Clinical and Experimental Nephrology
https://doi.org/10.1007/s10157-024-02511-9

ORIGINAL ARTICLE

The comparison of four hypoxia-inducible factor prolyl hydroxylase inhibitors on drug potency and cost for treatment in patients with renal anemia

Enyu Imai[1,2,3] · **Atsuhiro Imai**[4]

Received: 27 March 2024 / Accepted: 2 May 2024

Abstract

Background Five hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) have been approved for marketing in Japan. However, marked differences exist in terms of drug potency, dose requirement, and pharmacokinetics.

Methods The primary evaluation in this study was the changes in hemoglobin levels, dose escalation, drug potency, and cost among HIF-PHIs, 3 months after the initiation of treatment.

Results All patients treated with HIF-PHI between August 2020 and December 2023 were enrolled in this study. In total, 124 patients were administered daprodustat (N = 37), enarodustat (N = 44), molidustat (N = 13), or vadadustat (N = 30). The mean hemoglobin levels of daprodustat, enarodustat, molidustat, and vadadustat at 3 months were 11.7 g/dL, 11.8 g/dL, 12.2 g/dL, and 11.3 g/dL, respectively. At 3 months, the mean doses of daprodustat, enarodustat, molidustat, and vadadustat increased by 110%, 177%, 125%, and 152%, respectively, from the initial dose. The HIF-PHI potency indices (HPI) of daprodustat, enarodustat, molidustat, and vadadustat at 3 months were 0.168, 0.307, 0.184, and 0.254, respectively. At 3 months, the mean daily costs of daprodustat, enarodustat, molidustat, and vadadustat were JPY 345, JPY 434, JPY 206, and JPY 565, respectively.

Conclusion The difference in dose escalation for anemia treatment among HIF-PHIs is due to differences in drug potency, where the HPI significantly differs among HIF-PHIs. The disparity between the HPI and the cost of the initial dose accounts for the variance in the daily costs of renal anemia treatment among HIF-PHIs.

Keywords CKD · HIF-PHI · Renal Anemia

Introduction

Renal anemia is a common comorbidity of advanced chronic kidney disease (CKD) [1]. Anemia associated with CKD can cause heart failure and exacerbate CKD [2]. In 1996, erythropoiesis-stimulating agents (ESAs) were introduced to treat renal anemia in Japan. In 2019, renal anemia could be treated with the hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI). Roxadustat was the first HIF-PHI approved for clinical use in patients undergoing dialysis [3]. In 2020, daprodustat [4] and vadadustat [5] were approved for clinical use, followed by enarodustat [6] and molidustat [7] in 2022. Currently, five compounds are approved for marketing in Japan; however, marked differences exist in terms of drug potency, dose requirements, and pharmacokinetics. Roxadustat is administered thrice weekly, whereas the other treatments are administered daily. Our previous study showed heterogeneous pharmacological actions of daprodustat and vadadustat [8]. In a network meta-analysis, the increase in hemoglobin (Hb) levels after treatment was inconsistent among HIF-PHIs [9].

We were interested in the relationship between differences in drug potency and the daily cost of HIF-PHIs. In this study, we have compared four HIF-PHIs (daprodustat,

✉ Enyu Imai
ads12069@nifty.com

1 Nakayamadera Imai Clinic, Takarazuka, Japan

2 Department of Nephrology, Fujita Health University, Toyoake, Aichi, Japan

3 Department of Nephrology and Rheumatology, Aich Medical University, Nagakute, Aichi, Japan

4 Department of Nephrology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

Published online: 20 May 2024

enarodustat, molidustat, and vadadustat) in terms of the Hb increase rate, drug potency, and treatment cost.

Methods

Study protocol

This was a retrospective, observational study. The Nakayamadera Imai Clinic treats approximately 1,800 patients per month, 95% of whom have chronic non-communicable diseases (mainly diabetes and CKD). All patients treated with HIF-PH inhibitors between August 2020 and December 2023 were enrolled in this study.

Clinically, we treated patients with HIF-PHIs by targeting a Hb level of 11 to 13 g/dL and transferrin saturation of ≥ 20% or ferritin level of ≥ 100 ng/mL, according to the 2018 Guidelines for the Diagnosis and Treatment of Chronic Kidney Disease (as published by the Japanese Society of Nephrology) [10].

In 2023, the costs of the initial dose of daprodustat, enarodustat, molidustat, and vadadustat were JPY 179.70 (2 mg) or JPY 316.80 (4 mg), JPY 270.50 (2 mg), JPY 163.80 (25 mg), and JPY 366.00 (300 mg), respectively.

The study protocol was approved by the Ethics Committee of Hyogo Medical Association (R4-005). As this was a retrospective study, we used an opt-out approach and waived the requirement for written informed consent. This study was conducted in accordance with the Declaration of Helsinki.

Patients' follow-up and study outcomes

Patients visited the clinic every month for the treatment of CKD, including renal anemia. Clinical data were obtained from patients' clinical records. We compared Hb levels, HIF-PHI dose, and daily cost of HIF-PHIs among patients treated with HIF-PHIs. The primary evaluation of this study was the difference in dose, drug potency, and cost among HIF-PHIs 3 months after the initiation of treatment. Drug potency was defined using the HIF-PHI potency index (HPI) as follows: HPI = (drug dose/starting dose) × 100/Hb (g/dL) /BW (kg).

Statistical analyses

One-way analysis of variance or Fisher's exact test was used to evaluate the significant differences among the backgrounds of the four groups. We evaluated the Hb time-series data using repeated-measures analysis of variance, but the sphericity assumption was violated by Mauchly's tests. In the repeated-measures analysis, we used the Greenhouse–Geisser correction. To evaluate HIF-PHI dose, HIF-PHI cost, and HPI, we performed a Kruskal–Wallis test. If there was a significant difference, we performed Dunn's multiple comparison test or pairwise comparisons using the Mann–Whitney U test with Bonferroni's *P*-value adjustment method.

Statistical significance was set at $P < 0.05$. Statistical analyses were performed using GraphPad Prism 10.2.1 software program (GraphPad Software, San Diego, CA, USA) or EZR 1.55. Data are expressed as the mean ± standard deviation or median (interquartile range).

Results

Participants

All patients treated with HIF-PHI between August 2020 and December 2023 at Nakayamadera Imai Clinic were enrolled in this study. In total, 124 patients were administered daprodustat (N = 37), enarodustat (N = 44), molidustat (N = 13), or vadadustat (N = 30). The mean age of the participants was 74.4 years, and 55.6% were male. The clinical characteristics relevant to renal anemia were similar between the groups, except for the pre-medicated individuals (Table 1). The participants had advanced CKD, with a mean estimated glomerular filtration rate of 22.3 mL/min/1.73 m^2. The mean baseline Hb was 10.7 g/dL. At baseline, the mean transferrin saturation was 29.3%, with a mean serum ferritin level of 153 ng/mL, indicating that the iron status for erythropoiesis was adequate. The number of patients who received pre-medication with ESA or HIF-PHIs differed significantly between the HIF-PHI groups. The proportion of patients premedicated with ESA or HIF-PHI was 59.5%, 36.4%, 30.8%, and 80.0% in the daprodustat, enarodustat, molidustat, and vadadustat groups, respectively.

Outcomes

Changes in Hb levels after HIF-PHI treatment are shown in Fig. 1. The mean Hb at 1 month did not change from baseline in the enarodustat and vadadustat groups but increased in the daprodustat and molidustat groups. The mean Hb levels of daprodustat, enarodustat, molidustat, and vadadustat at 3 months were 11.7 g/dL, 11.8 g/dL, 12.2 g/dL, and 11.3 g/dL, respectively. The percentage of participants who reached the target Hb level of 11–13 g/dL was 59.5%, 45.4%, 76.9%, and 33.3% for daprodustat, enarodustat, molidustat, and vadadustat, respectively. Given that the target Hb level was 10–13 g/dL, according to the 2023 Guidelines for the Diagnosis and Treatment of Chronic Kidney Disease, the percentages of participants who reached the target Hb level of 10–13 g/dL were 81.1%, 65.9%, 84.6%, and 63,3% for daprodustat, enarodustat, molidustat, and vadadustat, respectively.

Table 1 Baseline Characteristics of Patients

	Daprodustat (N = 37)	Enarodustat (N = 44)	Molidustat (N = 13)	Vadadustat (N = 30)	P value
Age	75.3 ± 10.9	72.0 ± 13.6	78.2 ± 9.0	75.2 ± 11.2	[a]0.318
Sex (%)	22 (59.5)	22 (44.9)	7 (53.8)	18 (60)	[b]0.474
Body weight (kg)	58.0 ± 12.4	57.2 ± 10.0	53.4 ± 9.1	57.2 ± 10.0	[a]0.62
Hb baseline (g/dL)	10.6 ± 1.1	10.7 ± 1.2	11.0 ± 1.2	10.7 ±0.8	[a]0.789
Ferritiin	156 ± 100	155 ± 106	133 ± 120	154 ± 90	[a]0.927
TSAT (%)	29.4 11.5	27.3 ± 11.5	31.3 ± 12.7	31.1 ± 8.5	[a]0.447
Premedication (%)	22 (59.5)	16 (36.4)	4 (30.8)	24 (80.0)	[b]0.001
Darbepoetin alpha	0	3	0	2	
Epoetin beta pegol	15	12	4	21	
PIF-PHI	7	1	0	1	

[a]one-way ANOVA

[b]Fisher's exact test

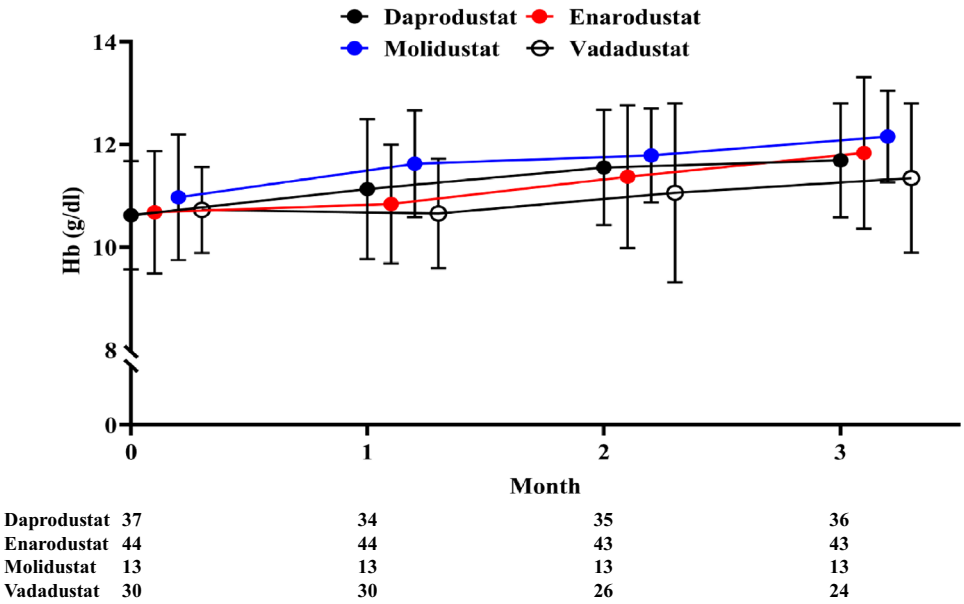

Fig. 1 Change in Hemoglobin levels during the study. The mean hemoglobin ± standard deviation is shown for 3 months after treatment with each HIF-PHI: daprodustat (N = 37), enarodustat (N = 44), molidustat (N = 13), and vadadustat (N = 30). Greenhouse–Geisser correction for departure from sphericity was performed after univariate type III repeated-measures analysis of variance, assuming sphericity. A time-dependent effect was observed ($P < 0.0001$); however, there were no significant differences in drug efficacy ($P = 0.2647$). HIF-PHI, hypoxia-inducible factor prolyl hydroxylase inhibitor

The HIF-PHI dose at 3 months is shown in Fig. 2. After 3 months, the mean doses of daprodustat, enarodustat, molidustat, and vadadustat increased by 110%, 177%, 125%, and 152%, respectively, from the initial dose. The treatment doses of enarodustat and vadadustat were significantly higher than that of daprodustat.

The HPI at 3 months is shown in Fig. 3. The HPIs of daprodustat, enarodustat, molidustat, and vadadustat at 3 months were 0.168, 0.307, 0.184, and 0.254, respectively (Fig. 3a). The HPI of daprodustat was significantly lower than those of enarodustat and vadadustat. In non-pre-medicated patients, the HPIs of daprodustat, enarodustat, molidustat, and vadadustat at 3 months were 0.169, 0.287, 0.158, and 0.237, respectively (Fig. 3b). The HPIs of daprodustat and molidustat tended to be lower than those of enarodustat and vadadustat but not significantly. The HPI at 6 and 12 months are shown in Fig. 3c and Fig. 3d. The HPIs of daprodustat, enarodustat, molidustat, and vadadustat at 6 months were 0.141, 0.296, 0.154, and 0.222, respectively (Fig. 3c). The HPIs of daprodustat, enarodustat, molidustat, and vadadustat at 12 months were 0.158, 0.297, 0.148, and 0.235, respectively (Fig. 3d).

The daily costs of HIF-PHI treatment are shown in Fig. 4. At 3 months, the mean daily costs of daprodustat, enarodustat, molidustat, and vadadustat were JPY 335, 434, 206, and 565, respectively. The cost of treatment with molidustat was significantly lower than that of vadadustat and enarodustat. The cost of daprodustat is significantly lower than that of vadadustat.

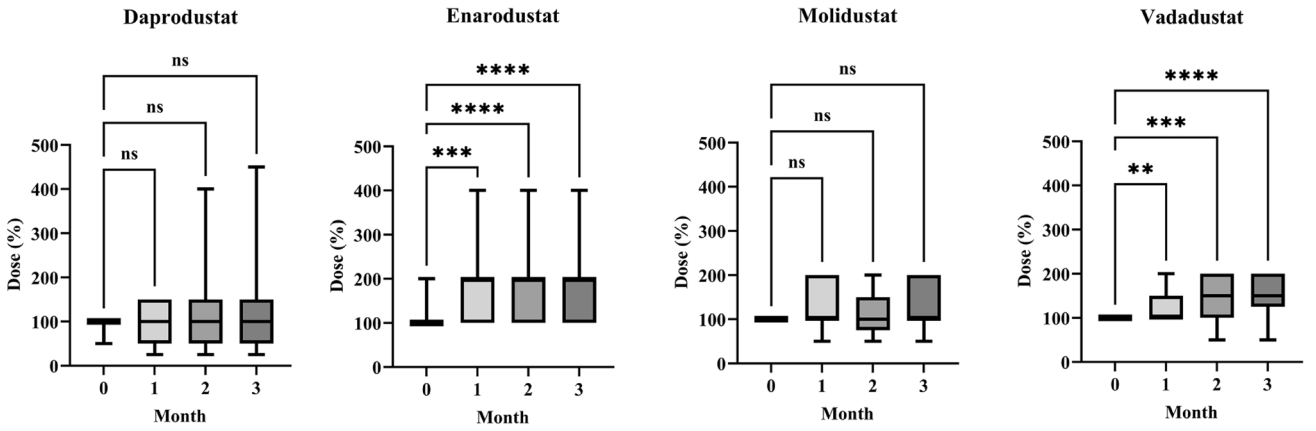

Fig. 2 Change in dose for the treatment with HIF-PHI. The percent change from the initial dose of each HIF-PHI is shown as the median (25% and 75%). Kruskal–Wallis test was used for daprodustat ($P=0.64$), enarodustat ($P<0.0001$), molidustat ($P=0.6215$), and vadadustat ($P<0.0001$). Pairwise comparison with Dunn's test, $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, $^{****}P<0.0001$. HIF-PHI, hypoxia-inducible factor prolyl hydroxylase inhibitor

Discussion

Four HIF-PHIs, daprodustat, enarodustat, molidustat, and vadadustat, were retrospectively evaluated in 124 patients with renal anemia between 2020 and 2023. We compared the effects of the four HIF-PHIs on the treatment dose, drug potency by HPI, and daily drug costs 3 months after treatment. Daprodustat and molidustat were maintained at the initial dose for treating renal anemia, whereas the doses for enarodustat and vadadustat were increased by approximately 50%. The difference in treatment dose seems to be due to the difference in drug potency, in which HPI significantly differed among HIF-PHIs, as shown in this study. The difference between the HPI and the cost of the initial dose accounts for the disparity in the daily costs of renal anemia treatment among HIF-PHIs.

Drug potency was significantly different among the HIF-PHIs. Daprodustat and molidustat were found to be more potent than vadadustat and enarodustat. Slow erythropoiesis with vadadustat and enarodustat, particularly in patients previously treated with ESA, was also observed in Japanese phase III trials compared to darbepoetin alfa [11–13]. In a Japanese phase III trial for vadadustat at a starting dose of 300 mg, Hb levels did not increase during the initial six weeks in patients who had previously used ESAs [12]. In patients who had not been previously treated with ESAs, Hb levels increased after four weeks; the dose of vadadustat needed to be increased in some patients after four weeks [12]. The vadadustat dose was increased to 450 mg/day after eight weeks. Hb levels did not increase but tended to decrease after treatment with 2 mg/day of enarodustat during the initial eight weeks in patients who had previously used ESAs [13]. These results suggest that slow erythropoiesis is a characteristic of vadadustat and enarodustat at the initiation of treatment in patients who have previously used ESAs. The initial dose of vadadustat may have been too low to increase Hb levels in the 1 month because Hb levels increased after administering higher doses of vadadustat (450 mg or 600 mg). In a phase II study, 450 mg vadadustat was administered as the initial dose. By the second week, the mean Hb levels had increased significantly from baseline, further increasing by 0.5 g/dL by the fourth week [14]. For enarodustat, a starting dose of 2 mg may be too low for treating patients previously treated with ESA, as Hb increased after eight weeks with up-titration to 4 mg at four weeks. In a phase III study of molidustat, the Hb level increased in the first eight weeks with 25 mg of the initial dose of molidustat in patients with CKD without dialysis [15]. In this study, a dose–response relationship was observed between 25 and 75 mg molidustat in patients with CKD without dialysis. In a transition study from darbepoetin alfa to molidustat, Hb levels were maintained within the target range without falling with 25 mg of molidustat [15]. In contrast, slow erythropoiesis has not been reported with daprodustat in patients with CKD or those on dialysis [16, 17]. The effect of daprodustat on the increase in Hb was better than that of darbepoetin alfa in patients who were not previously treated with ESA, whereas the Hb increase seemed to be comparable between daprodustat and darbepoetin alfa groups in patients previously treated with ESA. Differences in the potency of HIF-PHIs may contribute to differences in the erythropoietic response to HIF-PHIs.

In the present study, we used HPI to indicate HIF-PHI potency. HPI was calculated as follows: HPI = treatment drug dose/starting dose × 100/Hb (g/dL) /BW (kg). This idea is based on the established HIF-PHI resistance index, which is calculated as follows: HRI = weekly dose of HIF-PHI (mg) /Hb (g/dL) /body weight (kg) [18]. HRI increased

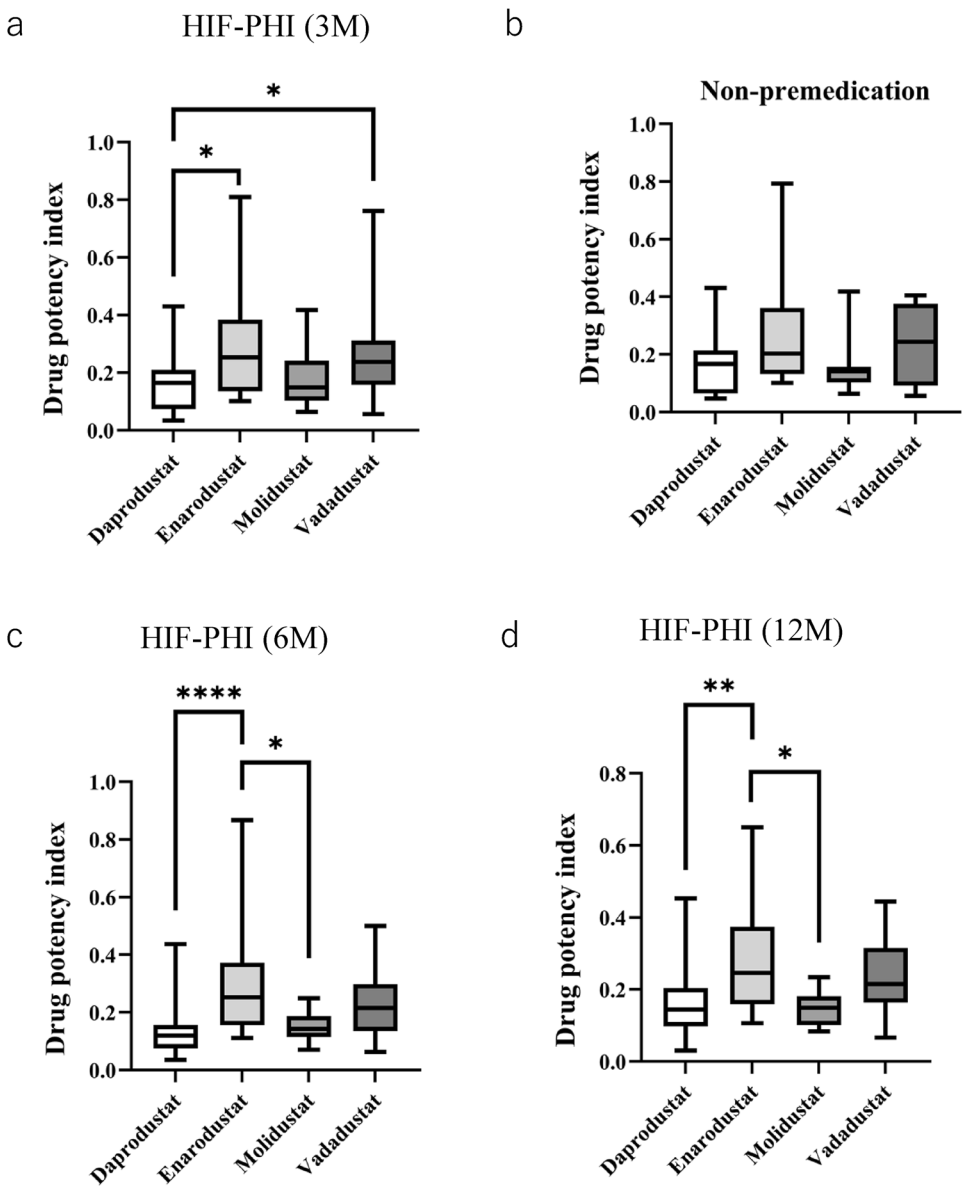

Fig. 3 HIF-PHI potency index (HPI). **a** The HPI is shown for each HIF-PHI in all patients at 3 months: daprodustat (N = 36), enarodustat (N = 41), molidustat (N = 13), and vadadustat (N = 22). Kruskal–Wallis test, $P = 0.007$. Pairwise comparison with Bonferroni adjustment; $^{*}P < 0.05$. **b** HPI for each HIF-PHI in patients without pre-medication. daprodustat (N = 15), enarodustat (N = 28), molidustat (N = 9), and vadadustat (N = 4). Kruskal–Wallis test, $P = 0.196$. HIF-PHI, hypoxia-inducible factor prolyl hydroxylase inhibitor. **c** The HPI is shown for each HIF-PHI in patients at 6 months. daprodustat (N = 25), enarodustat (N = 27), molidustat (N = 11), and vadadustat (N = 16). Kruskal–Wallis test, $P = 0.0002$. Pairwise comparison with Bonferroni adjustment; $^{*}P < 0.05$, $^{****}P < 0.0001$. **d** HPI is shown for each HIF-PHI in patients at 12 months. daprodustat (N = 24), enarodustat (N = 23), molidustat (N = 10), and vadadustat (N = 14). Kruskal–Wallis test, $P = 0.0009$. Pairwise comparison with Bonferroni adjustment; $^{*}P < 0.05$, $^{**}P < 0.01$

in proportion to increased resistance to renal anemia treatment. Thus, HPI decreased in proportion to an increase in drug potency. A lower HPI indicates a higher potency of HIF-PHIs in erythropoiesis. Based on this, the HPIs were in the following order of strength of drug potency: daprodustat, molidustat, enarodustat, and vadadustat (Fig. 3a–d).

The cost of treating renal anemia using HIF-PHIs depends on the initial dose. To reduce the daily costs of HIF-PHIs, molidustat, daprodustat, enarodustat, and vadadustat have been used. Molidustat had the lowest initial daily cost of treatment and a good PHI, contributing to the lower daily cost of treatment at 3 months. In the present study, patients treated with daprodustat were pre-medicated with ESAs; however, the low daily cost and high PHI of daprodustat contributed to the low cost of treatment at 3 months.

The target Hb level for treating renal anemia in patients with CKD without dialysis is expected to change by 2023. In the present study, the target Hb level was 11–13 g/dL, set according to the 2018 Japanese CKD guidelines [10], requiring a relatively high HIF-PHIs dose. The Japanese Guidelines for the Diagnosis and Treatment of Chronic Kidney Disease were revised in 2023 [22], and the target hemoglobin level for treating renal anemia was reduced to 10–13 g/dL. This may improve the gap between guideline recommendations and real-world clinical practice. The proportion of participants who reached the targeted Hb level of 11–13 g/dL was less than 50%, except those treated with daprodustat and molidustat. Given that the target Hb level was 10–13 g/dL according to the 2023 Guidelines for the Diagnosis and Treatment of Chronic Kidney Disease,

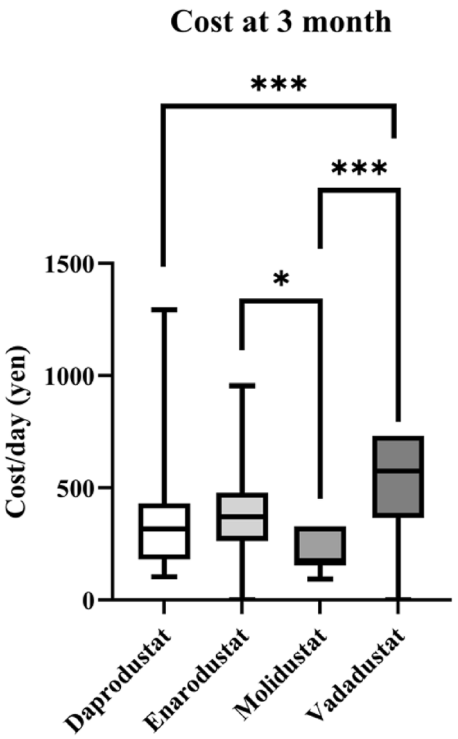

Fig. 4 Daily cost for treatment with HIF-PHI. Daily costs are presented as medians (25% and 75%). The Kruskal–Wallis test was used for daprodustat ($P=0.64$), enarodustat ($P<0.0001$), molidustat ($P=0.6215$), and vadadustat ($P<0.0001$). Pairwise comparison with Dunn's test, $*P<0.05$, $**P<0.01$, $***P<0.001$, $****P<0.0001$. HIF-PHI, hypoxia-inducible factor prolyl hydroxylase inhibitor

more than 80% of the participants reached the target Hb level of 10–13 g/dL after treatment with daprodustat or molidustat, and more than 60% of them maintained the target Hb level after treatment with enarodustat or vadadustat. This may improve the gap between guideline recommendations and real-world clinical practice.

The present study had several limitations. First, this was a retrospective observational study conducted at a single center. Therefore, randomization could not be performed. Secondly, the sample size was small. Subtle changes in clinical parameters may not be detected in some patients; therefore, a real-world prospective multicenter study is warranted. Third, the number of patients previously treated with ESAs varied among HIF-PHIs. Patients previously treated with ESAs or HIF-PHIs are often resistant to HIF-PHIs. In other words, a high dose of HIF-PHIs may be needed to treat renal anemia in patients who were premedicated. Vadadustat and daprodustat groups had a significantly higher proportion of patients with pre-medication with ESA or HIF-PHI than enarodustat and molidustat groups. This may partly account for the requirement for dose escalation in the initial phase of vadadustat compared with daprodustat.

In conclusion, heterogeneity exists among HIF-PHIs, and differences in drug potency affect dosage changes during renal anemia treatment in patients with CKD without dialysis. The cost of renal anemia treatment is related to the initial daily costs of HIF-PHIs and HPI. HIF-PHIs with a lower initial dose cost and lower HPI impose less economic burden and a better clinical outcome for maintaining Hb at target levels of 11–13 g/dL.

Acknowledgements English language editing was provided by Editage.

Author contributions Enyu Imai was responsible for the conception, design, and interpretation of the data and writing of the manuscript. Atsuhiro analyzed the data.

Funding This research was conducted with the help of Enyu Imai, the corresponding author.

Declarations

Conflict of interest Enyu Imai and Atsuhiro Imai declare no conflicts of interest.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (Hyogo Medical Association IRB approval number R4-005) and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent As this was a retrospective study, we used an opt-out approach and waived the requirement for written informed consent.

References

1. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol. 2012;23:1631–4.
2. Silverberg DS, Wexler D, Iaina A, Steinbruch S, Wollman Y, Schwartz D. Anemia, chronic renal disease and congestive heart failure—The cardio renal anemia syndrome: The need for cooperation between cardiologists and nephrologists. Int Urol Nephrol. 2006;38:295–310.
3. Roxadustat DS. First global approval. Drugs. 2019;79:563–72.
4. Daprodustat DS. First approval. Drugs. 2020;80:1491–7.
5. Vadadustat MA. First approval. Drugs. 2020;80:1365–71.
6. Enarodustat MA. First approval. Drugs. 2021;81:169–74.
7. Böttcher M, Lentini S, Arens ER, Kaiser A, van der Mey D, Thuss U, Kubitza D, Wensing G. First-in-man-proof of concept study with molidustat: A novel selective oral HIF-prolyl hydroxylase inhibitor for the treatment of renal anaemia. Br J Clin Pharmacol. 2018;84:1557–65.
8. Imai E, Imai A. The comparison between vadadustat and daprodustat regarding dose, cost, and safety of treatment for renal anemia in non-dialysis patients with chronic kidney diseases. Intern Med. 2023. https://doi.org/10.2169/internalmedicine.2501-23.
9. Zheng Q, Yang H, Sun L, et al. Efficacy and safety of HIF prolyl-hydroxylase inhibitor vs epoetin and darbepoetin for anemia in chronic kidney disease patients not undergoing dialysis: A network meta-analysis. Pharmacol Res. 2020;159: 105020. https://doi.org/10.1016/j.phrs.2020.105020.

10. Japanese Society of Nephrology. The guideline for the diagnosis and treatment of chronic kidney disease 2018, Tokyo Igakusya, Topkyo 2018.
11. Chertow GM, Pergola PE, Farag YMK, et al. Vadadustat in patients with anemia and non-dialysis-dependent CKD. N Engl J Med. 2021;384:1589–600.
12. Nangaku M, Kondo K, Kokado Y, et al. Phase 3 randomized study comparing vadadustat with darbepoetin alfa for anemia in Japanese patients with nondialysis-dependent CKD. J Am Soc Nephrol. 2021;32:1779–90.
13. Akizawa T, Nangaku M, Yamaguchi T, Koretomo R, Maeda K, Miyazawa Y, Hirakata HA. A Phase 3 study of enarodustat in anemic patients with CKD not requiring dialysis: The SYMPHONY ND study. Kidney Int Rep. 2021;6:1840–9.
14. Pergola PE, Spinowitz BS, Hartman CS, Maroni BJ, Haase VH. Vadadustat, a novel oral HIF stabilizer, provides effective anemia treatment in nondialysis-dependent chronic kidney disease. Kidney Int. 2016;90:1115–22.
15. Macdougall IC, Akizawa T, Berns JS, Bernhardt T, Krueger T. Effects of molidustat in the treatment of anemia in CKD. Clin J Am Soc Nephrol. 2019;14:28–39.
16. Singh AK, Carroll K, McMurray JJV, et al. Daprodustat for the treatment of anemia in patients not undergoing dialysis. N Engl J Med. 2021;385:2313–24.
17. Nangaku M, Hamano T, Akizawa T, et al. Daprodustat compared with epoetin beta pegol for anemia in Japanese patients not on dialysis: A 52-week randomized open-label Phase 3 trial. Am J Nephrol. 2021;52:26–35.
18. Hanafusa N, Abe M, Joki N, Hoshino J, Tankguchi M, Kikuchi S, Hasegawa T, Goto S. 2022 Annual Dialysis Data Report JSDT Renal Data Registry. J Dial Ther. 2023;56:473–536.
19. Japanese Society of Nephrology. The guideline for the diagnosis and treatment of chronic kidney disease. Tokyo Igakusya; 2023.