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Research Article

Different Effects of Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitors on Serum Lipid Levels in Patients on Hemodialysis

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Abstract

Background: This study examined the impact of hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) on serum lipid levels among dyslipidemia patients undergoing hemodialysis.

Methods: We assessed Hemoglobin (Hb), serum Total Cholesterol (TC), Low-Density Lipoprotein Cholesterol (LDL-C), High-Density Lipoprotein Cholesterol (HDL-C), Triglycerides (TG), iron, Total Iron-Binding Capacity (TIBC), Transferrin Saturation (TSAT), and ferritin levels in the three groups. Study 1, 2, and 3 tested the efficacy of roxadustat (13 patients, 24 weeks), daprodustat (9 patients, 24 weeks), and enarodustat (15 patients, 12 weeks), respectively, in patients with renal anemia and dyslipemia undergoing hemodialysis.

Results: In Study 1, roxadustat treatment showed no significant changes in mean Hb values (10.4-10.7 g/dL) or mean serum iron, TG, and ferritin levels. However, mean TC (p=0.0002), LDL-C (p=0.0002), HDL-C (p=0.0005), and TSAT (p=0.0479) decreased significantly, while mean TIBC levels increased significantly (p=0.0002). In Study 2, daprodustat treatment resulted in no significant changes in mean Hb, TC, LDL-C, TG, TSAT, and ferritin levels. However, a significant decrease was observed in mean HDL-C levels (p=0.0117), while serum iron level (p=0.0078) and the mean TIBC level (p=0.0039) increased significantly. In Study 3, enarodustat treatment yielded no significant changes in mean Hb, TC, LDL-C, HDL-C, TG, TSAT, ferritin, and iron levels. However, the mean TIBC increased significantly (p=0.0151).

Conclusions: Different HIF-PHIs have varying effects on serum lipid levels in patients undergoing hemodialysis. Roxadustat improved iron metabolism, stabilized Hb levels, and significantly decreased LDL-C and HDL-C levels. Daprodustat improved iron metabolism, maintained stable Hb levels, and significantly decrease HDL-C levels. Enarodustat improved iron metabolism, maintained stable Hb levels, and did not decrease LDL-C or HDL-C levels.

Keywords: Anemia; Dyslipidemia; Hemodialysis; Hypoxia-inducible factor; Prolyl hydroxylase inhibitor; Serum iron

Introduction

The activity of Hypoxia-Inducible Factor (HIF), an oxygen-sensitive transcription factor involved in erythropoiesis, is regulated by HIF-prolyl hydroxylases. Reduced oxygen tension suppresses the activity of these enzymes, thereby increasing erythropoiesis. Chen et al. reported that the decrease in Total Cholesterol (TC) was greater with roxadustat than with epoetin alfa, as was the decrease in Low-Density Lipoprotein Cholesterol (LDL-C) in patients undergoing long-term dialysis [1]. Chen et al. reported that in patients with chronic kidney disease who were not undergoing dialysis, TC levels decreased by 23% during eight weeks of roxadustat therapy [2]. Csiky et al. reported that roxadustat was superior to an erythropoiesis-stimulating agent (ESA) in decreasing LDL-C from baseline to an average of 12-28 weeks in patients with end-stage kidney disease on stable dialysis [3]. Roxadustat is an oral HIF-Prolyl Hydroxylase Inhibitor (HIF-PHI) developed for dialysis-dependent Chronic Kidney Disease (CKD) anemia. While the impact of HIF-PHI on mean hemoglobin (Hb) levels in patients undergoing Hemodialysis (HD) has already been investigated [1], its effects on serum lipid levels have yet to be explored. Clarity regarding these effects is crucial because patients with chronic HD generally have lower plasma high-density lipoprotein cholesterol (HDL-C) levels than healthy participants. Low HDL-C levels are associated with an increased risk of death in patients undergoing chronic HD [4]. However, the effects of HIF-PHIs on dyslipidemia in patients undergoing HD remain unclear. This study aimed to investigate the effects of HIF-PHIs on serum lipid levels in patients undergoing HD.

Materials and Methods

Study Design, Population, and Data Sources

To investigate the effects of HIF-PHIs, we measured the levels of Hb, serum TC, LDL-C, HDL-C, Triglycerides (TG), iron, Total Iron-Binding Capacity (TIBC), Transferrin Saturation (TSAT), and ferritin in all three groups. In Study 1, we evaluated the efficacy of roxadustat in 13 patients (1 female and 12 male) with hemodialysis-dependent CKD anemia and dyslipidemia over 24 weeks. We investigated Hb, TC, TG, LDL-C, HDL-C, iron, TIBC, TSAT, and ferritin levels. The patients were assigned an initial dose of roxadustat (20 mg/week ~ 200 mg/week), and they self-administered roxadustat at two- or three-day intervals. The doses were adjusted to maintain the Hb levels within 10-12 g/dL. In any case, the dose of roxadustat did not exceed 3 mg/kg. In Study 2, we evaluated the efficacy of daprodustat in nine patients (2 female and 7 male) with hemodialysis-dependent CKD anemia and dyslipidemia over 24 weeks. We investigated the levels of Hb and serum TC, TG, LDL-C, HDL-C, iron, TIBC, TSAT, and ferritin. Treatment with daprodustat (1 mg/week-40 mg/week) was initiated, and the dosage was adjusted daily within the 1-24 mg range to maintain Hb within the target range (10-12 g/dL).

In Study 3, we evaluated the efficacy of enarodustat in 15 patients (3 female and 12 male) with hemodialysis-dependent CKD anemia and dyslipidemia over 24 weeks. We investigated the levels of Hb and TC, TG, LDL-C, HDL-C, iron, TIBC, TSAT, and ferritin. The enarodustat dose was adjusted daily to within 1-8 mg range to maintain Hb within the target range (10-12 g/dL).

Statistical Analysis

Data are expressed as mean±standard deviation for continuous variables and frequency (percentage) for categorical variables. The Wilcoxon signed-rank test was used for proportional assessments. Statistical significance was set up at $p < 0.05$. All statistical analyses were performed using SAS Statistics software (version 9.4; SAS Institute, Cary, North Carolina, USA).

Ethics Statement

This study was approved by the ethics committee of the Zenjinkai Group (approval number: 0000408974) and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, the International Council Harmonization of Technical Requirements for Pharmaceuticals for Human Use guideline. Written informed consent was obtained from all patients before the study.

Results

In the Study 1 cohort, the mean age and HD vintage of the participant was 77.7 and 6.6 years, respectively (Table 1). After roxadustat treatment, no significant changes were observed in mean Hb values (from 10.4 to 10.7g/dL) or mean serum iron, TG, and ferritin levels. However, mean TC (from 138.4 to 106.6mg/dL, p=0.0002), LDL-C (from 77.7 to 53.8mg/dL, p=0.0002), HDL-C (from 43.3 to 35.9mg/dL, p=0.0005), and TSAT (from 32.6 to 31.2%, p=0.0479) decreased significantly. The mean TIBC levels increased significantly (from 220.5 to 265.1 μg/dL, p=0.0002) (Table 2).

	Study 1 Roxadustat	Study 2 Daprodustat	Study 3 Enarodustat
N	13	9	15
Age, years (mean±SD)	77.7±6.1	74.6±10.2	69.3±10.7
Sex			
Male	12	7	12
Female	1	2	3
Time on dialysis, years (mean±SD)	6.6±4.2	3.2±2.6	8.9±10
CKD etiology, n (%)			
Diabetic nephrology	3	3	5
Glomerulonephritis	4	3	5
Nephrosclerosis	4	0	3
Polycystic kidney	1	0	0
Unknown	1	2	0
Gouty kidney	0	1	0
Interstitial nephritis	0	0	1
Microscopic polyangiitis	0	0	1

Table 1: Baseline demographics and characteristics (N=37).

	Before	After	p
Hb (g/dL), (mean±SD)	10.4 (0.3)	10.7 (0.6)	0.3396
Serum iron (pg/dL), (mean±SD)	67.4 (16.2)	76.2 (35.1)	0.5417
TIBC (pg/dL), (mean±SD)	220.5 (44.9)	265.1 (53.7)	0.0002
TSAT (%), (mean±SD)	32.6 (14.5)	31.2 (19.2)	0.0479
Ferritin (ng/mL), (mean±SD)	197.1 (148.2)	198.1 (156.3)	0.8394
Total cholesterol	138.4 (29.2)	106.6 (25.7)	0.0002
LDL-C	77.7 (26.8)	53.8 (21.7)	0.0002
HDL-C	43.3 (8.8)	35.9 (7.2)	0.0005
TG	87.7 (18.8)	79.2 (30.4)	0.1909

Hb: Hemoglobin; TIBC: Total Iron-Binding Capacity; TSAT: Transferrin Saturation; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; TG Triglycerides (TG).

Table 2: Baseline demographics and characteristics in study 1 (roxadustat).

In Study 2 cohort, the mean age and HD vintage were 74.6 and 3.2 years, respectively (Table 1). After daprodustat treatment, no significant changes were observed in the mean Hb, TC, LDL-C, TG, TSAT, and ferritin levels. However, the mean HDL-C levels decreased significantly (from 50.4 to 45.3mg/dL, p=0.0117). Furthermore, the serum iron level (from 72.5 to 89.1 μg/dL, p=0.0078) and the mean TIBC level (from 229.7 to 272.8 μg/dL, p=0.0039) increased significantly (Table 3).

In Study 3 cohort, the mean age and HD vintage were 69.3 and 8.9 years, respectively (Table 1). After enarodustat treatment, no significant changes were observed in the mean Hb, TC, LDL-C, HDL-C, TG, TSAT, ferritin, and iron levels. The mean TIBC increased significantly (from 230.0 to 259.4 μg/dL, p=0.0151) (Table 4).

	Before	After	p
Hb (g/dL), (mean±SD)	10.6 (0.4)	10.6 (0.6)	0.6523
Serum iron (pg/dL), (mean±SD)	72.5 (14.2)	89.1 (25.0)	0.0078
TIBC (pg/dL), (mean±SD)	229.7 (32.0)	272.8 (40.3)	0.0039
TSAT (%), (mean±SD)	32.4 (8.3)	33.7 (11.0)	0.5703
Ferritin (ng/mL), (mean±SD)	128.9 (51.6)	142.2 (71.4)	0.3008
Total cholesterol	159.7 (37.2)	146.9 (36.3)	0.0742
LDL-C	86.4 (25.8)	77.1 (24.1)	0.0547
HDL-C	50.4 (16.2)	45.3 (14.1)	0.0117
TG (mg/dL), (mean±SD)	135.8 (83.1)	134.4 (74.8)	1.0000

Hb: Hemoglobin; TIBC: Total Iron-Binding Capacity; TSAT: Transferrin Saturation; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; TG Triglycerides (TG).

Table 3: Baseline demographics and characteristics in study 2 (daprodustat).

	Before	After	p
Hb (g/dL), (mean±SD)	9.9 (1.2)	10.8 (0.9)	0.0874
Serum iron (pg/dL), (mean±SD)	64.3 (26 0)	96.0 (65.0)	0.071
TIBC (pg/dL), (mean±SD)	230.0 (50.8)	259.4 (66.1)	0.0151
TSAT (%), (mean±SD)	29.9 (15.5)	37.5 (25.0)	0.4543
Ferritin (ng/mL), (mean±SD)	215.6 (194.1)	232.1 (237.9)	0.5897
TC (mg/dL), (mean±SD)	134.5 (33.9)	129.4 (46.3)	0.2235
LDL-C (mg/dL), (mean±SD)	66.3 (21.8)	65.4 (22.9)	0.9012
HDL-C (mg/dL), (mean±SD)	39.1 (11.8)	44.4 (21.8)	0.1686
TG (mg/dL), (mean±SD)	156.0 (121.2)	148.8 (188.8)	0.1925

Hb: Hemoglobin; TIBC: Total Iron-Binding Capacity; TSAT: Transferrin Saturation; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; TG Triglycerides (TG).

Table 4: Baseline demographics and characteristics in study 3 (enarodustat).

Discussion

In previous studies [1-3], roxadustat has been reported to be superior to ESA in its ability to lower LDL-C from baseline to the average of 12-28 weeks. Kim et al. have reported that HIF-dependent effects on acetyl coenzyme A are required for the first step of cholesterol synthesis [5]. In mouse model of hypoxia, HIF-1α was found to activate insulin-induced gene 2 (Insig-2) transcription, leading to the accumulation of Insig-2 protein, which binds to 3-Hydroxy-3-Methylglutaryl (HMG)-CoA reductase and triggers its accelerated ubiquitination and degradation in the liver [6-7]. Chen et al. reported that the decrease in TC was greater with roxadustat than with epoetin-α, as was the decrease in LDL-C levels in patients undergoing long-term dialysis [1]. Chen et al. reported that in patients with CKD who were not undergoing dialysis, TC levels decreased by 23% during eight weeks of roxadustat therapy [2]. Csiky et al. reported that roxadustat was superior to an ESA in decreasing LDL-C levels from baseline to an average of 12-28 weeks in patients with end-stage kidney disease on stable dialysis [3]. We found that different HIF-PHIs affect serum lipid levels differently in patients undergoing HD: in this case, roxadustat decreased LDL-C levels, while daprodustat and enarodustat did not. The physiological and clinical effects of reduced LDL-C levels over time in this population warrant further investigation.

Low blood HDL-C level is an independent risk factor for Cardiovascular Diseases (CVD) [8]. Patients with chronic HD generally have lower HDL-C levels than healthy individuals. Low HDL-C levels are associated with an increased risk of mortality in chronic HD patients [4]. In this study, roxadustat and daprodustat decreased the HDL-C levels, while enarodustat did not. The clinical effects of reduced HDL-C levels over time in patients undergoing HD also warrant further investigation. In previous studies, the superiority of roxadustat over ESA has been demonstrated for the using intravenous iron in reducing the proportion of patients requiring intravenous iron supplementation from baseline. In both treatment groups, the baseline serum ferritin levels were higher than those recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [1,3,9,10]. A significant decrease in ferritin levels was observed in the roxadustat group. In previous studies [1,10], a relative reduction in hepcidin levels was observed in the roxadustat group compared to the ESA group. Because increased hepcidin levels have been are associated with functional iron deficiency and inflammation, reduced hepcidin levels may improve iron absorption and mobilization. Gupta et al. reported that HIF-PHIs improved iron mobilization in the bone marrow [11].

Akizawa et al. reported that the mean hepcidin levels decreased more with daprodustat than with darbepoetin alfa, and an increase in TIBC was observed in the daprodustat group [12]. In the present study, we observed increased TIBC and iron levels after daprodustat treatment. Rolfs et al. reported that the observed increases in TIBC were likely due to transferrin, which is increased by HIF [13]. Shah et al. reported that HIF upregulates divalent metal transporter 1 and duodenal cytochrome B to increase intestinal iron absorption [14]. Akizawa et al. reported that increased serum iron levels observed in the daprodustat group may be due to the upregulation of divalent metal transporter 1 and duodenal cytochrome B by HIF stabilization [12]. In a previous study [1], a relative reduction in hepcidin levels was observed in the roxadustat group compared with the ESA group. Because increased hepcidin levels are associated with inflammation and functional iron deficiency [15], reduced hepcidin levels may result in improved iron absorption and mobilization.

In the present study, roxadustat, daprodustat, and enarodustat treatment improved iron metabolism and maintained stable Hb levels. This study had some limitations, including an insufficient study duration (24 weeks) and a very small sample size. Furthermore, this study used a non-comparative design that may reduce the interpretability of the results owing to the lack of a control group.

Conclusions

We discovered that different HIF-PHIs have different effects on serum lipid levels in patients undering HD. Roxadustat treatment improved iron metabolism-stabilized hemoglobin levels and significantly decreased low-density lipoprotein cholesterol levels. Daprodustat and enarodustat treatments improved iron metabolism and maintained stable hemoglobin levels.

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