustat treatment during the observation period. (B) Enarodustat maintained the target levels of hemoglobin. *p<0.05. These data are expressed as means±SD.*

of renal anemia in both dialysis-dependent and non-dialysis-dependent patients with CKD (16).

Because enarodustat has only been approved for the treatment of renal anemia in Japan and is still in clinical development in the United States and South Korea, few real-world data on the treatment of renal anemia with enarodustat have been reported. Thus, in this study, we tested the efficacy and safety of enarodustat in Japanese patients with non-dialysis CKD.

Patients and Methods

This study is a retrospective review of medical records. We analyzed the medical records of 14 patients. They underwent outpatient care at the Department of Nephrology, Osaka Medical and Pharmaceutical University (Osaka, Japan). All patients were Japanese and over 20 years of age. The inclusion criteria were hemoglobin >7.0 g/dl, serum ferritin ≥35 ng/ml, and transferrin saturation ≥10%. The exclusion criteria were history of cancer, proliferative diabetic retinopathy or apparent thrombosis before the study. For five patients, data were insufficient or progress could not be followed because they were transferred to other hospitals during the observation period. As a result of applying this criterion, nine patients with non-dialysis CKD were enrolled in the study (age: 78±11 years). Eligible patients received enarodustat orally (2-6 mg) daily for 2-7 months (Table I). The safety or tolerability of enarodustat was evaluated using vital signs, laboratory findings, 12-lead electrocardiograms (ECGs), and adverse events. The dose was increased by 4 or 6 mg to achieve the target hemoglobin levels of 10.0-11.0 g/dl. Blood samples were collected at the routine visit to our hospital. Serum iron, transferrin saturation, ferritin, and C-reactive protein (CRP) levels were measured before and at the end of the observation period of the 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, enarodustat was being given to only a small number of carefully selected patients because of its early launch.

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. This is a retrospective medical record review study. The patients were treated

as per protocol, the requirement to obtain informed consent was waived, and ethical review was not performed by the institutional (Osaka Medical and Pharmaceutical University) review board rule because the patient number in this study was less than nine.

Statistical analysis. Statistical significance was determined by the interquartile range and Wilcoxon test. All analyses were performed using StatView (SAS Institute, Cary, NC, USA) and Excel software (Microsoft, Redmond, WA, 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 78±11 years. The observation period was 4.8±2.0 months. Three patients were treated with ESAs before administration of enarodustat. The mean enarodustat dose was 2 mg at the start and 3.8±1.9 mg at the end of study. ESAs were discontinued prior to enarodustat administration in some patients.

Baseline hemoglobin levels were 9.0±1.2 g/dl and enarodustat increased its level to 10.9±0.1 g/dl (Figure 1A, $p<0.05$). Figure 1B shows the time series of hemoglobin, and the rate of change in hemoglobin baseline and on therapy was 17.9%.

Next, we analyzed the levels of CRP, ferritin, and transferrin saturation. Levels of CRP significantly decreased with enarodustat treatment (baseline *vs*. on therapy: 2.7±2.2 mg/l and 1.0±0.7 mg/l, respectively, $p=0.039$, Figure 2A). Additionally, levels of ferritin also decreased after enarodustat treatment (baseline *vs*. on therapy: 406±309 mg/l and 221±299 mg/l, respectively, $p=0.043$, Figure 2B). However, transferrin saturation was not changed during the observation period (baseline *vs*. on therapy: 34.8±14.6% and 36.7±20.7%, respectively, $p=0.715$, Figure 2C).

Lastly, we have analyzed the effect of enarodustat on renal function. Administration of enarodustat did not change renal function during the observation period [serum creatinine, baseline *vs*. on therapy: 3.1±2.3 mg/dl and 3.9±4.3 mg/dl ($p=0.354$); estimated glomerular filtration, baseline *vs*. on therapy: 23.1±14.2 ml/min/1.73 m^2 and 22.8±14.6 ml/min/1.73 m^2 ($p=0.158$), respectively] (Figure 3A and B). During the observation period, adverse events such as thrombosis, cerebral infarction, convulsion, nausea, or vomiting were not recognized.

Discussion

Due to the paucity of real-world data on enarodustat, this study was conducted to confirm the efficacy and safety of enarodustat for renal anemia in Japanese patients with non-dialysis CKD. Our results showed that enarodustat increased the levels of hemoglobin. However, no significant differences were recognized in the levels of CRP and iron metabolic markers. In addition, no adverse events were observed during the study.

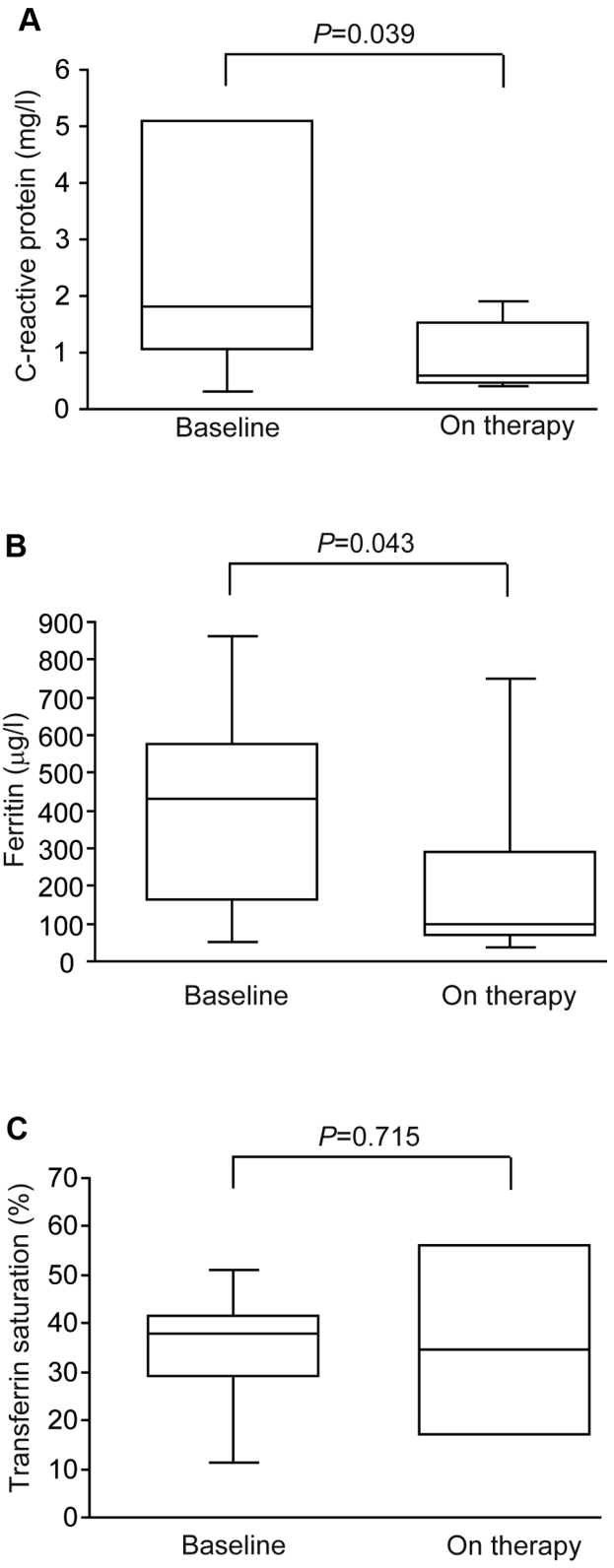

Figure 2. *Box plots showing the levels of C-reactive protein (A), ferritin (B), and transferrin saturation (C) at baseline and during enarodustat treatment.*

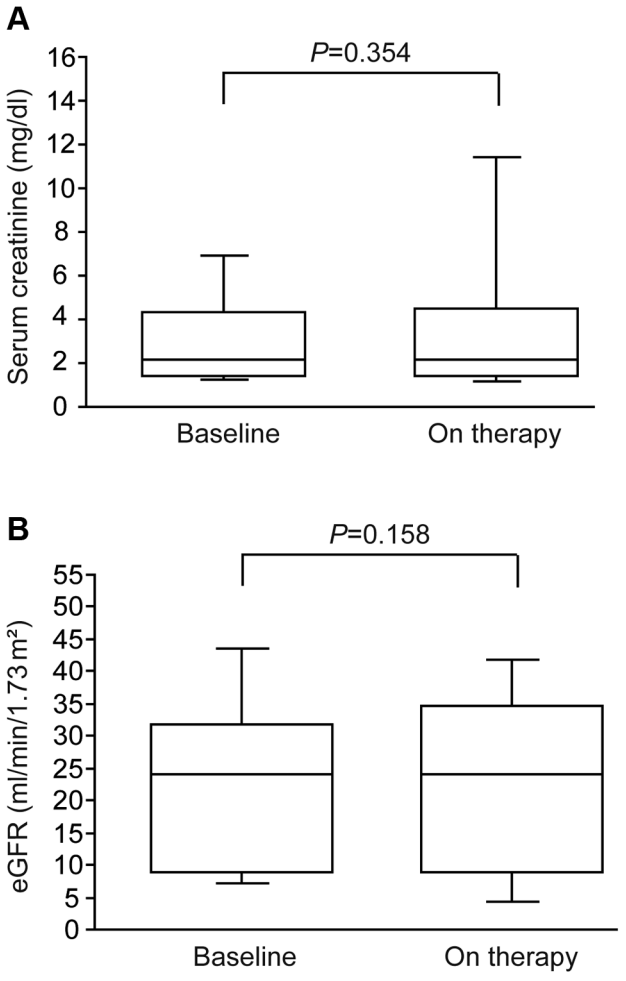

Figure 3. *Box plots showing changes in the levels of serum creatinine (A) and estimated glomerular filtration rate (eGFR) (B) by enarodustat treatment during the observation period.*

It has been reported that inhibition of VEGF-A decreases proteinuria and mesangial expansion (17). Furthermore, some patients treated with anti-VEGF monoclonal antibodies exhibited proteinuria, hypertension, and renal failure (18). Supporting this, VEGF-A knockdown mice showed proteinuria, glomerulosclerosis, and renal failure. Thus, VEGF-A may be a reno-protective factor (19).

We have shown that diabetes increases protein kinase (PKC)d/p38 mitogen-activated protein kinase (MAPK) activation and Src homology-2 domain-containing phosphatase-1 (SHP-1) expression, which can inhibit VEGF signaling, resulting in podocyte apoptosis (20). Adenovirus E1A binding P300 and CREB binding (CBP) are homologous transcriptional adaptor proteins, and a DNA binding complex containing P300/CBP is formed under hypoxic conditions. In addition, P300/CBP contributes to the activation of the VEGF promoter induced by HIF-1a (21). Therefore, the exquisite balance induced by HIF-PHI in the regulation of VEGF-A activity may be important for renal protection (5).

Hepcidin is known to be elevated by inflammatory cytokines (22), such as interleukin-6 or tumor necrosis factor-a, which are increased in diabetic kidney disease (DKD) and CKD (6, 23, 24). Simultaneous changes in ESAs, hepcidin and iron indices have been reported to improve iron supply to erythrocytes by decreasing hepcidin and increasing transferrin saturation, thereby controlling erythropoiesis (25). Although a small number of cases was analyzed in our study, enarodustat treatment significantly decreased the levels of ferritin and CRP. This implies that enarodustat may exhibit reno-protective effects via its anti-inflammatory action.

Previous reports have shown that HIF-PHIs may increase the risk of thrombosis. Thrombosis markers, such as plasminogen activator inhibitor-1 or von Willebrand factor, which are also increased in CKD, were not measured in our study (23); however, no obvious thrombosis was observed, confirming the safety of enarodustat.

Data from a phase III study conducted in Japan showed that Hb 10.0-11.0 g/dl was reached within 8 to 16 weeks after treatment with enarodustat (unpublished), and average administration dose of enarodustat in this study was 3.0±2.1 mg. On the other hand, the average dose in our study was 3.8±1.9 mg, which is higher than that used in the phase III study. Therefore, it is unlikely that the administration dose used in our study was low to avoid side effects.

As we have previously reported, the reduction in transferrin saturation, signifying improvements and inflammatory status, was again not changed during the observation (26). However, this could be attributed to the short observation period. This may be a limitation of our study. Further prospective studies with a larger sample size will be needed.

Conclusion

Oral enarodustat increases hemoglobin levels slowly and safely. Furthermore, administration of enarodustat could be useful to improve the prognosis of patients with renal anemia in non-dialysis CKD.

Conflicts of Interest

Akira Mima received a speaker honorarium from Otsuka, Kyowa Kirin, Mitsubishi Tanabe, Torii, Kowa, Bayer, Eli Lilly, Mochida, Sumitomo Pharma, and Boehringer Ingelheim.

Acknowledgements

This work was supported by JSPS KAKENHI Grant Number 22K08368. Akira Mima received research grants from Kyowa Kirin, Sumitomo Pharma, Otsuka, Torii, Daiichi-Sankyo, Mitsubishi Tanabe, Mochida, Boehringer Ingelheim, and Eli Lilly.

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Received December 14, 2022
Revised December 30, 2022
Accepted January 11, 2023