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Erythropoietin Hyporesponsiveness in Dialysis Patients: Possible Role of Statins

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Statins · Erythropoietin · Anemia · Hemodialysis

Abstract
Background: Hypothesizing that statins may be useful as adjuvant treatment for renal anemia, we examined the association between statin prescription (Rx) and erythropoiesis-stimulating agent (ESA) hyporesponsiveness in Japanese hemodialysis (HD) patients prescribed ESAs. ***Methods:*** We examined 3,602 patients in 60 HD facilities dialyzed 3 times/week for ≥4 months from the Japan Dialysis Outcomes and Practice Patterns Study phases 3–5 (2005–2015). Statin Rx was reported at the end of a 4-month interval (baseline) for each patient. ESA hyporesponsiveness in the subsequent 4 months was then defined as a binary indicator (mean hemoglobin [Hgb] level <10 g/dL and mean ESA dose >6,000 units/week) and separately as the ESA resistance index (ERI; mean ESA dose/[dry weight × mean Hgb]). We used adjusted logistic and linear regressions to evaluate the associations between statin Rx and ESA hyporesponsiveness. ***Results:*** At baseline, 16.2% of patients reported statin Rx; 12.8% were classified as having ESA hyporesponsiveness during 4 months of follow-up. Compared to patients without statin Rx, patients with statin Rx had lower odds of ESA hyporesponsiveness (OR 0.87; 95% CI 0.66–1.15). Similarly, the ERI was lower for those with statin Rx than without (ratio of means, 0.94; 95% CI 0.89–0.99) after adjustment for possible confounders. ***Conclusions:*** Our results suggest that statins may slightly reduce ESA hyporesponsiveness in HD patients. However, any causal inference is limited by the observational study design and unmeasured compliance with statin Rx.

Introduction

Cumulative evidence supports the efficacy and safety of lipid-lowering therapy with statins in patients with normal or modestly reduced renal function [1, 2]. A meta-analysis showed that statins decreased the risk of mortality in early-stage chronic kidney disease (CKD) patients [2]. However, several randomized controlled trials in hemodialysis (HD) patients have shown no clinical benefit of lipid-lowering therapy with statins [3, 4]. Further, a recent meta-analysis found that statins had little or

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no effect on reducing the mortality rate or risk of cardiovascular events in patients on dialysis [5]. Accordingly, the latest Kidney Disease: Improving Global Outcomes (KDIGO) guidelines now advise against starting statin use in dialysis patients [6]. However, the findings of an observational study have indicated that statin prescription was associated with reduced mortality in HD patients [7]. The current clinical guidelines [6, 8] do not recommend initiating statin use in dialysis patients but also do not require that patients cease taking statins upon initiating dialysis. Therefore, it seems reasonable to expect a certain proportion of dialysis patients to have a valid statin prescription for mortality and cardiovascular disease (CVD) risk reduction. Indeed, the United States (US) Dialysis Outcomes and Practice Patterns Study (DOPPS) Practice Monitor indicates that 45–50% of US HD patients were prescribed statins as of 2016 [9].

Statins have pleiotropic effects, including anti-inflammatory and anti-oxidative actions [10–12]. Statins may, therefore, be effective as an adjuvant treatment for renal anemia in HD patients. However, only a few small-scale, short-term, before-after studies have published findings suggesting that statins lead to the improvement in erythropoiesis-stimulating agent (ESA) responsiveness in HD patients [13–15]. Therefore, its clinical effectiveness for ESA resistance remains controversial in this population.

Hypothesizing that statins may indeed improve ESA efficacy in hyporesponsive patients, in this study, we examined the association between statin prescription (Rx) and ESA hyporesponsiveness in Japanese HD patients prescribed ESAs in the Japan DOPPS (JDOPPS) cohort.

Materials and Methods

Study Design, Population, and Data Source

JDOPPS is a nationally representative prospective cohort study of randomly selected, prevalent HD patients aged 18 years or older from facilities across Japan. JDOPPS applies a common protocol with standardized questionnaires to capture detailed longitudinal patient-level information, as well as dialysis-facility practices and processes of care. We obtained demographic, clinical, and medication data from JDOPPS phases 3 (2005–2008), 4 (2009–2011), and 5 (2012–2015). This data source includes clinical data collection for approximately 7,000 Japanese HD patients from 58 to 62 dialysis facilities per phase of data collection.

Prevalent JDOPPS patients who were prescribed HD at a frequency of 3 times per week and had been on HD for at least 4 months were eligible for analysis (n = 6,625). Patients who died within 4 months of follow-up, who had polycystic kidney disease as a primary cause of ESRD, or who had a history of malignancy, gastrointestinal bleeding, liver disease, HIV, or prior transplant were excluded (n = 1,906). Baseline for each patient was defined as the time of JDOPPS study entry or the first time after JDOPPS study entry at which the patient was on HD for at least 4 months. Patients were required to have ESA administered at baseline as well as at each month during the subsequent 4-month period, referred to as the "outcome period" (n = 3,803). Patients with missing statin data at baseline or any missing data on hemoglobin (Hgb), postdialysis weight, or ESA dose in the outcome period were excluded (n = 3,602).

Primary Exposure

The primary exposure of interest was having a statin prescription at baseline. The JDOPPS medications database was searched for the following terms to identify statins (including commercial names and drug combinations [e.g., Vytorin] as necessary): atorvastatin, fluvastatin, HMG-CoA reductase inhibitors, lovastatin, pravastatin, rosuvastatin, and simvastatin.

Primary Outcome

The primary outcome of interest was ESA hyporesponsiveness in the outcome period. ESA hyporesponsiveness was defined dichotomously as mean Hgb <10 g/dL and a standardized mean ESA dose >6,000 units/week during the outcome period [16]. We also measured the ESA resistance index (ERI) [17, 18] in the outcome period, calculated as ERI = mean ESA dose (units/week)/(dry weight [kg] × mean Hgb [g/dL]), where the dry weight was the postdialysis body weight averaged across 3 dialysis sessions at the end of the outcome period. For a given Hgb level and dry weight, higher ERI values indicate a greater ESA dose requirement. Because single-month ESA and Hgb values may not reflect the "usual" or targeted values, we used the average of monthly ESA doses and Hgb values during the outcome period to define these outcomes.

The ESA prescription was obtained monthly in the JDOPPS and standardized to a weekly dose. In Japan, ESAs used to treat anemia include "short-acting" epoetin alfa (and certain biosimilars), "long-acting" darbepoetin alfa, and Mircera (pegylated epoetin beta; Merck). To standardize the ESA dose between these different preparations, we converted Mircera doses to darbepoetin doses using a 1.2:1 ratio [19] and converted darbepoetin doses to epoetin doses using a 250:1 ratio [20].

Covariates

The following covariates were assessed during the baseline period: age, gender, years on dialysis (vintage), and 11 summary comorbidities (coronary artery disease, other CVD, cerebrovascular disease, congestive heart failure, diabetes, hypertension, lung disease, neurologic disease, psychiatric disorder, peripheral vascular disease, recurrent cellulitis/gangrene), albumin, transferrin saturation, ferritin, C-reactive protein (CRP), treatment time per session, single-pool Kt/V, hospitalization in the past 3 months, and postdialysis weight.

Analysis Models

The association between statin prescription in the baseline period and ESA hyporesponsiveness in the outcome period was estimated using logistic generalized estimating equations regression models, with an exchangeable working covariance matrix to account for within-facility patient clustering. The association between statin prescription in the baseline period and ERI was estimated using linear mixed regression models with a random inter-

cept for each study facility. Because the ERI in the outcome period was not normally distributed, we used the log-transformed ERI in the regression models.

For each outcome, we estimated the effect of statin prescription with increasing levels of covariate adjustment in 4 models (see footnotes in Table 2 for adjustments). To compare patients prescribed a statin with those not prescribed a statin, we reported the adjusted odds ratios for ESA hyporesponsiveness and adjusted ratios of means for ERI.

Statins are thought to exhibit anti-inflammatory properties, which might indirectly influence ESA hyporesponsiveness. Therefore, we also examined whether CRP was a mediator of the effect of statin prescription on ESA hyporesponsiveness. The mediation analysis was conducted using the SAS mediation macro developed by Valeri and Vanderweele [21].

Treatment of Missing Data

We used the Sequential Regression Multiple Imputation Method implemented by IVEware to create an augmented dataset with 10 imputed values for each missing covariate value [22]. Analyses were conducted independently for each imputed dataset and combined using Rubin's rules [23] as implemented by the SAS MIAnalyze procedure in SAS/STAT 9.3 [24]. The statin prescription and outcome variables, including ESA dose and Hgb levels, were not imputed but were included in the imputation models.

Ethical Considerations

The Ethics Committee of Tokyo Women's Medical University approved the JDOPPS as a lead-managing institution (approval number: #678), and the institutional review boards at each facility also approved the study, as required. Informed consent was obtained for each sampled patient in accordance with the requirements of the institutional review board and facility. Data collection was performed in a manner that maintained patient anonymity.

Results

Statin Prescription and Patient Characteristics

A total of 3,602 patients met the inclusion criteria. Baseline patient characteristics by statin prescription are listed in Table 1. During the baseline period, 16.2% (585/3,602) of patients were prescribed a statin. Compared to those not prescribed a statin, patients who were prescribed a statin were more likely to be female, have larger body mass index, have shorter dialysis vintage, and have coronary artery disease, diabetes mellitus, or hospitalization in the 3 months prior to the baseline period. Patients prescribed a statin had lower levels of total cholesterol and low-density lipoprotein cholesterol and higher levels of high-density lipoprotein cholesterol and triglycerides than those not prescribed a statin. Serum albumin, CRP, treatment time per HD session, single pool Kt/V, and intravenous iron use and dose were similar between the 2 Rx groups.

Association between Statin Prescription and ESA Hyporesponsiveness

ESA hyporesponsiveness, which was defined as Hgb <10 g/dL and standardized mean ESA dose >6,000 units/week during the outcome period, was observed in 12.8% (460/3,602) of patients. The proportion with ESA hyporesponsiveness was 11.3% in patients prescribed a statin and 13.1% in patients not prescribed a statin. Table 2 shows the estimated associations between statin prescription and subsequent ESA hyporesponsiveness with increasing levels of covariate adjustment. The odds of ESA hyporesponsiveness for patients prescribed a statin was 12–15% lower than for patients not prescribed a statin, depending on the covariate adjustment; for example, in model 4, the fully adjusted OR was 0.87 (95% CI 0.66–1.15; Table 2a).

ESA resistance measured by ERI was 5–8% lower in patients with statin prescription compared with patients without statin prescription (models 3 and 4, adjusted ratio of means = 0.94; 95% CI 0.89–0.99; Table 2b).

Results of the CRP mediation analyses indicated that there was no CRP-mediated indirect effect of statin prescription on ESA hyporesponsiveness, as statins are not significant in predicting CRP.

Discussion

We investigated the association between statin prescription and ESA hyporesponsiveness using a representative cohort of Japanese maintenance HD patients enrolled in JDOPPS phases 3–5 (2005–2015). A total of 16.2% of patients reported statin prescription at baseline period, and 12.8% were classified as having ESA hyporesponsiveness during follow-up (outcome period). Our results showed that HD patients prescribed statins were slightly less likely than patients not prescribed statins to exhibit ESA hyporesponsiveness during the following 4 months (outcome period) than those not prescribed statins, even after adjusting for potential confounders, including indices of iron metabolism, inflammation, and nutrition status.

As expected, our findings are similar to those of previous small-scale investigations mentioned below. A retrospective cohort study at a single US center first described the possibility of a clinical effect of statin therapy on reducing ESA requirements in HD patients [13]. These authors compared the ESA dose pre- and post-statin therapy among 19 patients and showed that the ESA requirement had decreased by a mean of 25% after therapy. A before-after observational study at a single center in Greece re-

Table 1. Baseline patient characteristics classified by statin prescription; JDOPPS phases 3–5 (2005–2015)

Characteristic	Prescribed a statin	Not prescribed a statin
Number of patients, *n* (%)	585 (16.2)	3,017 (83.8)
Demographics		
Age, years	63.8 (11.9)	63.7 (12.5)
Male, %	52	63
BMI, kg/m^2	22.6 (4.0)	21.2 (3.3)
Time on dialysis, years	4.63 (5.55)	7.08 (6.73)
Comorbidities, %		
Coronary artery disease	39	29
Other cardiovascular disease	21	25
Cerebrovascular disease	15	13
Congestive heart failure	22	19
Diabetes mellitus	55	37
Hypertension	83	80
Lung disease	2	4
Neurological disease	8	8
Psychiatric disorder	3	4
Peripheral vascular disease	15	14
Recurring cellulitis/gangrene	3	3
Hospitalization in the past 3 months	18	12
Lab measurements		
Albumin, g/dL	3.74 (0.37)	3.74 (0.39)
TSAT, %	23.0 (16.8–31.0)	24.2 (18.0–32.9)
Ferritin, ng/mL	87.0 (37.0–185.0)	99.5 (41.9–213.0)
CRP, mg/L	1.00 (0.50–3.00)	1.00 (0.50–3.00)
Total cholesterol, mg/dL	151 (34)	157 (35)
LDL cholesterol, mg/dL	76.0 (26.1)	84.7 (28.7)
HDL cholesterol, mg/dL	48.3 (16.0)	47.6 (15.7)
Triglycerides, mg/dL	128 (73)	119 (126)
Treatment		
Treatment time per session, min	237 (28)	236 (28)
Single pool, Kt/V	1.37 (0.28)	1.38 (0.28)
IV iron use, %	27	27
IV iron dose, mg/month*	204 (129)	201 (146)

BMI, body mass index; JDOPPS, Japan Dialysis Outcomes and Practice Patterns Study; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TSAT, transferrin saturation; IV, intravenous.

Continuous variables are expressed as mean (SD) or median (interquartile range). Categorical variables are expressed as percentages.

* Among patients prescribed IV iron.

ported that atorvastatin prescription for 9 months improved ESA hyporesponsiveness among 33 iron-repleted HD patients [15]. Another group of investigators found in their before-after study at a single Taiwanese HD unit that atorvastatin prescription for 4 months decreased the erythropoietin-to-hematocrit ratio among 30 patients with hyperlipidemia [14]. That study also found that statin prescription was associated with a decrease in the levels of proinflammatory cytokines, such as interleukin-6 and tumor necrotic factor-alpha.

A recent JDOPPS study showed that low-grade inflammation status represented by mild CRP elevation was related to future incidence of ESA hyporesponsiveness [25]. A retrospective cohort study of 1,754 patients receiving care at chain facilities in North America showed that elevated the CRP level was related to higher subsequent ESA dose requirements after adjusting for potential confounders [26]. However, another cohort study among HD patients found that statin prescription improved ESA hyporesponsiveness without a reduction in CRP levels [15]. We conducted a mediation analysis, but our results indicated that CRP did not mediate the effect of statin therapy on subsequent ESA hyporesponsiveness, as statins are not significant for predicting CRP.

A clear definition of ESA hyporesponsiveness has not yet been established, and guidelines have used different

Table 2.

a Association between statin prescription and subsequent ESA hyporesponsiveness by increasing levels of adjustment

Outcome	Statin Rx	Number of patients	Number of events, *n* (%)	OR (95% CI)			
				model 1[b]	model 2[c]	model 3[d]	model 4[e]
Hgb <10 g/dL	+	585	66 (11.3)	0.88 (0.67–1.13)	0.86 (0.65–1.14)	0.85 (0.64–1.13)	0.87 (0.66–1.15)
ESA dose[a] >6,000 units/week	–	3,017	394 (13.1)				

ESA, erythropoiesis-stimulating agent; Hgb, hemoglobin.
[a] Mircera doses were converted to darbepoetin doses using a 1.2:1 ratio, and darbepoetin doses were converted to epoetin doses using a 250:1 ratio.
[b] Model 1: adjusted for DOPPS phase and accounting for facility clustering.
[c] Model 2: adjusted for model 1+ age, gender, vintage, 11 summary comorbidities and post dialysis weight.
[d] Model 3: adjusted for model 2+ Kt/V, treatment time, hospitalization in past 3 months.
[e] Model 4: adjusted for model 3+ CRP, albumin, TSAT, ferritin.

b Association between statin prescription and subsequent ESA resistance index by increasing levels of adjustment

Outcome	Statin Rx	Number of patients	Average ERI	Ratio of means (95% CI)			
				model 1[b]	model 2[c]	model 3[d]	model 4[e]
logERI[a, f]	+	585	10.1	0.92 (0.87–0.97)	0.95 (0.90–1.00)	0.94 (0.89–0.99)	0.94 (0.89–0.99)
	–	3,017	10.7				

ESA, erythropoiesis-stimulating agent; ERI, ESA resistance index.
[a] Mircera doses were converted to darbepoetin doses using a 1.2:1 ratio, and darbepoetin doses were converted to epoetin doses using a 250:1 ratio.
[b] Model 1: adjusted for DOPPS phase and accounting for facility clustering.
[c] Model 2: adjusted for model 1+ age, gender, vintage, 11 summary comorbidities and post dialysis weight.
[d] Model 3: adjusted for model 2+ Kt/V, treatment time, hospitalization in past 3 months.
[e] Model 4: adjusted for model 3+ CRP, albumin, TSAT, ferritin.
[f] ERI = ESA/(dry weight × Hgb).

definitions to describe their findings [27, 28]. The 2008 Japanese Society for Dialysis Therapy guidelines for renal anemia in CKD [29] defined hyporesponsiveness to ESA therapy as a failure to achieve anemia correction and the target Hgb level in HD patients despite the use of 9,000 IU/week of epoetin or 60 μg/week of darbepoetin alfa. In 2012, the Kidney Disease: Improving Global Outcomes clinical practice guideline for anemia in CKD was released [30], defining ESA hyporesponsiveness as no increase in Hgb concentration from baseline after the first month of ESA treatment at an appropriate weight-based dosing. This definition was developed based on the secondary analysis results of the Trial to Reduce Cardiovascular Events with Aranesp Therapy [31] in which ESA hyporesponsiveness was associated with subsequent poor prognosis in CKD patients with type 2 diabetes mellitus [32].

This study suggested a small possible benefit of statins for improving ESA responsiveness. A retrospective multicenter cohort study in Europe suggested that ESA hyporesponsiveness secondary to hypoalbuminemia and an elevated serum CRP level might be a prognostic factor in HD patients [18]. Japanese national cohort data showed that mortality in HD patients is influenced by ESA hyporesponsiveness, independent of the interactive effects of ESA dose and Hgb level [16]. A subsequent meta-analysis of 10 studies in HD patients revealed that a higher ESA dose was associated with an approximately twofold increased mortality risk, independent of Hgb level [33]. Taken together, these findings suggest that statins may be useful as an adjuvant treatment for renal anemia in HD patients and could consequently improve their outcomes.

The current investigation has several strengths. First, the JDOPPS data were collected from a nationally representative sample of HD facilities in Japan, which provides broad generalizability of our findings for the Japanese population. Second, the detailed inclusion-exclusion criteria, which eliminated major factors influencing ESA hyporesponsiveness and targeted relatively stable and homogenous prevalent patients undergoing HD, enhance the validity of the analytical results.

However, several limitations to the present study warrant mention and should be considered when interpreting the findings. Oral medication data (e.g., statin Rx) are collected once every 4 months in JDOPPS. This data collection is limited to prescription only and therefore does not capture adherence (including skipped/reduced dosing). If statin use is low relative to the prescription rate (due to poor adherence), then our estimates could be biased. We assumed that statins were not prescribed primarily to reduce ESA hyporesponsiveness in this population (i.e., no treatment-by-indication bias). However, other residual or unmeasured factors may have simultaneously influenced both statin use and either ESA dose or Hgb. Therefore, because of the observational study design, causal inference is limited regarding the effect of statin use on ESA hyporesponsiveness. The generalizability of our findings to non-Japanese populations also merits further study, as the rate of statin prescription is relatively low in Japan compared to that in the United States [9] and the prevalence of ESA hyporesponsiveness is also lower than in other regions [34]. Finally, the clinical effectiveness of statins for ESA resistance was marginal, suggesting only a possible role for statins in ESA hyporesponsiveness.

In summary, we examined the association between statin prescription and ESA hyporesponsiveness within a nationally representative cohort of Japanese HD patients (JDOPPS data). Our results support the hypothesis that statins may reduce ESA hyporesponsiveness in HD patients, but the magnitude of the adjusted association was small and further investigations are needed in different populations.

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