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# Hemoglobin Level Stability after a Switch from Darbepoetin Alfa to Epoetin Beta Pegol for the Treatment of Renal Anemia in Hemodialysis Patients

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## Abstract

**Background: New erythropoiesis-stimulating agents (ESAs) with a longer half-life have been developed for the treatment of anemia as a complication of patients with end-stage renal disease. Objectives: The objective of the present study was to assess the hemoglobin (Hb) stability of a Japanese cohort of hemodialysis (HD) patients who were simultaneously switched from darbepoetin alfa (DA) to epoetin beta pegol (CERA). Methods: This was an observational, prospective study of HD patients 20 years of age or more who were switched from intravenous (IV) DA to IV CERA and continued on HD for at least 3 months. The dose was adjusted to maintain the Hb level to within 1.0 g/dl of the baseline value. Results: A total of 68 HD patients (75.0% male, median age 63.0 years) were enrolled. The patients' mean Hb levels were 10.8 ± (0.6) g/dl at Month 0, 10.9 ± 0.7 at Month 1, 10.8 ± 0.7 at Month 2, and 10.9 ± 0.8 at Month 3, and the differences from the level at Month 0 were not significant. After the switch, the ESA dose decreased significantly ($P < 0.0001$) from an annual mean DA dose of 549.0 ± 246.6 IU/kg/month to a mean CERA dose at Month of 3 491.0 ± 291.7 IU/kg/month. The ESA resistance index (ERI) decreased from 51.7 ± 24.4 IU/kg/month/g/dl on DA at Month 0 to 46.4 ± 29.3 on CERA at 3 Month 3 ($P < 0.0001$). Conclusion: Switching from DA to CERA was associated with approximate 89% reduction of the required dose in Japanese HD patients being treated with an ESA and showed a favorable impact on the treatment of renal anemia, including the need for less frequent injections and a reduction of the ESA dose.**

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## Keywords

**Darbepoetin Alfa, Epoetin Beta Pegol, Hemoglobin, ESA Resistance, Hemodialysis**

## 1. Introduction

Since renal anemia is a complication of advanced chronic kidney disease (CKD), administration of erythropoiesis-stimulating agents (ESAs) has led to a great improvement in clinical management [1], because ESA treatment significantly reduces the need for transfusions, hospital admissions, and overall mortality [2]-[4]. The first ESA available for clinical use namely epoetin alfa and beta, had a short half-life and needed to be administered twice or thrice a week [5]. Although ESAs are basically administered thrice a week to hemodialysis (HD) patients, anemia is the complication that has the greatest impact on perceived quality of life in HD patients.

Dalbepoetin alfa (DA) has a much longer half-life and longer erythropoietic effect than epoetin alfa [6] [7]. The initially recommended conversion rate was 200 IU of epoetin alfa per 1 μg of DA [8]. Nevertheless, administration of DA at 2-week intervals is necessary in patients whose anemia is not adequately improved by DA therapy at a 4-week dosing interval. Continuous erythropoietin receptor activator (CERA) is a newer ESA that has a long half-life and requires less frequent dosing, *i.e.*, once every two weeks or even once monthly [9]. CERA has a longer half-life, approximately 134 hours, when administered intravenously to HD patients [10].

However, it is uncertain if switching HD patients from DA to CERA stabilizes their target Hb level. The aim of the present study was to assess the effects of switching from DA to CERA on the Hb level of a cohort of Japanese HD patients with renal anemia.

## 2. Materials

### 2.1. Subjects and Protocol

This was a prospective cohort study conducted at a single center in Japan. The subjects were recruited from among patients who had been routinely treated through an arteriovenous fistula in the dialysis unit of the Shinjuku Ishikawa Clinic for at least 6 months. The Institutional Review Board of the Shinjuku Ishikawa Clinic approved all study protocols, and they were performed in accordance with the Declaration of Helsinki guidelines regarding ethical principles for medical research involving human subjects. Informed consent was obtained from all of the subjects [11].

HD patients who had malignancy, active inflammation, liver cirrhosis, gastrointestinal bleeding, or severe illness were excluded from participation. The patients who enrolled as subjects (n = 68) were undergoing stable regular HD with a bicarbonate dialysate. Their underlying renal diseases were chronic glomerulonephritis (38.2%), diabetic nephropathy (25.0%), hypertensive nephrosclerosis (5.9%), and others (30.9%). All patients were on thrice-weekly HD, and no further patient selection was performed. The main inclusion criteria were 20 years of age or more, a switch from DA to CERA (index date) after being on HD for at least 6 months, and having remained on HD for at least 3 months after the switch.

The date of the switch from DA to CERA was considered the index date (Month 0). The baseline conversion rate was left to the discretion of each nephrologist. Both ESAs were intravenously injected with pre-filled syringes. The DA dose frequency was once weekly, and CERA was administered twice monthly. Hb was measured monthly, and the ESA dose was adjusted to maintain the Hb level to within 1.0 g/dl of the Month-0 value. The target Hb was 10 - 12 g/dl, and iron supplementation was started when the serum ferritin level was <100 ng/mL or transferrin saturation (TSAT) was <20%, as recommended by the Japanese Society for Dialysis Therapy (JSDT) [12]. The ESA resistance index (ERI) was calculated by dividing the ESA dose by the Hb level [13] [14].

The prospective follow-up period was 3 months. The DA and CERA doses were converted to IU/kg/month by using the 200:1 conversion rattio of epoetin alfa. We collected data on Hb, serum ferritin, TSAT, ESA dose, and ERI. Only adverse reactions leading to discontinuation of CERA were recorded.

### 2.2. Statistical Analysis

Normally distributed, unpaired continuous values were expressed as means ± SD and compared by performing

an analysis of variance. Nonparametric values were expressed as median values and compared by performing the Kruskal-Wallis test. Categorical values were expressed as percentages and compared by performing Fisher's exact test. Changes from Month 0 values at subsequent visits were evaluated by using the paired *t*-test and Wilcoxon signed-rank test. Changes in continuous variables over time were evaluated by repeated-measures analysis of variance. The statistical analysis was performed by using SAS software (v 9.2; SAS Institute, Cary, NC, USA).

## 3. Results

### 3.1. Patients

There were 126 HD patients at the index date, and 68 of them were included in this study. Subjects who did not complete the study because of insufficient data or transfer to another dialysis institute were excluded. Patient characteristics are summarized in **Table 1**. The median age of the 68 subjects was 63 years (53 - 68 years), and their median dialysis vintage was 144 months (85 - 227 months). Their prevalence of diabetes was 25.0%. The study population included 17 women and 51 men.

### 3.2. Hb Levels over Time

No significant changes in mean monthly Hb values were observed during the follow-up period (10.8 ± 0.6 at Month 0, 10.9 ± 0.7 at Month 1, 10.8 ± 0.7 at Month 2, 10.9 ± 0.8 at Month 3; **Table 2**). Only a slight increase in mean Hb level was observed at 5 weeks after the switch and the Hb level rapidly returned to its baseline level after minor dose adjustments at 7 weeks after the start of CERA administration (**Figure 1**). There were no significant changes over time in the number of bleedings or transfusions (data not shown). A bleeding episode was experienced by <1% and none of the patients required a blood transfusion after the switch. CERA was not discontinued because adverse reactions in any of the patients during the follow-up period.

We compared the Hb levels and ESA doses of a diabetic group (n = 16) and nondiabetic group (n = 45) at the time of the switch and at the end of the follow-up period. There were no significant changes in the Hb level in the diabetic group (Month 0: 10.5 ± 0.6 vs. Month 3: 10.6 ± 0.7 g/dl) or in the nondiabetic group (Month 0: 10.8 ± 0.7 vs. Month 3: 10.8 ± 0.8 g/dl). Nor were there any significant changes in the ESA doses in the diabetic group (Month 0: 524.9 ± 245.8 vs. Month 3: 498.0 ± 258.6 IU/kg/month) nor nondiabetic group (Month 0: 557.6 ± 249.0 vs. Month 3:507.7 ± 303.5 IU/kg/month), suggesting that there was no difference in the effect of CERA in the two groups.

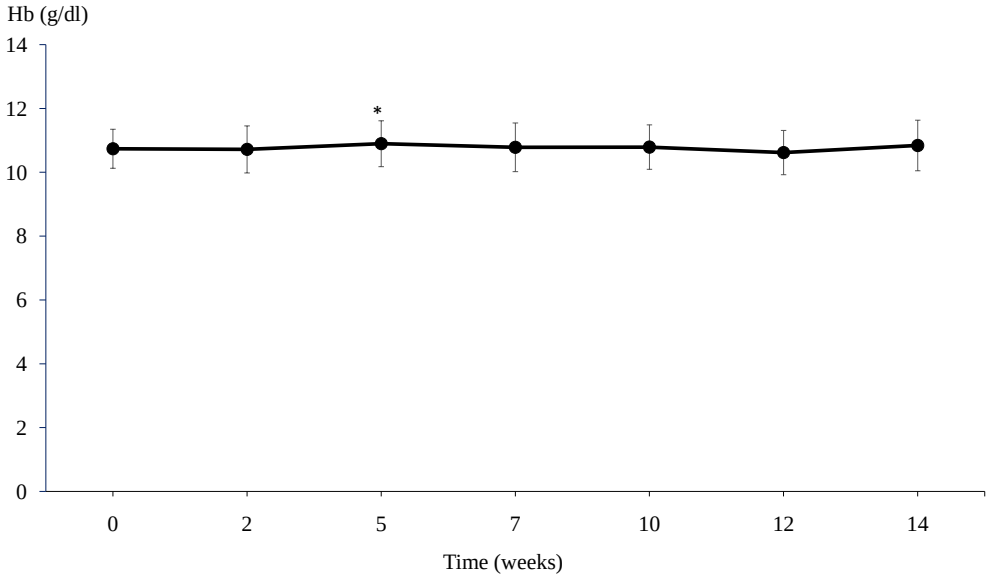


**Figure 1.** Changes in hemoglobin levels after switching from dalbepoetin alfa to epoetin beta pegol. *$P < 0.05$ vs. baseline.

**Table 1.** Baseline characteristics of the study population.

| | (n = 68) |
|---|---|
| Age, years | 63 (53 - 68) |
| Male gender, % | 51 (75.0) |
| Dialysis vintage, months | 144 (85 - 227) |
| CKD etiology, % | |
| Diabetes mellitus | 25.0 |
| Glomerulonephritis | 38.2 |
| Nephrosclerosis | 5.9 |
| Others | 30.9 |
| Smoking, % | 27.9 |
| History of cardiovascular disease[1], % | 42.6 |
| Body mass index, $kg/m^2$ | 21.8 (19.2 - 24.2) |
| Mean blood pressure, mmHg | 99.0 (90.3 - 107.9) |
| Pulse pressure, mmHg | 68 (59 - 80) |
| Single pool Kt/V | 1.5 (1.3 - 1.6) |
| Hemoglobin, g/dl | 10.7 (10.5 - 11.0) |
| Albumin, g/dl | 3.8 (3.6 - 4.0) |
| C-reactive protein, mg/dl | 0.12 (0.05 - 0.23) |
| Total cholesterol, mg/dl | 148 (130 - 169) |
| HDL-cholesterol, mg/dl | 44 (35 - 53) |
| Non-HDL-cholesterol, mg/dl | 103 (82 - 123) |
| Triglyceride, mg/dl | 93 (63 - 121) |
| Calcium, mg/dl | 9.1 (8.9 - 9.4) |
| Phosphorus, mg/dl | 5.4 (4.6 - 6.4) |
| Intact parathyroid hormone, pg/ml | 123 (86 - 181) |
| NT-proBNP, pg/ml | 1990 (4634 - 10,255) |
| Antihypertensive agents | |
| RAS inhibitors, % | 69.1 |
| CCBs, % | 60.3 |
| Beta-blockers, % | 48.5 |
| Statin, % | 25.0 |
| EPA, % | 11.8 |
| $CaCO_3$, % | 85.3 |
| Phosphate binders, % | 70.6 |

Data are expressed as median (range) or percentage. [1]History of heart disease has been defined as congestive heart failure determined by echocardiography within the 3 previous months, myocardial infarction, cerebrovascular disease and peripheral artery disease. Abbreviations: CKD, chronic kidney disease; HDL, high-density lipoprotein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAS, renin-angiotensin system; CCB, calcium channel blocker; EPA, eicosapentaenoic acid.

### 3.3. ESA doses and ERI over time

After the switch from DA to CERA, the ESA dose decreased abruptly and significantly ($P < 0.001$), and remained unchanged thereafter (**Figure 2**). At the time of the switch, the mean ESA dose was 549.0 ± 246.6 IU/kg/month, and a significant decrease from the dose at the time of the switch was observed at Month 1 (517.6 ± 259.6 IU/kg/month), Month 2 (510.0 ± 278.2 IU/kg/month), and Month 3 (491.0.0 ± 291.7 IU/kg/month) ($P < 0.05$) (**Table 2**).

The reduction in ESA dose was significantly greater in the low-dose group at baseline (<420 IU/kg/month) than in the high dose group (≥420 IU/kg/month) (**Table 3**).

The ERI decreased from an annual mean of 51.7 ± 24.4 IU/kg/month/g/dl on DA to 48.6 ± 25.8 IU/kg/month/g/dl at Month 1, 48.3 ± 27.4 IU/kg/month/g/dl at Month 2, and 46.4 ± 29.3 IU/kg/month/g/dl at Month 3 ($P < 0.05$) (**Table 2**, **Figure 3**).

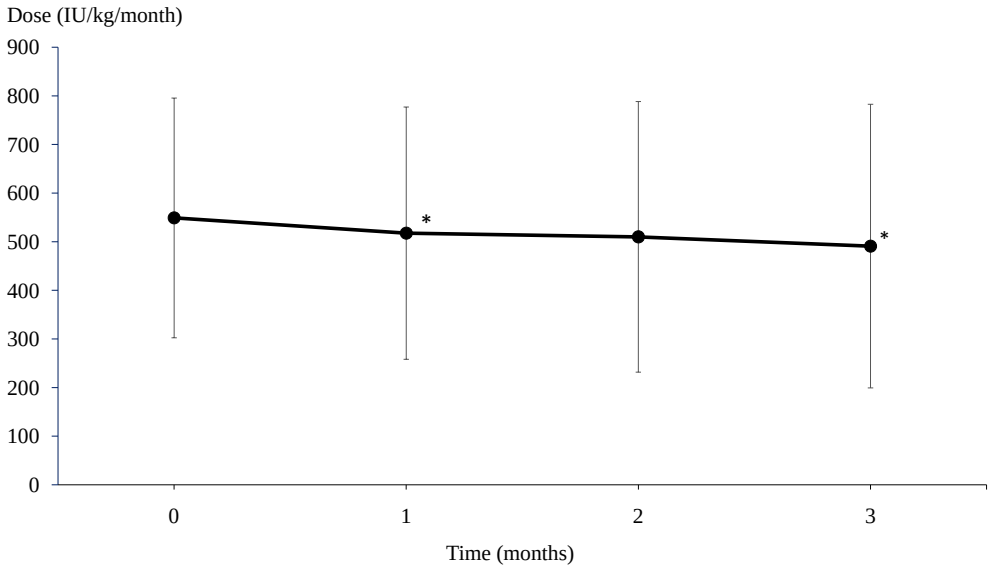


**Figure 2.** Changes in erythropoiesis-stimulating agent (ESA) dose after switching from dalbepoetin alfa to epoetin beta pegol. $^{*}P < 0.05$ vs. baseline.

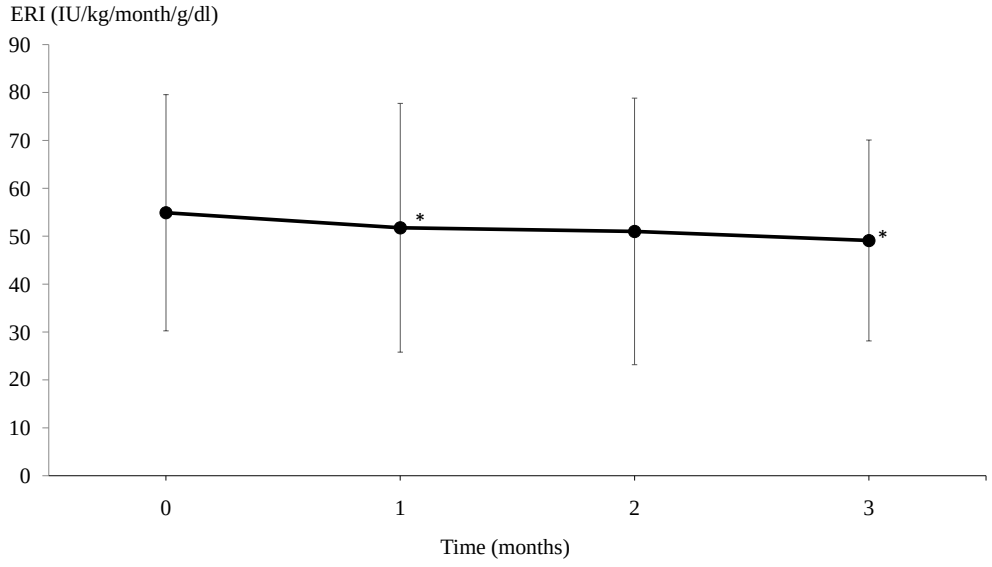


**Figure 3.** Changes in erythropoiesis-stimulating agent resistance index (ERI) after switching from dalbepoetin alfa to epoetin beta pegol. $^{*}P < 0.05$ vs. baseline.

**Table 2.** Changes in hematological parameters after switching of ESA.

| | 0 month | 1st month | 2nd month | 3rd month |
|---|---|---|---|---|
| Hemoglobin (g/dl) | 10.8 ± 0.6 | 10.9 ± 0.7* | 10.8 ± 0.7 | 10.9 ± 0.8 |
| TSAT (%) | 17.0 ± 6.5 | 25.0 ± 7.8** | 24.5 ± 8.7** | 18.6 ± 7.8 |
| Ferritin (ng/ml) | 52.7 ± 30.0 | 68.3 ± 50.0* | 61.2 ± 39.5 | 57.6 ± 34.6 |
| ESA dose (IU/kg/month) | 549.0 ± 246.6 | 517.6 ± 259.6* | 510.0 ± 278.2 | 491.0 ± 291.7* |
| ERI (IU/kg/month/g/dl) | 51.7 ± 24.4 | 48.6 ± 25.8* | 48.3 ± 27.4 | 46.4 ± 29.3* |
| TSAT (month average) | 17.9 ± 6.3 | 22.1 ± 7.2** | 22.0 ± 7.2** | 18.6 ± 7.8 |
| Ferritin (month average) | 50.9 ± 22.7 | 59.4 ± 40.0 | 57.7 ± 34.0 | 57.6 ± 34.6 |

*$P < 0.05$, **$P < 0.001$ vs. 0 month. Abbreviations: TSAT, transferrin saturation time; ESA, erythropoiesis-stimulating agent; ERI, erythropoiesis-stimulating agent resistance index.

**Table 3.** Changes in erythropoiesis-stimulating agent (ESA) dose and ESA resistance index (ERI).

| | Dose of epoetin at conversion | | |
|---|---|---|---|
| | Low (<420 IU/kg/month) (n = 30) | High (≥420 IU/kg/month) (n = 31) | Total (n = 61) |
| ESA dose (IU/kg/month), mean (SD) | | | |
| Darbepoetin alfa | 310.3 (79.0) | 641.8 (178.5) | 478.8 (216.5) |
| Epoetin beta pegol | | | |
| At the time of switch | 390.7 (111.9) | 702.3 (245.3) | 549.0 (246.6) |
| First month | 380.0 (142.9) | 650.8 (278.8) | 517.6 (259.6) |
| Second month | 366.1 (195.5) | 649.3 (277.7) | 510.0 (278.2) |
| Third month | 338.7 (244.4) | 638.4 (258.3) | 491.0 (291.7) |
| ESA dose reduction (%), mean (SD) | | | |
| At the time of switch | 100.0 | 100.0 | 100.0 |
| First month | 99.5 (40.6) | 90.7 (16.0) | 95.0 (30.7) |
| Second month | 95.5 (46.9) | 90.8 (26.2) | 93.1 (37.6) |
| Third month | 86.3 (58.5) | 90.7 (28.3) | 88.5 (45.4) |
| ERI (IU/kg/month/g/dl), mean (SD) | | | |
| Darbepoetin alfa | 29.2 (7.6) | 62.3 (19.1) | 46.0 (22.1) |
| Epoetin beta pegol | | | |
| At the time of a change | 36.5 (11.0) | 66.4 (25.0) | 51.7 (24.4) |
| First month | 35.6 (14.7) | 61.2 (28.1) | 48.6 (25.8) |
| Second month | 34.5 (19.7) | 61.7 (27.4) | 48.3 (27.4) |
| Third month | 32.3 (25.7) | 60.0 (26.3) | 46.4 (29.3) |
| ERI reduction (%), mean (SD) | | | |
| At the time of a change | 100.0 | 100.0 | 100.0 |
| First month | 99.7 (44.9) | 89.9 (16.4) | 94.7 (33.7) |
| Second month | 96.2 (50.1) | 91.1 (27.3) | 93.6 (39.9) |
| Third month | 87.2 (61.6) | 90.3 (30.9) | 88.7 (48.1) |

### 3.4. Changes in Serum Ferritin and TSAT

There were no significant changes in serum ferritin levels during the follow-up period (**Figure 4(a)**), but temporal changes in TSAT (**Figure 4(b)**) were observed during the follow-up period, suggesting that there was no change in iron metabolism after switching from DA to CERA.

## 4. Discussion

The present study investigated changes in the Hb levels of Japanese HD patients after switching from DA to CERA. The mean ESA dose gradually decreased after the switch, and the reduction was sustained during the subsequent 3 months without any noticeable changes in Hb levels. The mean ERI values had also significantly decreased at the end of the follow-up period. These findings support the results of a previous study by Hirai *et al.* [15].

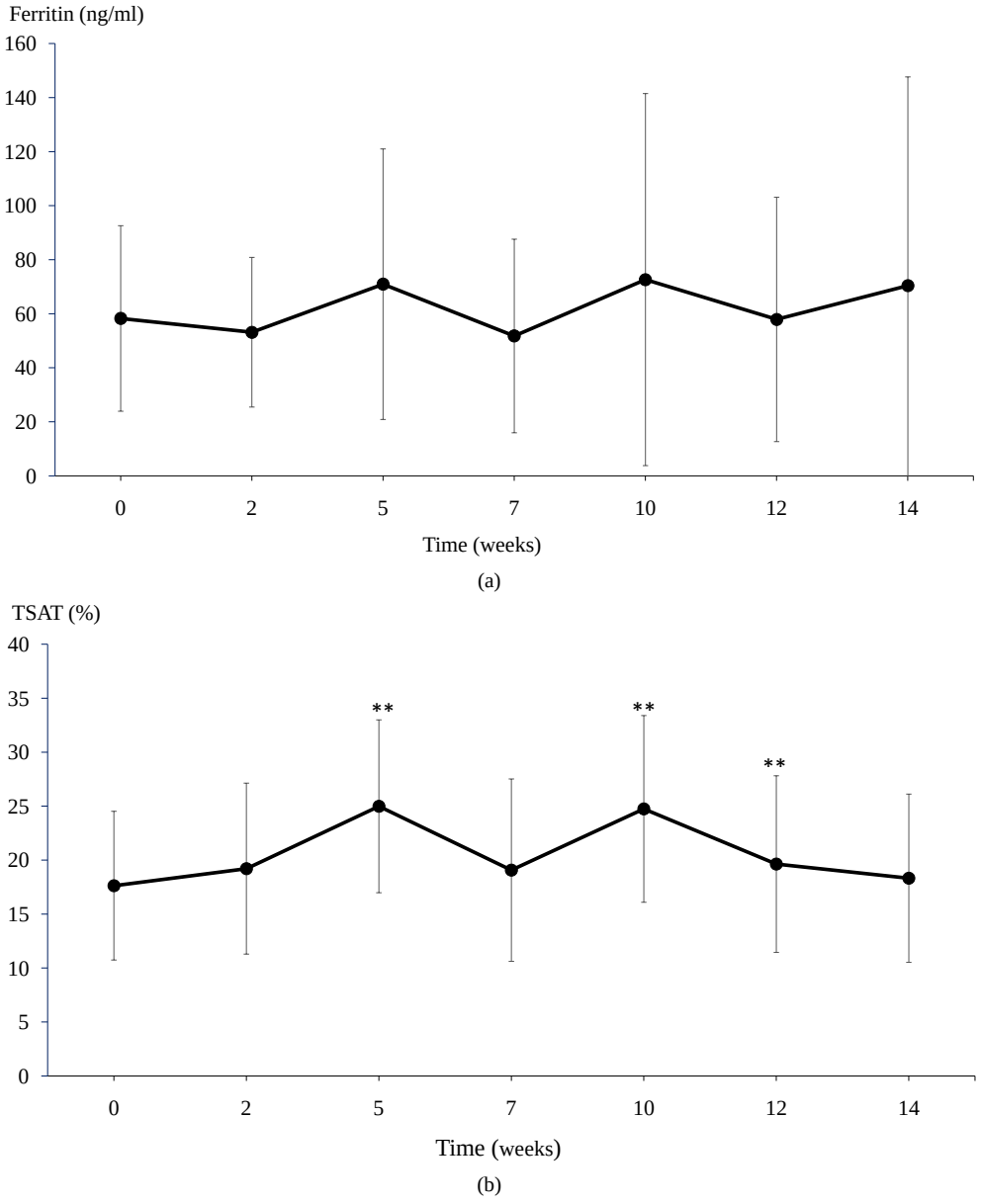


**Figure 4.** Changes in serum ferritin levels (a) and transferrin saturation (TSAT, (b)) after switching from dalbepoetin alfa to epoetin beta pegol. $^{*}P < 0.05$ vs. baseline.

We used the manufacturer's recommended starting dose of CERA when we switched the patients from DA to CERA. There are no guidelines for switching from DA to CERA in Japan [12]. The mean Hb levels were generally maintained within the target range (10.0 - 12.0 g/dl) during the follow-up period after the switch. Hb variability [16] and ESA overdosing are important issues for the treatment of renal anemia. In our study, the Hb level had increased slightly at 5 weeks after the switch, but the reduction in CERA dose necessary to maintain the target Hb levels appeared. A lower starting dose of CERA may reduce Hb variability after switching from DA.

The conversion ratio based on the actual doses of DA and CERA was estimated to be 1.0:1.0 at the time of the switch. However, the CERA dose gradually decreased from 549.0 ± 246.6 IU/kg/month at the baseline to 491.0.0 ± 291.7 IU/kg/month (89%) during the follow-up period. This finding is evidence that CERA should be started at approximately 80% - 90% of the DA dose to maintain equivalent Hb levels when the switching ESA from DA to CERA, suggesting that the CERA dose is reducible during the maintenance phase of the CERA therapy [17]. However, determination of the optimal dose of CERA will require further investigation.

Morikami *et al.* have recently reported finding that biweekly administration of CERA showed a significant decrease in serum ferritin levels in association with temporal changes in TSAT in Japanese HD patients [18]. The results of the present study showed that switching from DA to CERA did not alter the subjects' serum ferritin levels with a slight fluctuation in TSAT levels during the follow-up period. The serum ferritin levels of our patients were maintained at low levels. When switching from DA to CERA, iron metabolism may not be changed with regard to erythropoiesis, suggesting that biweekly CERA administration is advantageous in regard to iron absorption and utilization, and would be preferable in the management of renal anemia in HD patients.

There were several limitations in this study that should be considered. First, this study was based on a relatively small sample of HD patients from a single center, thereby limiting the possibility of generalizing our findings. Second, we excluded around 50% of all of the prevalent HD patients from the analysis and there was a possible bias due to the inclusion of survivors.

## 5. Conclusion

The results of this study demonstrated that switching from DA to CERA was associated with an 89% reduction of the required ESA dose in Japanese HD patients being treated with an ESA for renal anemia and they showed that the switch had a favorable impact on treatment of renal anemia, including a need for less frequent injections and reduction of the ESA dose.

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## Disclosure

The authors have no conflicts of interest to declare.

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