Effect of Roxadustat on Thyroid Function in Patients With Renal Anemia

Takuya Haraguchi,1,2,3 Yoshiyuki Hamamoto,1,2 Hitoshi Kuwata,1,2 Yuji Yamazaki,1,2 Susumu Nakatani,1,2 Takanori Hyo,1,2 Yuichiro Yamada,1,2 Daisuke Yabe,2,3 and Yutaka Seino1,2

1Center for Diabetes, Endocrinology and Metabolism, Kansai Electric Power Hospital, Osaka 553-0003, Japan
2Yutaka Seino Distinguished Center for Diabetes Research, Kansai Electric Power Medical Research Institute, Kobe 650-0047, Japan
3Department of Diabetes, Endocrinology and Metabolism/Department of Rheumatology and Clinical Immunology, Gifu University Graduate School of Medicine, Gifu 501-1194, Japan

Correspondence: Yoshiyuki Hamamoto, MD, PhD, Center for Diabetes, Endocrinology and Metabolism, Kansai Electric Power Hospital, Osaka, 2-1-7 Fukushima, Fukushima-ku, Osaka 553-0003, Japan. Email: hamamoto.yoshiyuki@b4.kepco.co.jp.

Abstract

Context: Roxadustat, a hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor, a recently developed class of drugs for treatment of anemia in chronic kidney disease (CKD), is reported to have a structure unlike that of other HIF-PH inhibitors but similar to that of triiodothyronine and bind to the thyroid hormone receptor in vitro. However, reports on the effects of roxadustat on thyroid function are limited and not detailed, and it remains unknown whether other HIF-PH inhibitors also affect thyroid function.

Objective: To compare the effect of roxadustat with daprodustat, another HIF-PH inhibitor, on thyroid function in patients with renal anemia in CKD.

Methods: This retrospective observational study included a total of 26 patients with anemia in CKD who were treated with roxadustat or daprodustat; thyroid-stimulating hormone (TSH) and free thyroxine (FT4) were measured before and after treatment with the drugs.

Results: After initiation of roxadustat, TSH showed a significant decrease (2.4732 [1.7858-4.9016] μIU/mL before treatment and 0.659 [0.112-2.005] μIU/mL after treatment, P < .05); FT4 showed a significant decrease (0.93 [0.84-1.05] ng/dL before treatment and 0.70 [0.53-0.85] ng/dL after treatment, P < .01). After daprodustat initiation, neither TSH nor FT4 showed a significant change (TSH: 3.044 [1.853-4.171] μIU/mL before treatment and 2.893 [1.866-4.894] μIU/mL after treatment, P = .635; FT4 was 0.93 [0.81-1.00] ng/dL before treatment and 0.97 [0.87-1.05] ng/dL after treatment, P = .328).

Conclusion: Roxadustat decreases TSH and FT4 levels while daprodustat does not.

Key Words: roxadustat, daprodustat, hypoxia-inducible factor prolyl hydroxylase inhibitor, thyroid-stimulating hormone (TSH), thyroid hormone receptor, hypothyroidism

Renal anemia is an important complications of chronic kidney disease (CKD) that is induced through decreased production of erythropoietin and alterations of iron metabolism (1); it and affects quality of life and is a risk factor for mortality in patients with CKD (2). Treating with recombinant human erythropoietin or erythropoiesis-stimulating agents (ESAs) has been found to increase hemoglobin (Hb) levels and lessens the frequency of transfusion for patients with CKD, particularly those with end-stage renal disease receiving hemodialysis. Nowadays, the combination of ESAs and iron has become the standard therapy for anemia of CKD, and improves quality of life in general (3, 4). On the other hand, several randomized controlled trials suggested that higher Hb-targeted treatments with ESAs would be associated with higher rates of cerebrovascular and cardiovascular events (4-6). However, it remains unclear whether these adverse events are due to the dosage of the ESA or the higher Hb levels (7). An emerging new idea is that enhancement of endogenous erythropoietin production has potential to reduce those adverse events, since the concentration of erythropoietin (EPO) is maintained at levels similar to the physiological level rather than that of the pharmacologic administration of EPAs (7).

Hypoxia-inducible factor (HIF) is a transcription factor induced when cells are hypoxic, and initiates production of erythropoietin; it is rapidly degraded by hypoxia-inducible factor prolyl hydroxylase (HIF-PH) under normal oxygenation. HIF-PH inhibitors are a novel category of drug that stimulate endogenous erythropoietin production by stabilizing HIF through the inhibition of HIF-PH, which results in more stable physiological levels of erythropoietin, which have been found to be associated with fewer adverse events than exogenous ESA drugs in clinical studies (7). Roxadustat was launched...
Subjects treated with daprodustat: n=13  Subjects treated with roxadustat: n=10

All subjects who were treated with HIF-PH inhibitors and measured TSH and FT4 before and after the treatment between November 2019 and March 2022: n=26
Roxadustat: n=11
Daprodustat: n=15

Subjects who died within 60 days of starting HIF-PH inhibitors: n=1

Subjects who already treated with thyroid hormone replacement therapy: n=2
Hashimoto’s thyroiditis: n=1
After total thyroidectomy for thyroid cancer: n=1

Eligible subjects: n=23

Subjects treated with roxadustat: n=10
Subjects treated with daprodustat: n=13

Figure 1. Schematic diagram of the study subjects. FT4, free thyroxine; TSH, thyroid-stimulating hormone.

in Japan in November 2019 as a novel HIF-PH inhibitor not inferior to darbepoetin alfa (8). Subsequently, other HIF-PH inhibitors were launched, and 5, including daprodustat, are currently on the market in Japan. Both roxadustat and daprodustat are orally administered; daprodustat is administered daily, and roxadustat is administered on 3 alternative days in a week.

Roxadustat is reported to have a structure unlike that of other HIF-PH inhibitors but similar to that of triiodothyronine (T3) and shows preferential activity toward thyroid hormone receptor (THR) β over THRα in in vitro conditions (9). There are few reports of thyroid-stimulating hormone (TSH) reduction after administration of roxadustat to hemodialysis patients as replacement therapy for hypothyroidism (10, 11). Because THRβ in the pituitary and hypothalamus plays an important role in thyroid hormone feedback regulation, roxadustat might be expected to affect regulation of thyroid hormone secretion (12). Notwithstanding the paucity and insufficient comprehensiveness of the current literature concerning the impact of roxadustat on thyroid function, in vitro observation in conjunction with case reports suggest a possible influence on thyroid hormone regulation in vivo. It remains unknown whether other HIF-PH inhibitors affect thyroid function. In this retrospective study, we compare the effects of roxadustat and daprodustat on thyroid function in patients with renal anemia in CKD.

Materials and Methods

Study Design and Participants

A total of 26 patients with anemia in CKD were retrospectively identified and analyzed; they were treated with roxadustat or daprodustat, and TSH and free thyroxine (FT4) were measured before and after treatment at Kansai Electric Power Hospital (Osaka, Japan) between November 2019 and March 2022. Patients who died within 60 days of starting HIF-PH inhibitors or were already treated with thyroid hormone replacement therapy were excluded. A schematic diagram of the process is shown in Fig. 1.

The study was approved by the Ethics Committee of Kansai Electric Power Medical Research Institute and carried out in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare of Japan. Patient consent was obtained by opt-out method using the webpage of our institute.

Measurements

Electronic medical records were used to retrospectively investigate HIF-PH inhibitor prescription status, age, gender, dialysis history, height, weight, TSH, FT4, Hb, creatinine, total cholesterol (T-Chol), and creatine kinase (CK) values.

Statistical Analysis

Patient characteristics and results are reported as median and interquartile range. Statistical analysis was carried out using Easy R (EZR version 1.54) (13). For examination of patient background factors, the Mann–Whitney U test was used for continuous variables and Fisher’s exact test for nominal variables. The Wilcoxon signed-rank test was used to test for continuous variable changes before and after HIF-PH inhibitor administration. Spearman’s rank correlation coefficient was used to test the correlation between the changes in thyroid function and the changes in various test results after HIF-PH inhibitor administration. P < .05 was considered to be statistically significant.

Results

Of the 26 patients with anemia in CKD who were treated with roxadustat or daprodustat, 3 were excluded due to the
exclusion criteria (1 died within 60 days of starting HIF-PH inhibitors; 2 were already being treated with thyroid hormone replacement therapy) and 23 patients (roxadustat, 10 patients; daprodustat, 13 patients) were analyzed (Fig. 1). Baseline characteristics are shown in Table 1. Patients treated with roxadustat included more dialysis patients and showed lower Hb levels than those who were treated with daprodustat, but there was no significant difference in the other parameters. Blood samples were collected 32.0 hours on average after administration of the drug (roxadustat, 7.7-9.2 hours; daprodustat, 26.3-35.0 hours). There was no increase in T-Cho and CK levels in patients in the roxadustat treatment group irrespective of the changes in FT4 (ΔT-Cho: −4 [−29-15] mg/dL, ΔCK: −21 [−43-1] U/L).

Figure 6 shows correlations of changes in Hb and suppression of TSH after initiation of the HIF-PH inhibitor. There was no significant correlation between changes in Hb and TSH with either roxadustat or daprodustat dose at measuring thyroid hormone after administration of the drug (roxadustat, mg/week; daprodustat, mg/day).

Discussion

The current study suggests that roxadustat affects FT4 and TSH levels without significant changes in T-Chol or CK, and, intriguingly, without symptoms of hypothyroidism despite the significantly reduced levels of FT4 and TSH. In contrast, daprodustat did not affect either FT4 or TSH levels. Thus, roxadustat, by reducing FT4 and TSH levels without increasing hypothyroidism indicates that the drug can function as a thyroid hormone mimetic. While a likely agonist effect of roxadustat on THRβ was previously reported (9-11), the

Table 1. Baseline characteristics of the patients with renal anemia before roxadustat or daprodustat treatment

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Roxadustat</th>
<th>Daprodustat</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline (years)</td>
<td>73 (59-80)</td>
<td>67 (51-80)</td>
<td>77 (71-79)</td>
<td>.495a</td>
</tr>
<tr>
<td>n (%male)</td>
<td>23 (65.2%)</td>
<td>10 (60.0%)</td>
<td>13 (69.2%)</td>
<td>.685b</td>
</tr>
<tr>
<td>BMI at baseline (kg/m²)</td>
<td>23.8 (20.2-26.6)</td>
<td>26.4 (23.1-29.7)</td>
<td>23.2 (19.9-26.1)</td>
<td>.088a</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodialysis (n)</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Peritoneal dialysis (n)</td>
<td>9</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>No (n)</td>
<td>11</td>
<td>2</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Time to thyroid function measurements prior to initiation of HIF-PH inhibitors (months)</td>
<td>4.0 (1.0-13.3)</td>
<td>4.7 (0.9-8.3)</td>
<td>4.0 (1.2-15.2)</td>
<td>.852a</td>
</tr>
<tr>
<td>Duration of HIF-PH inhibitors treatment at measuring thyroid hormone after administration of the drug (months)</td>
<td>2.1 (0.7-3.2)</td>
<td>1.3 (0.3-3.4)</td>
<td>2.1 (1.2-3)</td>
<td>.419a</td>
</tr>
<tr>
<td>TSH (μIU/mL)</td>
<td>3.044 (1.794-4.859)</td>
<td>2.473 (1.786-4.902)</td>
<td>3.044 (1.853-4.171)</td>
<td>.976a</td>
</tr>
<tr>
<td>FT4 (ng/dL)</td>
<td>0.93 (0.82-1.04)</td>
<td>0.93 (0.84-1.05)</td>
<td>0.93 (0.81-1.00)</td>
<td>.555a</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.4 (8.2-10)</td>
<td>8.2 (7.7-9.2)</td>
<td>9.5 (9.2-10.4)</td>
<td>.018a</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>4.8 (3.2-11.4)</td>
<td>8.3 (4.8-11.7)</td>
<td>4.3 (2.5-5.3)</td>
<td>.101a</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>145 (125-168)</td>
<td>130 (111-169)</td>
<td>149 (138-166)</td>
<td>.368a</td>
</tr>
<tr>
<td>Creatine kinase (U/L)</td>
<td>74 (50-138)</td>
<td>78 (39-124)</td>
<td>74 (52-142)</td>
<td>.598a</td>
</tr>
</tbody>
</table>

*Each value represents the median (interquartile range).

*P values were calculated by the Mann–Whitney U-test or Fisher’s exact test where appropriate for patients treated with roxadustat vs daprodustat.

Abbreviations: BMI, body mass index; FT4, free thyroxine; HIF-PH, hypoxia-inducible factor prolyl hydroxylase; TSH, thyroid-stimulating hormone.
The present results are the first to report clinical evidence that roxadustat can act as a THRβ agonist.

Roxadustat is a compound with a molecular structure similar to that of thyroid hormones and interacts with many of their molecular targets (9). Analysis of the distribution of nuclear THRα and THRβ subtypes indicates that both THRα and THRβ are involved in cardiac and metabolic responses, and several selective THRβ agonists have been developed for the purpose of treating dyslipidemia to avoid cardiac thyrotoxicosis. Sobetirome, one of these analogues, is a clinical stage thyroid stimulant that is known to act in this manner (14, 15). Sobetirome is also the only thyroid hormone

---

**Figure 2.** TSH and FT4 levels before and after initiation of HIF-PH inhibitors. (A) TSH levels treated with roxadustat. (B) TSH levels treated with daprodustat. (C) FT4 levels treated with roxadustat. (D) FT4 levels treated with daprodustat. All boxes and horizontal bars denote interquartile range and median, and the endpoints of the whiskers correspond to the maximum and minimum values below the median ± 1.5 times the interquartile range. *P < .05 by the Wilcoxon signed rank test. **P < .01 by the Wilcoxon signed rank test. FT4, free thyroxine; TSH, thyroid-stimulating hormone.

---

**Figure 3.** TSH and FT4 changes after initiation of HIF-PH inhibitors. FT4, free thyroxine; TSH, thyroid-stimulating hormone.
analogue reported to cross the blood–brain barrier and be distributed to the central nervous system upon systemic dose administration \((16, 17)\). Treatment of male C57BL/6 mice with sobetirome at a concentration of \(\geq 10\, \mu\text{g/kg/day}\) for a short-term of 7 days suppressed TSH level; long-term 29-day treatment induced a state resembling that characteristic of central hypothyroidism, including reduced circulating T4 and T3 with normal TSH levels \((18)\). Interestingly, these mice showed no signs of hypothyroidism despite systemic T4 and T3 depletion, which may well have been due to the thyroid hormone–mimicking effects of sobetirome in the central and peripheral target organs. In our current clinical study, not only FT4 but also TSH remained suppressed, unlike the findings in the long-term animal experiment with the analogue. This anomaly might be the effect of the strong suppression by sobetirome on T3 and T4 when used for a long period of time in conjunction with its inhibition of TSH that induces positive feedback against TSH through reduced thyroid hormone levels; roxadustat, on the other hand, does not so strongly suppress TSH, allowing a balanced reduction in FT4 and TSH.

Figure 4. Correlations between the times to blood collection after administration of HIF-PH inhibitor and changes in (A) FT4 and (B) TSH after initiation of the drugs. FT4, free thyroxine; Hb, hemoglobin; TSH, thyroid-stimulating hormone.

Figure 5. (A) T-Cho and FT4 changes after initiation of HIF-PH inhibitors. (B) CK and FT4 changes after initiation of HIF-PH inhibitors. CK, creatine kinase; FT4, free thyroxine; T-Cho, Total cholesterol.
Alternatively, the TSH-suppressing effect might vary in individuals depending on the dose of roxadustat. In this investigation, one of the indications that roxadustat does not precipitate hypothyroidism is the finding that T-Cho levels remained unchanged in patients exhibiting reduced FT4. In addition, it has been documented that HIF attenuates cholesterol levels. The putative mechanism includes suppression of the 3-hydroxy-3-methylglutaryl coenzyme A reductase pathway, which constitutes the rate-limiting phase in cholesterol metabolism and culminates in accumulation of low-density lipoprotein and very-low-density lipoprotein receptors (19, 20). Further more, both roxadustat and daprodustat have been demonstrated to lower cholesterol levels (21-23). Even so, in patients with markedly decreased thyroid function, some alteration in lipid profiles might be expected. Because of the absence of significant effects on lipid profiles in patients with low FT4, roxadustat would not appear to result in significant hypothyroidism.

This study has several limitations. First, we did not examine any HIF-PH inhibitors other than roxadustat and daprodustat, so it remains unclear whether the current findings are specific to roxadustat. However, roxadustat has a carboxyl group on its head, which THR ligands have in common, but unlike T3, it possesses an extended hydrophobic phenyl group, which is highly selective for THRβ (9). Daprodustat, on the other hand, does not have a thyroid hormone–like structure, suggesting poor binding to THR. Among the other HIF-PH inhibitors, enarodustat and vadadustat have carbonyl and hydrophobic phenyl groups similar to those of roxadustat, suggesting that their effects on thyroid function should be investigated. Second, since this is a retrospective study, confounding with other potentially relevant factors is unavoidable. We also used data of differently timed blood test measurements before and after HIF-PH inhibitor initiation. In addition, the period after drug administration of blood collection was longer in some roxadustat cases, which could result in underestimation of its effect on thyroid function. Third, if roxadustat affected thyroid function, hypothyroidism or tissue thyrotoxicosis manifesting in physical findings such as body weight, blood pressure, and heart rate would be expected. However, many of our participants were undergoing hemodialysis or peritoneal dialysis, which significantly impacts these parameters, so we were unable to thoroughly examine these aspects. This limitation highlights the need for further research in this patient population. Lastly, given the small sample size, we cannot rule out the possibility that the accumulation of a larger number of cases would lead to different results.

In conclusion, this retrospective analysis demonstrates that roxadustat decreases TSH and FT4 levels while daprodustat does not. Because the drug may act as a thyroid hormone agonist, supplemental thyroid hormone therapy is not recommended even if blood tests in CKD with anemia treated with roxadustat reveal persistent central hypothyroidism. Further prospective studies are required to provide more detailed information on the effects of HIF-PH inhibitors on thyroid function.

**Acknowledgments**

The authors are deeply grateful to all past and present members of Center for Diabetes, Endocrinology and Metabolism who contributed to the work. The authors also thank the patients and colleagues who contributed to this study.

**Funding**

This study was conducted without external funding/fellowship support.

**Disclosures**

Y.H. received grants from Sumitomo Pharma and Nippon Boehringer Ingelheim. Y.H. also received consulting or speaker fees from Novo Nordisk Pharma and Sumitomo Pharma. H.K. received grants from Ono, Taisho, and Novo Nordisk. H.K. also received speaker fees from Sanofi and Taisho. Yui.Y. received grants from Ono, Daiichi Sankyo, Mitsubishi Tanabe, Sumitomo Pharma, Takeda, and Novo

---

**Figure 6.** Correlations between changes in Hb and TSH after initiation of HIF-PH inhibitors. Hb, hemoglobin; TSH, thyroid-stimulating hormone.
Nordisk. Yui.Y. also received consulting or speaker fees from Mitsubishi Tanabe, MSD, Ono, Sumitomo Pharma, Sanofi, Takeda, Daiichi Sankyo, and Novo Nordisk. D.Y. received grants from Novo Nordisk, Ono, Terumo, Taisho, and Arklay. D.Y. also received consulting or speaker fees from Nippon Boehringer Ingelheim, Astellas, MSD, Novo Nordisk, Sumitomo Pharma, Ono, Eli Lilly, and Takeda. Y.S. received grants from Eli Lilly, Terumo, MSD, Taisho, Ono, Arklay, Novo Nordisk, and Nippon Boehringer Ingelheim. Y.S. also received consulting or speaker fees from Glaxo-Smith-Kline, Johnson & Johnson, Eli Lilly, Taisho, Sanofi, Novo Nordisk, Astellas, Takeda, Nippon Boehringer Ingelheim, and BD. The other authors declare no conflict of interest.

Data Availability
Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References