Clinical Kidney Journal, 2022, vol. 15, no. 5, 1024–1026

https://doi.org/10.1093/ckj/sfac015
Advance Access Publication Date: 17 January 2022
Letter to the Editor

LETTER TO THE EDITOR

Hypoxia-inducible factor prolyl hydroxylase inhibitors in kidney transplant recipients

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Since 2019, hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) have been approved for clinical use in Japan and China to treat renal anaemia. As erythropoiesis-stimulating agents (ESAs), HIF-PHIs are used to treat anaemia in dialysis-dependent/independent chronic kidney disease cases [1, 2]. They are oral agents that promote endogenous erythropoietin production and reduce functional iron deficiency and ESA-resistant anaemia caused by chronic inflammation-induced hepcidin production [3]. HIF-PHIs are not universally available and reports on their efficacy in kidney transplant recipients (KTRs) are scarce, since any randomized controlled trials investigating the efficacy and safety of HIF-PHIs in dialysis-independent patients excluded KTRs [1, 4].

We retrospectively observed five KTRs who underwent transplantation and subsequently received the HIF-PH roxadustat, for post-transplant anaemia (PTA). Roxadustat was indicated for participants who did not achieve target haemoglobin levels (>11 g/dL) either using ESA or not. Three patients had ESA-resistant anaemia, one wished to avoid injections and the other was not using ESA. Roxadustat was initiated according to Japan pharmaceutical reference (70 or 100 mg thrice weekly for patients with ESA and 50 mg thrice weekly for ESA-naïve patients). Patients on statins were switched to ezetimibe. Iron supplements were prescribed to maintain transferrin saturation and ferritin >20% and >100 ng/mL, respectively.

Mean ± SD age was 49.4 ± 11.2 years and all patients were female. The mean estimated glomerular filtration rate was 24.9 ± 10.2 mL/min/1.73 m^2. The mean ESA dose before roxadustat was 161 ± 85.7 μg/month as the adjusted epoetin beta pegol dose. The initial average roxadustat dose was 64.0 ± 21.9 mg thrice weekly. The trajectories of haemoglobin level and iron-related parameters are shown in Figure 1. Two of three patients who received 50 mg roxadustat initially had no increased haemoglobin levels. The haemoglobin level of one patient who received 100 mg roxadustat increased to 2.2 g/dL after 1 month. Ferritin levels decreased and the total iron-binding capacity (TIBC) increased as expected [3]. In all patients, low-density lipoprotein (LDL) cholesterol decreased (range: −15 to −58 mg/dL at 1 month) and in two of three patients, thyroid-stimulating hormone (TSH) levels decreased (Figure 2). No allograft function deterioration or adverse events such as thrombosis were observed.

Our results show the short-term (up to 3 months) efficacy and safety of HIF-PHIs for PTA regarding haemoglobin level elevation or preservation. Interestingly, TSH decreased in some patients and LDL cholesterol decreased in all patients, even in patients without any cholesterol-lowering drugs. Roxadustat has a molecular structure similar to triiodothyronine and binds to thyroid hormone receptors, decreasing hypothalamic TSH secretion through negative feedback [5], while its LDL cholesterol-lowering ability might result from a pleiotropic effect [2]. LDL cholesterol in two patients (one switched from statin to ezetimibe and the other did not take any cholesterol-lowering drugs) reascended at 2 to 3 months; however, the reason was unclear. Since this report consisted of small numbers and evaluated short-term outcomes, we cannot verify mid- and long-term efficacy and safety. Further long-term studies are needed to precisely establish the efficacy and safety of HIF-PHIs for PTA.

Received: 29.12.2021; Editorial decision: 11.1.2022

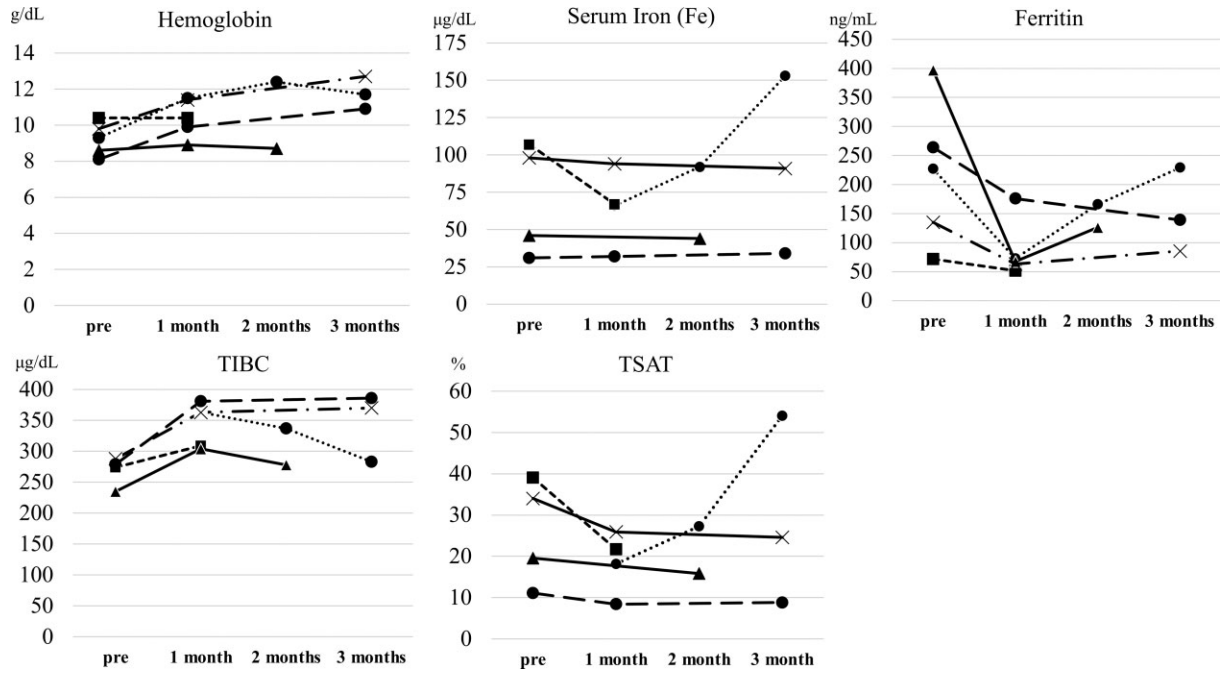

FIGURE 1: Trajectories of haemoglobin, TIBC, serum iron, ferritin and transferrin saturation (TSAT) from pre-administration to 3 months post-administration of HIF-PHI.

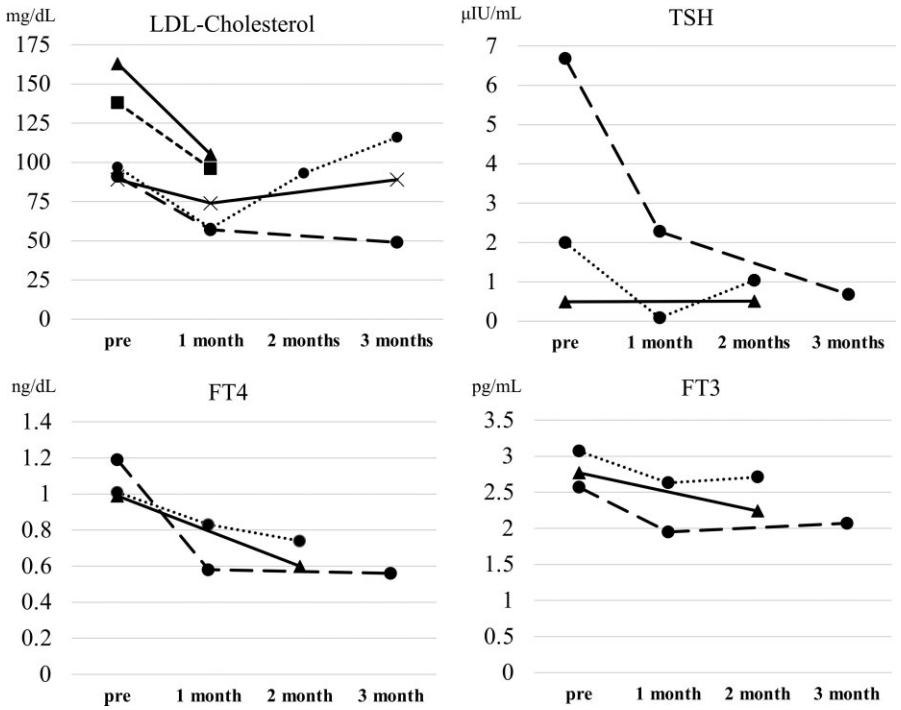

FIGURE 2: Trajectories of LDL cholesterol, TSH, free triiodothyronine (FT3) and free thyroxine (FT4) from pre-administration to 3 months post-administration of HIF-PHI. The normal values of TSH, FT3 and FT4 are from 0.5 to 5.0 μIU/mL, from 2.3 to 4.0 pg/mL and from 0.9 to 1.7 ng/dL, respectively.

ETHICS APPROVAL

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee at the St Marianna University School of Medicine and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

HIF-PHIs have already been approved by the Ministry of Health, Labour and Welfare in Japan, and we have used them in daily clinical practice based on indications, namely renal anaemia. There was no need to obtain informed consent from participants since this was a retrospective, observational study that included fewer than 10 patients without any new interventions or invasive procedures. According to the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Health, Labour and Welfare (Japan) and the institutional review board at St Marianna University School of Medicine, the need for written informed consent from all participants was waived.

CONFLICT OF INTEREST STATEMENT

The authors of this manuscript have no conflicts of interest to disclose.

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