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Long-term maintenance of hemoglobin levels in hemodialysis patients treated with bi-weekly epoetin beta pegol switched from darbepoetin alfa: A single-center, 12-month observational study in Japan --Manuscript Draft--

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Abstract:	<p>Recent evidence on maintenance administration of epoetin beta pegol, a continuous erythropoiesis receptor activator (CERA), in dialysis patients shows the clinical benefit of bi-weekly administration (Q2W) in improving hematopoiesis and iron use efficiency. We undertook a single-center observational study of 33 Japanese maintenance dialysis patients, whose anemia had been kept stable through weekly administration (Q1W) of darbepoetin (DA), to evaluate the effectiveness of CERA Q2W switched from DA in maintaining hemoglobin (Hb) levels over a 12-month period. The target Hb level was 10.0-12.0 g/dL. Throughout the 12-month period, the mean Hb was stably maintained at 10.5-10.8 g/dL, 69.7-87.9% of the patients achieving the target Hb level. The mean CERA dose was within the range of 62.9-78.8 µg/2 weeks. The average CERA dose adjustment frequency after switching was low at 0.42-0.67 times/3 months. In both subgroups stratified by the DA dose prior to the switch, Hb levels were kept stable during CERA administration; however, in the low-dose group (10-20 µg/week of DA), the CERA and iron doses decreased over time, whereas in the high-dose group (30-60 µg/week of DA) they remained unchanged. CERA Q2W achieved long-term successful anemia management in Japanese maintenance dialysis patients after switching from DA Q1W. CERA dose was adjusted based on an overall consideration of past changes in Hb levels, erythropoiesis-stimulating agent (ESA) and iron doses. Subgroup analysis showed the CERA dose in the low-dose group decreased continuously, due possibly to a long-term improvement in iron use efficiency.</p>

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Author Comments:	<p>Dr. Yoshiki Sawa Editor-in-Chief Journal of Artificial Organs</p> <p>Dear Dr. Sawa,</p> <p>We are pleased to submit our manuscript titled "Long-term maintenance of hemoglobin levels in hemodialysis patients treated with bi-weekly epoetin beta pegol switched from darbepoetin alfa: A single-center, 12-month observational study in Japan" for consideration as an original article for the field "Artificial Kidney/Dialysis" in the Journal of Artificial Organs.</p> <p>This study is a single-center retrospective observational study of Japanese hemodialysis patients under the treatment of renal anemia with erythropoiesis-stimulating agent (ESA). It remains a problem for clinicians involved in dialysis patient care how to use ESA for successful anemia management. We found that bi-weekly administration of epoetin beta pegol (CERA Q2W) controlled anemia at a stable level for 12 months in Japanese hemodialysis patients after switching from darbepoetin alfa</p>

	<p>(DA Q1W), with the frequency of CERA dose adjustment maintained lower than usual in hemodialysis therapy. Our results suggested that it may be favorable to make an overall decision on CERA dose adjustment in light of past changes in Hb changes, CERA and iron doses over the previous year, rather than to adjust the dose in response to short-term fluctuations in Hb levels.</p> <p>We believe that these findings and suggestions will be of interest to the readers of your journal, because they will be helpful to improve the reliability of anemia management with ESA administration in hemodialysis patients, which is essential for the vital prognosis of those patients.</p> <p>We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. All authors have approved the manuscript and agree with its submission to Journal of Artificial Organs. All study participants provided informed consent, and the study design was approved by the appropriate ethics review boards. There are no conflicts of interest to declare.</p> <p>Please consider, as a potential referee Dr. Tadashi Tomo (Clinical Engineering Research Center Faculty of Medicine, Oita Unniversity, 1-1 Idaigaoka, Hasama-machi, Yufu-City OITA 879-5503, JAPAN, tomo@oita-u.ac.jp).</p> <p>We hope you find our manuscript suitable for publication and look forward to hearing from you in due course.</p> <p>Sincerely,</p> <p>Toru Kawai, MD Chuo Naika Clinic 1-4-58 Hiroekimae, Kure, Japan TEL: 0823-71-8585 FAX: 0823-71-8586 Email: t.kawai@do.enjoy.ne.jp</p>
Suggested Reviewers:	<p>Tadashi Tomo, Ph.D.,M.D. Clinical Professor, Oita Unniversity tomo@oita-u.ac.jp Dr. Tomo is a member of the editorial board of Journal of Artificial Organs. And he is one of the leading researchers on renal anemia management in maintenance hemodialysis patients, which is the subject of our manuscript.</p>
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Title:

Long-term maintenance of hemoglobin levels in hemodialysis patients treated with bi-weekly epoetin beta pegol switched from darbepoetin alfa: A single-center, 12-month observational study in Japan

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Abstract

Recent evidence on maintenance administration of epoetin beta pegol, a continuous erythropoiesis receptor activator (CERA), in dialysis patients shows the clinical benefit of bi-weekly administration (Q2W) in improving hematopoiesis and iron use efficiency. We undertook a single-center observational study of 33 Japanese maintenance dialysis patients, whose anemia had been kept stable through weekly administration (Q1W) of darbepoetin (DA), to evaluate the effectiveness of CERA Q2W switched from DA in maintaining hemoglobin (Hb) levels over a 12-month period. The target Hb level was 10.0–12.0 g/dL. Throughout the 12-month period, the mean Hb was stably maintained at 10.5–10.8 g/dL, 69.7–87.9% of the patients achieving the target Hb level. The mean CERA dose was within the range of 62.9–78.8 $\mu\text{g}/2$ weeks. The average CERA dose adjustment frequency after switching was low at 0.42–0.67 times/3 months. In both subgroups stratified by the DA dose prior to the switch, Hb levels were kept stable during CERA administration; however, in the low-dose group (10–20 $\mu\text{g}/\text{week}$ of DA), the CERA and iron doses decreased over time, whereas in the high-dose group (30–60 $\mu\text{g}/\text{week}$ of DA) they remained unchanged. CERA Q2W achieved long-term successful anemia management in Japanese maintenance dialysis patients after switching from

DA Q1W. CERA dose was adjusted based on an overall consideration of past changes in Hb levels, erythropoiesis-stimulating agent (ESA) and iron doses. Subgroup analysis showed the CERA dose in the low-dose group decreased continuously, due possibly to a long-term improvement in iron use efficiency.

Introduction

Epoetin beta pegol is a continuous erythropoiesis receptor activator (CERA) that has the longest half-life of any erythropoiesis-stimulating agent (ESA), extending from 5 to 10 times longer than the half-lives of other conventional ESAs [1]. Frequent ESA administration to hemodialysis patients is an onerous task for medical staff, and CERA may help to mitigate this burden [2]. CERA also acts to enhance iron mobilization from body stores during hematopoiesis, through inhibiting hepcidin-25, suggesting that it may provide more efficient iron mobilization compared with darbepoetin alfa (DA), which is often used to treat hemodialysis patients [3].

The dose interval for the maintenance administration of CERA to dialysis patients approved by Japanese regulatory agencies is once every 4 weeks (Q4W); however, this can be adjusted to once every 2 weeks (Q2W) if hemoglobin (Hb) levels are not maintained within the target range. Although clinical studies have confirmed that target Hb levels are kept stable through the administration of CERA Q4W or once monthly [4, 5], recent studies have suggested that Q2W administration may be clinically useful in maintaining Hb levels with greater reliability than Q4W administration [6], enabling reduction of CERA dose [7, 8], improving iron use efficiency

[7,9,10], and increasing erythropoiesis [6]. The guidelines on the management of renal anemia, published by the Japanese Society for Dialysis Therapy (JSDT) as the 2015 edition, suggest that CERA Q2W may be more effective than Q4W [11].

In terms of patients switched from another ESA to CERA Q2W, the STRIATA trial, a Phase III international joint trial of CERA, found that Hb levels were kept stable for 12 months after patients were switched from DA once weekly (Q1W) or Q2W to CERA Q2W [12]. A number of Japanese hospitals have also published reports of patients switching from DA to CERA Q2W or twice a month, but most of these reports have only described a short monitoring period following the switch [13-16]. Evidence is still lacking on how to use CERA and iron for long-term reliable anemia management following the switch from DA.

We undertook a single-center observational study in Japan of 33 Japanese maintenance dialysis patients whose anemia had been kept stable through DA Q1W and who were switched to CERA Q2W, and we evaluated its effectiveness in maintaining hemoglobin (Hb) levels over a 12-month period and methods of anemia management, with a focus on CERA dose adjustment and iron replacement.

Methods

Patients

This was a retrospective cohort observational study undertaken at a single center in Japan. The study participants were 33 patients, who met all of the following criteria: (1) undergoing outpatient maintenance dialysis three times a week; (2) had switched from intravenous DA Q1W (10 µg to 60 µg) to CERA Q2W between July 21, 2014 and April 1, 2016; (3) had been receiving intravenous DA Q1W (10 µg to 60 µg) for at least 3 months immediately prior to the switch to CERA, during which period the Hb levels had been maintained within a range from 9.0 g/dL to 12.0 g/dL and; (4) had been undergoing dialysis for ≥ 1 year when they were switched to CERA.

All patients enrolled in this study have given their informed consent, which has been approved by the Ethics Committee of the International Kidney Evaluation Association Japan (No. 2901), and this protocol has been found acceptable by them.

CERA dosage, administration, and iron replacement

All the study participants were switched from intravenous DA Q1W to intravenous CERA Q2W and were monitored for 12 months following the switch. The initial CERA

Q2W dose was calculated on the basis of the DA Q1W dose prior to the switch in accordance with the CERA formulation specifications as DA 10 µg Q1W = CERA 25 µg Q2W, DA 15 µg – 20 µg Q1W = CERA 50 µg Q2W, DA 30 µg Q1W = CERA 75 µg Q2W, DA 40 µg Q1W = CERA 100 µg Q2W, and DA 60 µg Q1W = CERA 150 µg Q2W, with an increase or decrease of one level permitted in light of Hb levels during the 3 months prior to the switch. CERA dose was adjusted, as necessary, to maintain Hb levels within the target range (10.0 g/dL to 12.0 g/dL), based on the blood test data described below.

Following the JSDT guideline recommendations for the management of renal anemia [17], iron replacement was started when serum ferritin level is <100 ng/mL and transferrin saturation (TSAT) level is <20%. Iron was administered as intravenous saccharated ferric oxide 40 mg once a week, and the procedure involved reviewing its administration after a 5-week course had been completed.

Blood sampling, assessments, and subgroup analysis

A complete blood count (white blood cells (WBC), red blood cells (RBC), Hb, and hematocrit (Ht)) was performed once a week during the 3 months prior to the switch and the following 12 months of CERA administration, for the purposes of anemia management and iron evaluation. Iron metabolism markers (serum iron, unsaturated

iron binding capacity, serum ferritin, and TSAT), nutritional markers (total serum protein, total serum albumin, and cholinesterase), and an inflammatory marker (C-reactive protein (CRP)) were also measured once a month.

The parameters evaluated were Hb levels prior to the CERA switch and during CERA administration, CERA dose, iron dose, iron metabolism markers, nutritional markers, an inflammatory marker, and dialysis indicators (protein catabolic rate (PCR) and Kt/V dose). The iron dose was calculated as the dose per week during the 3 months prior to the switch to CERA and during months 1 to 3, 4 to 6, 7 to 9, and 10 to 12 following the switch. The target Hb level achievement rate during CERA administration was also evaluated. The frequency with which CERA dose was adjusted (increased or decreased) in months 1 to 3, 4 to 6, 7 to 9, and 10 to 12 following the switch was also calculated and evaluated.

The participants were divided into 2 subgroups, depending on whether they had been receiving a low dose (10, 15, or 20 $\mu\text{g}/\text{week}$) or a high dose (30, 40, or 60 $\mu\text{g}/\text{week}$) of DA prior to the switch, and their Hb levels, CERA dose, iron dose, frequency of CERA dose adjustment, and various markers were investigated. To analyze changes in iron metabolism dynamics following the switch to CERA in the low-dose and high-dose groups, we also investigated correlations between the magnitude of changes in any

parameters including CERA and iron doses that exhibited changes over time during the 12 months following the switch.

Statistical analysis

Data were expressed as means \pm standard deviations. Changes over time were analyzed using a Wilcoxon signed-rank test. Comparisons between the low-dose and high-dose groups were made using a Wilcoxon rank-sum test. Correlations between the magnitude of changes in parameters that exhibited changes over time during the 12 months following the switch were evaluated using a Spearman rank correlation analysis. For all tests, $p < 0.05$ was regarded as statistically significant.

Results

Participant characteristics

Table 1 shows the characteristics of the 33 study participants, who comprised 15 men and 18 women with a mean age of 67.7 ± 11.5 years. The mean length of dialysis for participants was 9.3 ± 7.9 years, involving 14 participants with diabetes-related nephropathy, 11 participants with chronic glomerulonephritis, 4 participants with nephrosclerosis, 1 participant with polycystic kidney disease, and 3 participants with other underlying conditions.

Clinical markers

Table 2 shows the results of laboratory tests prior to the switch to CERA and during CERA administration. The dialysis indicators, PCR and Kt/V, and the nutritional markers for total serum protein, serum albumin, and cholinesterase all remained extremely stable throughout these periods. Although CRP rose transiently to an abnormally high value of ≥ 1.0 mg/dL in some participants, there was no significant change compared with baseline. None of the iron metabolism markers exhibited any marked fluctuation, with no significant change compared with baseline. Mean serum

ferritin was maintained in a range between 43.9 ng/dL and 62.8 ng/dL, and mean TSAT ranged between 13.9% and 19.9%.

Hb levels, CERA dose, and the frequency of CERA dose adjustment

Fig. 1a shows monthly changes in mean Hb levels prior to the switch to CERA and during CERA administration. Hb levels remained stable throughout these periods, with no significant change. The target Hb level achievement rate was maintained within a range between 69.7% and 87.9% during CERA administration.

When converted to one dose/2 weeks, the mean DA dose prior to the switch was 65.2 ± 29.98 $\mu\text{g}/2$ weeks. The mean CERA dose at the switch was 77.3 ± 30.8 $\mu\text{g}/2$ weeks, with the mean initial dose conversion ratio from DA of 1.24 ± 0.33 . Following the switch, the mean CERA dose was 76.5 ± 36.4 $\mu\text{g}/2$ weeks at 12 weeks, 73.5 ± 38.0 $\mu\text{g}/2$ weeks at 26 weeks, 65.9 ± 41.8 $\mu\text{g}/2$ weeks at 38 weeks, and 68.2 ± 40.6 $\mu\text{g}/2$ weeks at 50 weeks, with no significant change over time throughout the duration of CERA administration compared with the dose at the switch (Fig. 1b).

The total number of times CERA dose was adjusted upward / downward in each 3-month period of CERA administration following the switch was 5 times / 9 times in Months 1 to 3, 8 times / 14 times in Months 4 to 6, 9 times / 11 times in Months 7 to 9,

and 9 times / 6 times in Months 10 and 12. The number of dose adjustments per patient was 0.42 ± 0.90 times in Months 1 to 3, 0.67 ± 0.82 times in Months 4 to 6, 0.61 ± 0.86 times in Months 7 to 9, and 0.45 ± 0.71 times in Months 10 to 12, with no significant change in these numbers over time (Fig. 1c).

Iron dose

The mean iron dose per week was 15.8 ± 8.4 mg/week in the 3 months prior to the switch, 15.8 ± 9.0 mg/week in Months 1 to 3, 17.7 ± 10.0 mg/week in Months 4 to 6, and 14.5 ± 11.4 mg/week in Months 7 to 9, with no significant change occurring throughout these periods. However, a tendency to decrease was evident in Months 10 to 12, when the mean iron dose was 10.7 ± 9.0 mg/week ($p=0.051$) (Fig. 1d).

Subgroup analysis

A subgroup analysis based on the DA dose prior to the switch comprised 11 patients in the low-dose group and 22 in the high-dose group.

Fig. 1e shows the monthly mean Hb levels in both groups prior to the switch to CERA and during CERA administration. Throughout these periods there were no major changes in Hb levels exhibited by either group, though there was a transient significant

increase ($p<0.05$) in the level in the low-dose group at the first month following the switch. The target Hb level achievement rates during CERA administration were maintained within the range between 59.1% and 81.8% in the high-dose group and between 81.8% and 100% in the low-dose group.

When converted to one dose/2 weeks, the mean DA doses prior to the switch were 33.6 ± 6.7 $\mu\text{g}/2$ weeks in the low-dose group and 80.9 ± 23.5 $\mu\text{g}/2$ weeks in the high-dose group. The mean CERA doses at the switch were 47.7 ± 17.5 $\mu\text{g}/2$ weeks in the low-dose group and 92.0 ± 24.9 $\mu\text{g}/2$ weeks in the high-dose group, with the mean initial dose conversion ratio of 1.42 ± 0.48 in the low-dose group, which was significantly higher than that of 1.16 ± 0.18 in the high-dose group ($p<0.05$). In the high-dose group, the CERA dose did not change significantly throughout the duration of CERA administration, but in the low-dose group it tended to decrease over time, and this decrease was significant at 32 weeks, and between 38 and 48 weeks following the switch ($p<0.05$) (Fig. 1f). The mean CERA dose conversion ratios for the low-dose and high-dose groups were 1.36 ± 0.99 and 1.14 ± 0.18 , respectively, at 12 weeks following the switch; 1.14 ± 0.39 and 1.14 ± 0.35 , respectively, at 26 weeks; 0.93 ± 0.39 and 1.09 ± 0.47 , respectively, at 38 weeks; and 1.08 ± 0.48 and 1.06 ± 0.47 , respectively, at 50 weeks, with no significant difference evident after 12 weeks.

There were also differences between the two subgroups in the trends following the mean weekly iron doses in each group (Fig. 1g). In the high-dose group, the mean iron dose remained stable from 16.1 ± 8.7 mg/week during the 3 months prior to the switch to 13.4 ± 8.9 mg/week during Months 10 to 12, with no significant change occurring during this period. In the low-dose group, however, it decreased significantly over time, from 15.2 ± 8.2 mg/week during the 3 months prior to the switch to 5.3 ± 6.9 mg/week during Months 10 to 12 ($p < 0.05$). In terms of iron metabolism markers, serum ferritin levels remained stable throughout CERA administration, and did not change significantly compared with the level at the switch in either group. TSAT also remained stable overall in the high-dose group exhibiting transient significant increase at Month 7 and 12 following the switch ($p < 0.05$), while in the low-dose group there was no significant change during CERA administration compared with the time of the switch.

In the low-dose group, there was a significant positive correlation between the change in CERA dose during the 12 months following the switch and the change in the mean weekly iron dose from the 3 months period prior to the switch to Months 10 to 12 ($r_s = 0.71$, $p < 0.05$). The change in TSAT during the 12 months following the switch was not significantly correlated with the change neither in CERA dose nor during the 12 months.

Discussion

Our study findings suggest that in Japanese maintenance hemodialysis patients with renal anemia, Hb levels could be kept stable for 12 months after switching from DA Q1W to CERA Q2W. The STRIATA study, a phase III international joint study with participation from European, Australian, and Canadian institutions, showed that stable Hb levels were maintained for 12 months when patients were switched from DA Q1W or Q2W to CERA Q2W. [12] While no Japanese facilities participated in the STRIATA study, our study targeting Japanese patients revealed the same results as those of the STRIATA study, confirming that long-term maintenance administration with CERA Q2W after switching from DA Q1W administration was clinically useful for renal anemia management after initiating dialysis. In addition, although the conversion method used in the present study from pre-switchover DA dosage to CERA initial dosage was clearly different to that used in the STRIATA study, Hb levels were stably maintained from directly after the switchover, as observed in the STRIATA study. In the STRIATA study, conversion was performed in three stages from <40 µg/week of DA to 60 µg/2 weeks of CERA, 40–80 µg/week of DA to 100 µg/2 weeks of CERA, and >80 µg/week of DA to 180 µg/2 weeks of CERA. In the present study, however, conversion was performed with more gradual changes, in five stages, to conform to the CERA

formulation specifications allowing for use in Japan (DA dosage in the range of 10–60 µg/week set within the range of 25–150 µg/2 weeks of CERA).

Dialysis patients treated with short-acting ESAs, who are switched to another ESA, may subsequently exhibit transient fluctuations in Hb levels [18-20]. Toida *et al.* carried out a randomized comparative study of Q2W and Q4W administration of CERA in patients switched from recombinant human erythropoietin (rHuEPO), and found that the Q2W administration maintained stable Hb levels with no decrease following the switch [21]. Although CERA greatly reduces blood hepcidin-25 levels after administration, its concentration is known to rise again 2 weeks later [22]. CERA Q2W suppresses hepcidin-25 in a more sustained manner than Q4W, improving iron metabolism and permitting more effective iron use in erythropoiesis [9, 10]. Therefore, this dosage regimen may be appropriate for maintaining stable Hb levels, not only after switching from DA but also during long-term maintenance administration. Hb variability in dialysis patients may elevate the risk of cerebrovascular and cardiovascular disease [23, 24], infection [23, 24], and death [25, 26], and it is important to adopt an ESA dosing strategy that can maintain stable Hb levels within the target range over the long term.

In terms of CERA dose adjustments, stabilizing CERA blood concentration takes

approximately 6 weeks [27]; therefore, frequent dose adjustments are undesirable, particularly immediately following the switch. We measured Hb levels together with RBC, WBC and Ht levels (a complete blood count) once a week. The main purpose of these frequent measurements was for early detection of the appearance or deterioration of anemia due to causes other than renal anemia, such as gastrointestinal bleeding, as well as other abnormalities such as infection, and they were not performed as a basis for frequent CERA dose adjustments. An overall determination on adjusting CERA dose was made each time CERA was administered, taking into account not only the monthly assessments of inflammation, nutritional status, and iron status, but also past changes in Hb levels, ESA dose, and iron dose over the previous year.

Regarding the optimum frequency of Hb monitoring and ESA dose adjustment for anemia management in dialysis patients, a retrospective analysis of 3-year observational data from 436,442 dialysis patients treated with the short-acting ESA epoetin alfa in 2,763 institutions in the United States found that the greater the frequency of Hb monitoring and ESA dose adjustment, the lower the Hb variability [28]. Gaweda *et al.* argued that more frequent Hb monitoring may enable more appropriate ESA dose adjustment by reducing the effects of short-term factors such as interdialytic weight gain and measurement error on the magnitude of Hb variability, concluding that

an optimum Hb monitoring frequency seems to be once a week [29]. However, Kalicki *et al.* pointed out that frequent ESA dose adjustment on the basis of the most recent short-term test results may result in unstable anemia management, and that it is important to take account of the lifespan of red blood cells in dialysis patients, which is approximately 2 to 4 months, when determining the frequency of ESA dose adjustment [30]. Following this, Lines *et al.* reported that long-term stable Hb levels within the target range was achieved by keeping a minimum interval of 2 months between ESA dose adjustments in the algorithm for the management of anemia with DA [31].

In this study, we made an overall decision on CERA dose adjustment in light of data from the previous year concerning Hb levels, ESA dose, and iron dose, in addition to various other data described above, with our priority being to maintain long-term stable Hb levels within the target range in future. As a result, Hb levels and CERA dose were both stably maintained during CERA administration (Fig. 1a, 1b), and the mean CERA dose adjustment frequency per 3 months was from 0.42 to 0.67 times, meaning that the dose was only adjusted once every 4.5 to 7.1 months (Fig. 1c).

In the subgroup analysis (Fig. 1e, 1f, 1g), we found that in the low-dose group, the doses of both CERA and iron decreased over time following the switch to CERA, though Hb levels maintained stable. In the high-dose group, however, Hb levels, CERA and iron

doses all remained stable with no major changes. The mean initial dose conversion ratio from DA to CERA was 1.42 ± 0.48 in the low-dose group, which was significantly higher than that in the high-dose group (1.16 ± 0.18), but this difference quickly diminished following the switch and, after 12 weeks, it was no longer significant. However, the CERA dose in the low-dose group continued to decrease even after 12 weeks and, from 32 weeks onwards, the difference between the two subgroups was significant. Because there was a transient increase in Hb levels in the low-dose group at the first month following the switch, the initially high dose conversion rate in that group may explain at least the initial decrease in CERA dose. With respect to the cause of the long-term CERA dose reduction in the low-dose group, the positive correlation between the dose reductions in CERA and iron during the 12 months following the switch suggested that continuous CERA Q2W administration may have resulted in the improvement of iron use efficiency, leading to the lower CERA dose and iron supplementation required for hematopoiesis.

However, iron metabolism markers remained stable in the low-dose group throughout CERA administration, with no significant changes over time in either serum ferritin or TSAT. Further studies are required to investigate whether switching from DA to CERA Q2W may have a long-term effect on the dynamics of iron metabolism.

The limitations of this study are that it was a retrospective observational study that only included participants who were able to continue CERA Q2W administration for 12 months after switching from DA. A prospective observational study comparing patients divided into two groups according to their responsiveness to ESA at baseline might more clearly establish the long-term advantages of CERA Q2W for anemia management in dialysis patients. Patients whose anemia could not be managed at a stable level using DA prior to switching to CERA were excluded from this study; therefore, further studies are required to establish whether the policies for CERA dose adjustment and iron replacement under CERA Q2W that had been used in this study are applicable to dialysis patients more generally.

Conclusions

In a single-center retrospective cohort observational study of 33 Japanese maintenance hemodialysis patients with renal anemia, we found that stable Hb levels were maintained for 12 months, after patients switched from DA Q1W to CERA Q2W, at the mean dose conversion ratio of 1.24 ± 0.33 . An overall decision on CERA dose adjustment was made through taking account of past changes in Hb levels, ESA dose, and iron dose over the previous year, in addition to the assessment of weekly complete blood count data including Hb and monthly measurements of nutritional, inflammatory, and iron metabolism markers. As a result, the mean frequency of CERA dose adjustment in each 3-month period was maintained as low, with the dose adjusted once every 4.5 to 7.1 months, and this may have contributed to the maintenance of stable Hb levels over a 12-month period. A subgroup analysis showed that for the patients who had been given lower maintenance doses of DA, CERA dose decreased continuously over the 12 months following the switch, possibly because the efficiency of iron use increased over time during that period.

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Authors' contributions

TK and TM designed the study. TK performed the statistical analysis and wrote the manuscript. TK, YK, KY, CU, and AK participated in the care of the patients. TK, YK, KY, CU, AK, and TM read and approved the final manuscript.

Conflict of interest

The authors declare that they have no competing interests.

References

- 1) Macdougall IC, Robson R, Opatrna S, et al. Pharmacokinetics and pharmacodynamics of intravenous and subcutaneous continuous erythropoietin receptor activator (CERA) in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2006;1:1211-5.
- 2) De Cock E, Kritikou P, Ravera S, et al. Time savings with once-monthly C.E.R.A.: A time and motion study conducted in 13 haemodialysis centres in Italy. Blood Purif. 2015;40:173-9.
- 3) Onuma S, Honda H, Kobayashi Y, et al. Effects of long-term erythropoiesis-stimulating agents on iron metabolism in patients on hemodialysis. Ther Apher Dial. 2015;19:582-9.
- 4) Locatelli F, Choukroun G, Truman M, et al. Once-monthly continuous erythropoietin receptor activator (C.E.R.A.) in patients with hemodialysis-dependent chronic kidney disease : pooled data from phase III trials. Adv Ther. 2016;33:610-25.
- 5) Sulowicz W, Locatelli F, Ryckelynck JP, et al. Once-monthly subcutaneous C.E.R.A. maintains stable hemoglobin control in patients with chronic kidney disease on dialysis and converted directly from epoetin one to three times weekly. Clin J Am

Soc Nephrol. 2007;2:637-46.

- 6) Daimon S, Nuka H, Kitada K, et al. Influence of continuous erythropoietin receptor activator (CERA) administration intervals on erythropoietic effect in hemodialysis patients. *Renal Replacement Therapy*. 2016;2:58.
- 7) Morikami Y, Fujimori A, Okada S, et al. Twice-monthly administration of a lower dose of epoetin beta pegol can maintain adequate hemoglobin levels in hemodialysis patients. *Ther Apher Dial*. 2015;19:138-43.
- 8) Forni V, Bianchi G, Ogna A, et al. Reticulocyte dynamic and hemoglobin variability in hemodialysis patients treated with Darbepoetin alfa and C.E.R.A.: a randomized controlled trial. *BMC Nephrol*. 2013;14:157.
- 9) Morikami Y, Fujimori A, Okada S, et al. Comparison of 2-week versus 4-week dosing intervals of epoetin beta pegol on erythropoiesis and iron metabolism in hemodialysis patients. *Ther Apher Dial*. 2014;18:414-20.
- 10) Kimura S, Soga Y, Kato Y, et al. Effects of the once- versus twice-monthly administration of epoetin beta pegol on ferrokinetics, including hepcidin-25 levels, in patients undergoing hemodialysis. *J Jpn Soc Dial Ther*. 2016;49:827-32. [in Japanese]
- 11) Yamamoto H, Nishi S, Tomo T, et al. 2015 Japanese Society for Dialysis Therapy:

- guidelines for renal anemia in chronic kidney disease. *Ren Replace Ther.* 2017;3:36.
- 12) Canaud B, Mingardi G, Braun J, et al. Intravenous C.E.R.A. maintains stable haemoglobin levels in patients on dialysis previously treated with darbepoetin alfa: results from STRIATA, a randomized phase III study. *Nephrol Dial Transplant.* 2008;23:3654-61.
- 13) Takahashi S, Tanaka Y, Takano M, et al. Hemoglobin level stability after a switch from darbepoetin alfa to epoetin beta pegol for the treatment of renal anemia in hemodialysis patients. *Int J Clin Med.* 2015;6: 652-60.
- 14) Goga T. About the clinical and economic important matter by the change of the erythropoiesis stimulating agents in a hemodialysis patient's renal anemia treatment. *Ther Res.* 2012;33:567-70. [in Japanese]
- 15) Kuratsune M, et al. Switch of erythropoiesis-stimulating agents therapy from darbepoetin-alfa to epoetin beta pegol in hemodialysis patients: a single-center experience. *Ther Res.* 2012;33:251-6. [in Japanese]
- 16) Kimura S, Tomosugi N. Switch from darbepoetin to epoetin beta pegol for hemodialysis patients, and comparison of iron dynamics and cost-effectiveness using hepcidin 25 • ERI as an index once a month and twice a month epoetin beta pegol. *Kidney and Dialysis.* 2017;83:122-6. [in Japanese]

- 17) Tsubakihara Y, Nishi S, Akiba T, et al. 2008 Japanese Society for Dialysis Therapy: guidelines for renal anemia in chronic kidney disease. *Ther Apher Dial.* 2010;14:240-75.
- 18) Hirai T, Nishizawa Y, Nakazono H, et al. Hemoglobin maintenance and dosing strategies using intravenous continuous erythropoietin receptor activator in Japanese hemodialysis patients. *Ther Apher Dial.* 2013;17:498-503.
- 19) Hirai T, Nakashima A, Shiraki N, et al. Dose conversion ratio one year after switching from epoetin alpha to darbepoetin alpha in Japanese hemodialysis patients. *Int J Artif Organs.* 2010;33:283-9.
- 20) Levin NW, Fishbane S, Cañedo FV, et al. Intravenous methoxy polyethylene glycol-epoetin beta for haemoglobin control in patients with chronic kidney disease who are on dialysis: a randomised non-inferiority trial (MAXIMA). *Lancet.* 2007;370:1415-21.
- 21) Toida T, Sato Y, Shibata N, et al. A randomized control study on the procedure for switching epoetin beta (EPO) to epoetin beta pegol (CERA) in the treatment of renal anemia in maintenance hemodialysis patients. *Blood Purif.* 2014;38:174-9.
- 22) Kakimoto-Shino M, Toya Y, Kuji T, et al. Changes in hepcidin and reticulocyte hemoglobin equivalent levels in response to continuous erythropoietin receptor

- activator administration in hemodialysis patients: a randomized study. *Ther Apher Dial.* 2014;18:421-6.
- 23) Kuragano T, Matsumura O, Matsuda A, et al. Association between hemoglobin variability, serum ferritin levels, and adverse events/mortality in maintenance hemodialysis patients. *Kidney Int.* 2014;86:845-54.
- 24) Ebben JP, Gilbertson DT, Foley RN, et al. Hemoglobin level variability: associations with comorbidity, intercurrent events, and hospitalizations. *Clin J Am Soc Nephrol.* 2006;1:1205-10.
- 25) Gilbertson DT, Ebben JP, Foley RN, et al. Hemoglobin level variability: associations with mortality. *Clin J Am Soc Nephrol.* 2008;3:133-8.
- 26) Yang W, Israni RK, Brunelli SM, et al. Hemoglobin variability and mortality in ESRD. *J Am Soc Nephrol.* 2007;18:3164-70.
- 27) Kinugasa E, Yumita S, Sato T, et al. A dose-finding study of C.E.R.A. (continuous erythropoietin receptor activator) in renal anemia patients on hemodialysis: a randomized double-blind comparative study. *Jpn Pharmacol Ther.* 2011;39:S9-19.
[in Japanese]
- 28) Khan I, Krishnan M, Kothawala A, et al. Association of dialysis facility-level hemoglobin measurement and erythropoiesis-stimulating agent dose adjustment

frequencies with dialysis facility-level hemoglobin variation: a retrospective analysis. BMC Nephrol. 2011;12:22.

29) Gaweda AE, Nathanson BH, Jacobs AA, et al. Determining optimum hemoglobin sampling for anemia management from every-treatment data. Clin J Am Soc Nephrol. 2010;5:1939-45.

30) Kalicki RM, Uehlinger DE. Red cell survival in relation to changes in the hematocrit: more important than you think. Blood Purif. 2008;26:355-60.

31) Lines SW, Lindley EJ, Tattersall JE, et al. A predictive algorithm for the management of anaemia in haemodialysis patients based on ESA pharmacodynamics: better results for less work. Nephrol Dial Transplant. 2012;27:2425-9.

Tables

Table 1 Baseline patient characteristics

	(n=33)
Age (years)	67.7 ± 11.5
Male/female	15/18
Dialysis vintage (years)	9.3 ± 7.9
Primary disease	
Diabetes mellitus	14
Glomerulonephritis	11
Nephrosclerosis	4
Polycystic kidney disease	1
Others	3
Darbepoetin alfa dose (µg/week)	32.6 ± 14.9
Hb (g/dL)	10.6 ± 0.6
Serum ferritin (ng/mL)	47.9 ± 30.1
TSAT (%)	17.0 ± 9.6
Serum albumin (g/dL)	3.6 ± 0.3

CRP (mg/dL)	0.16 ± 0.36
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Kt/V	1.73 ± 0.29
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Data are expressed as the mean \pm standard deviation, or as the number.

Hb, hemoglobin; TSAT, transferrin saturation; CRP, C-reactive protein.

Table 2 Temporal changes in parameters prior to and following ESA switching in all patients (n=33)

	3 Months prior	Baseline	Month 3	Month 6	Month 9	Month 12
Hb (g/dL)	10.6±0.6	10.6±0.6	10.5±0.7	10.8±0.7	10.8±0.9	10.7±0.9
Serum total protein (g/dL)	6.4±0.3*	6.3±0.4	6.3±0.4	6.4±0.4	6.3±0.4	6.3±0.4
Serum albumin (g/dL)	3.6±0.3	3.6±0.3	3.5±0.3	3.6±0.3	3.6±0.3	3.6±0.3
Cholinesterase (IU/L)	249±73	245±68	244±65	252±69*	251±73	248±66
CRP (mg/dL)	0.21±0.57	0.16±0.36	0.13±0.26	0.13±0.27	0.29±0.96	0.16±0.25
Serum ferritin (ng/mL)	46.2±43.2	47.9±30.1	43.9±35.0	48.1±30.4	53.5±41.9	62.8±76.9
TSAT (%)	18.1±9.2	17.0±9.6	16.6±11.9	19.4±11.9	18.2±12.2	19.9±10.8
Serum iron (µg/dL)	50±23	46±23	44±27	53±30	48±30	53±26

UIBC (µg/dL)	237±54	236±61	240±63	235±65	231±62	225±57
PCR (g/kg/day)	0.86±0.16	0.87±0.15	0.86±0.11	0.87±0.18	0.85±0.13	0.86±0.19
Kt/V	1.72±0.31	1.73±0.29	1.70±0.30*	1.73±0.31	1.71±0.29	1.74±0.30

Data are expressed as the mean ± standard deviation. * $p<0.05$ vs. baseline.

Hb, hemoglobin; CRP, C-reactive protein; TSAT, transferrin saturation; UIBC, unsaturated iron binding capacity;

PCR, protein catabolism rate.

Legends

Fig.1

Temporal changes in Hb levels (a), CERA doses (b), the frequency of CERA dose adjustment (c) and iron doses (d) in all patients (n=33), and the results of the subgroup analysis (e, f, g) stratified by the DA dose prior to ESA switching into the higher-dose group (n=22) and lower-dose group (n=11). **a** Monthly changes in Hb levels prior to and following ESA switching. **b** Bi-weekly changes in CERA doses after switching from DA. **c** The frequency of CERA dose adjustment during every 3 months after switching from DA. **d** The mean weekly iron dose during 3 months prior to switching from DA and every 3 months after switching from DA. **e** Monthly Hb levels prior to and following ESA switching (subgroup analysis). **f** Bi-weekly CERA doses after switching from DA (subgroup analysis). **g** The mean weekly iron dose during 3 months prior to switching from DA and every 3 months after switching from DA (subgroup analysis). All data are expressed as the mean \pm standard deviation. *p<0.05 vs. baseline; BL, baseline

Figure (a)

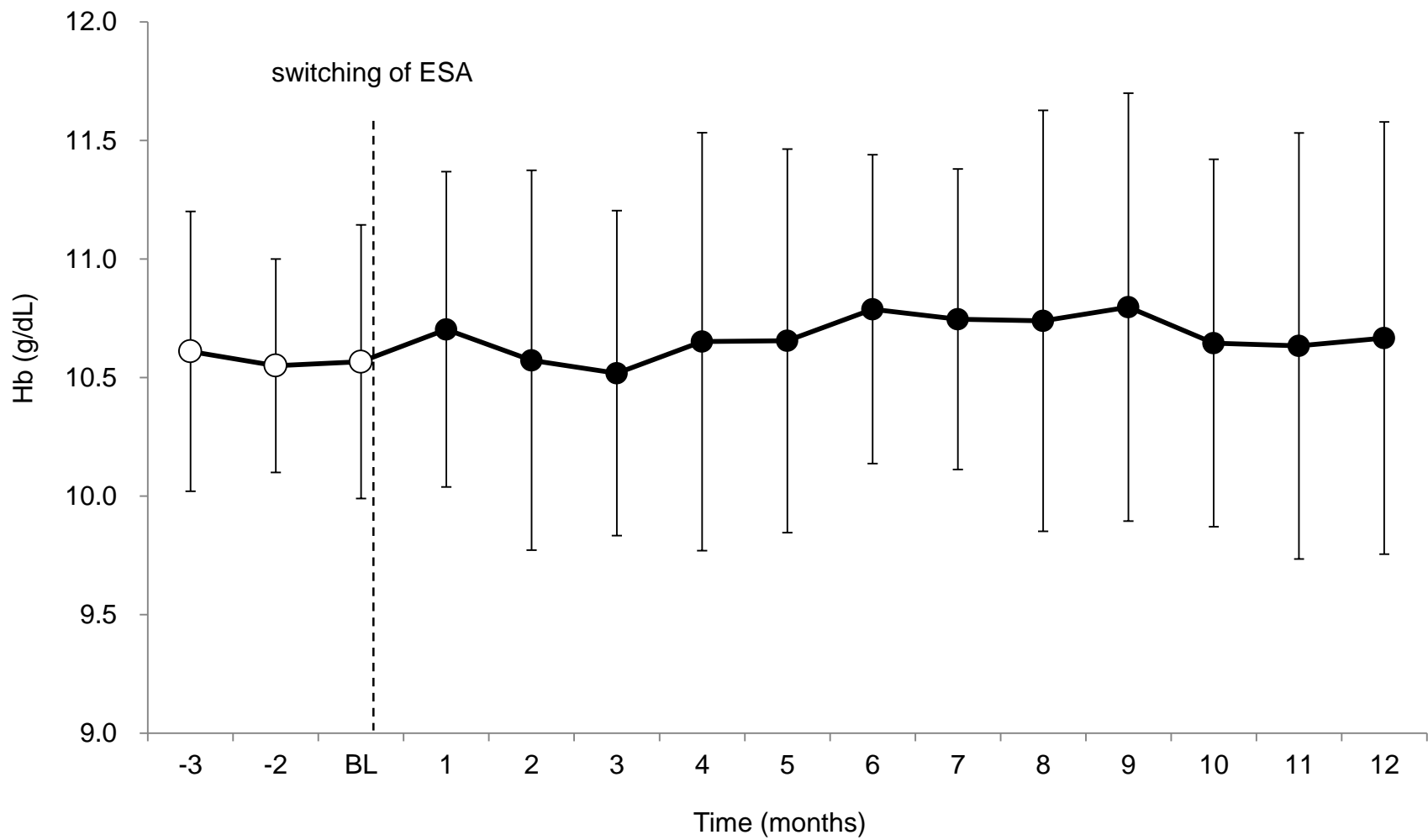


Fig. 1a

(b)

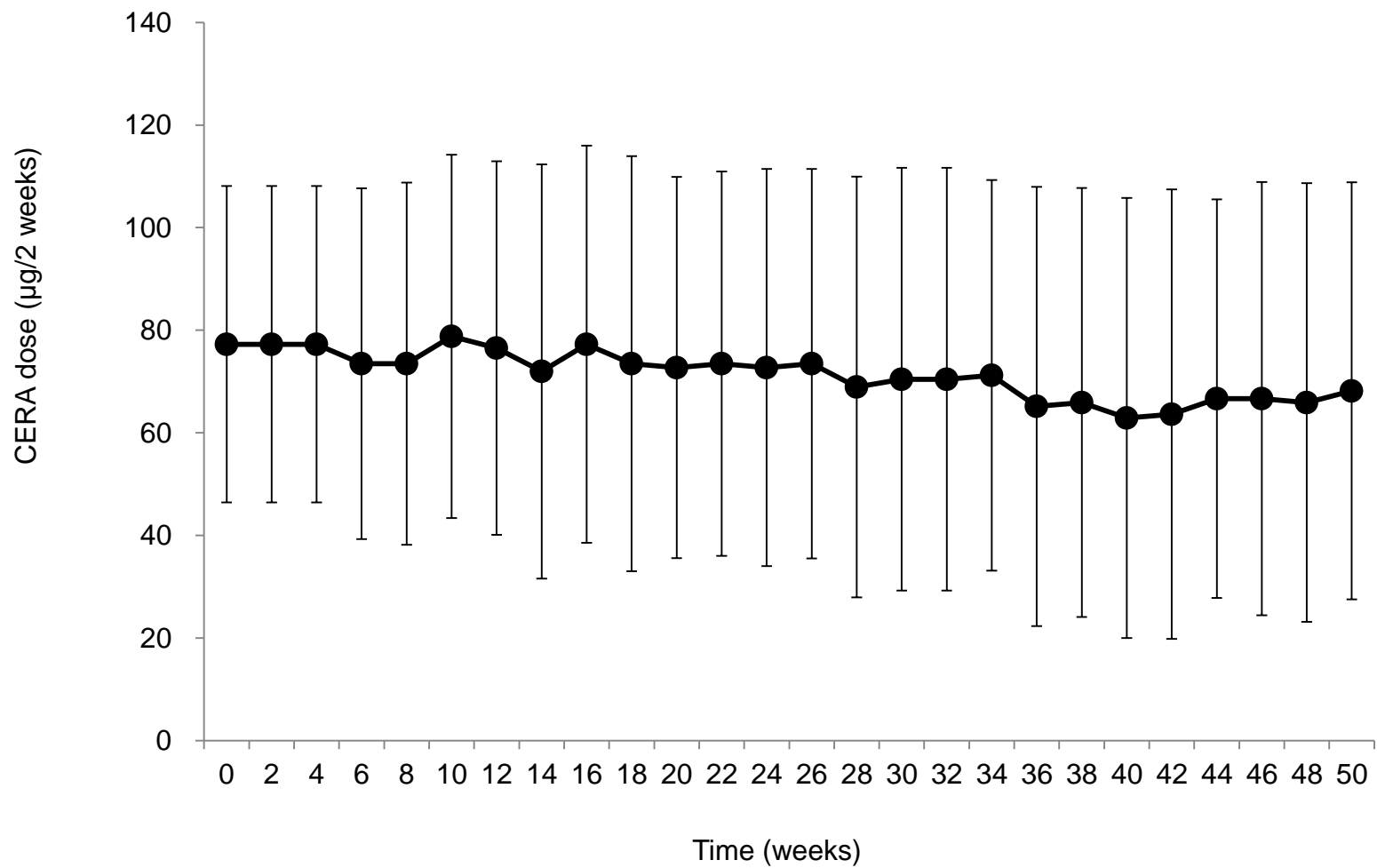


Fig. 1b

(c)

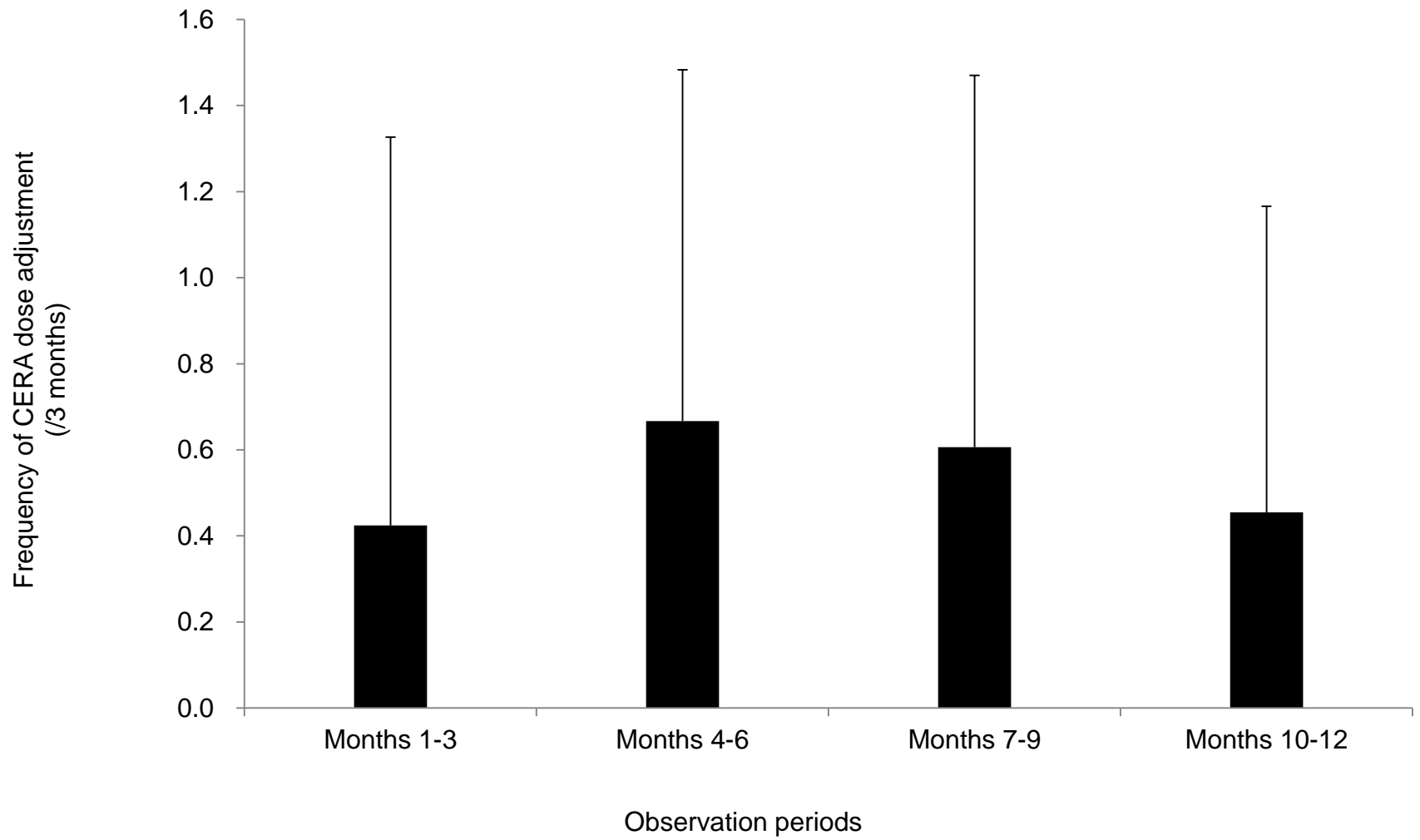


Fig. 1c

(d)

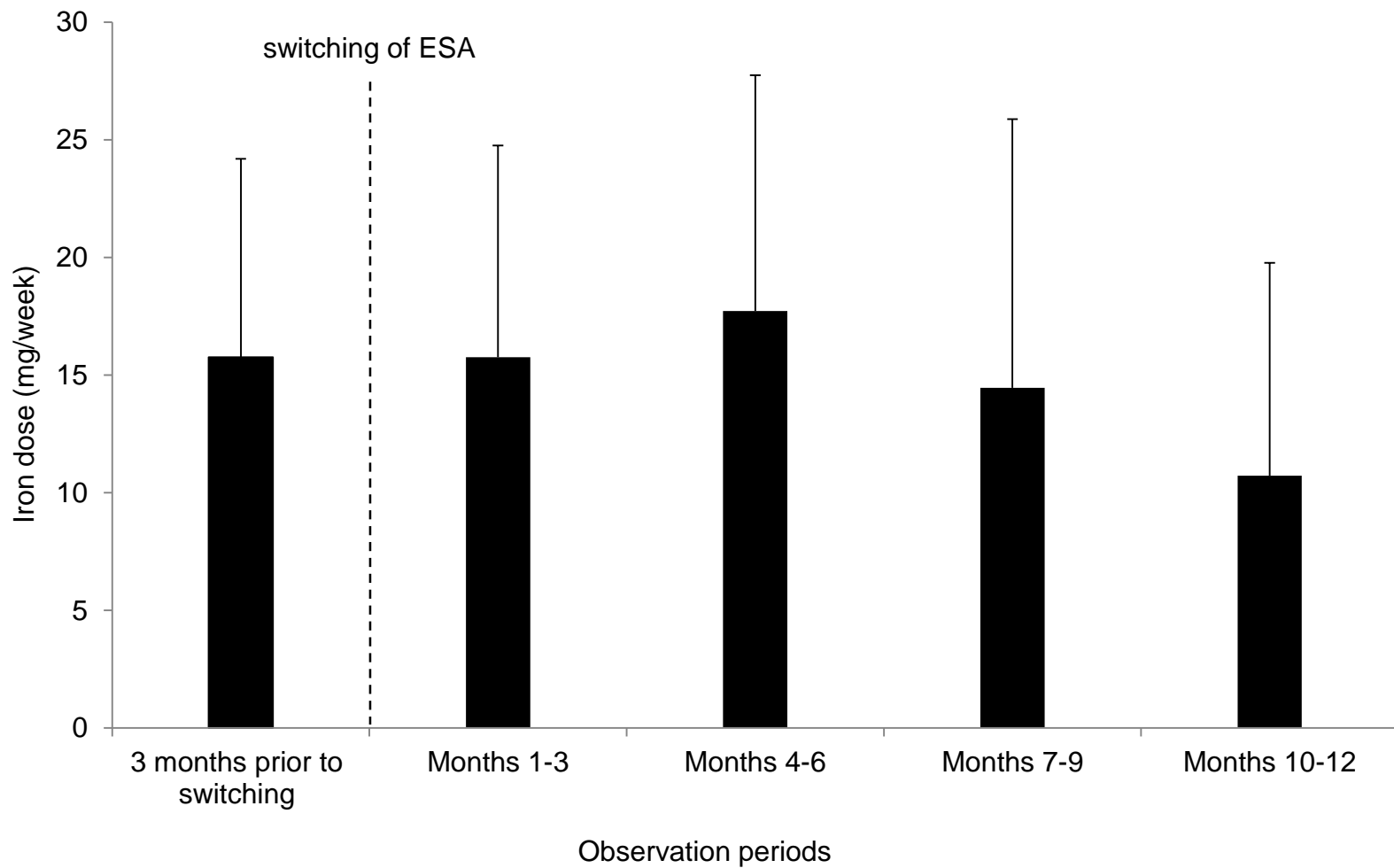


Fig. 1d

(e)

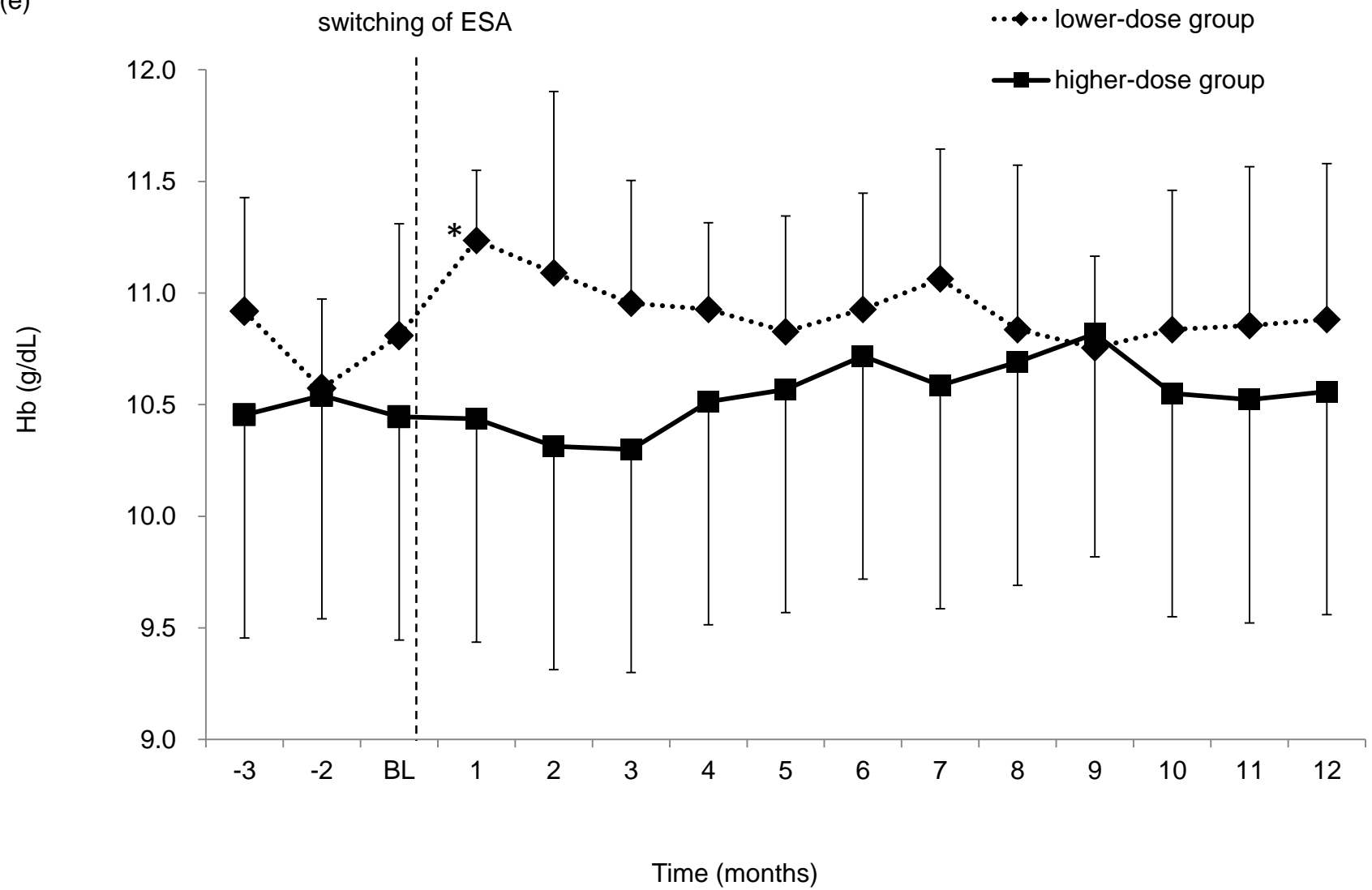


Fig. 1e

(f)

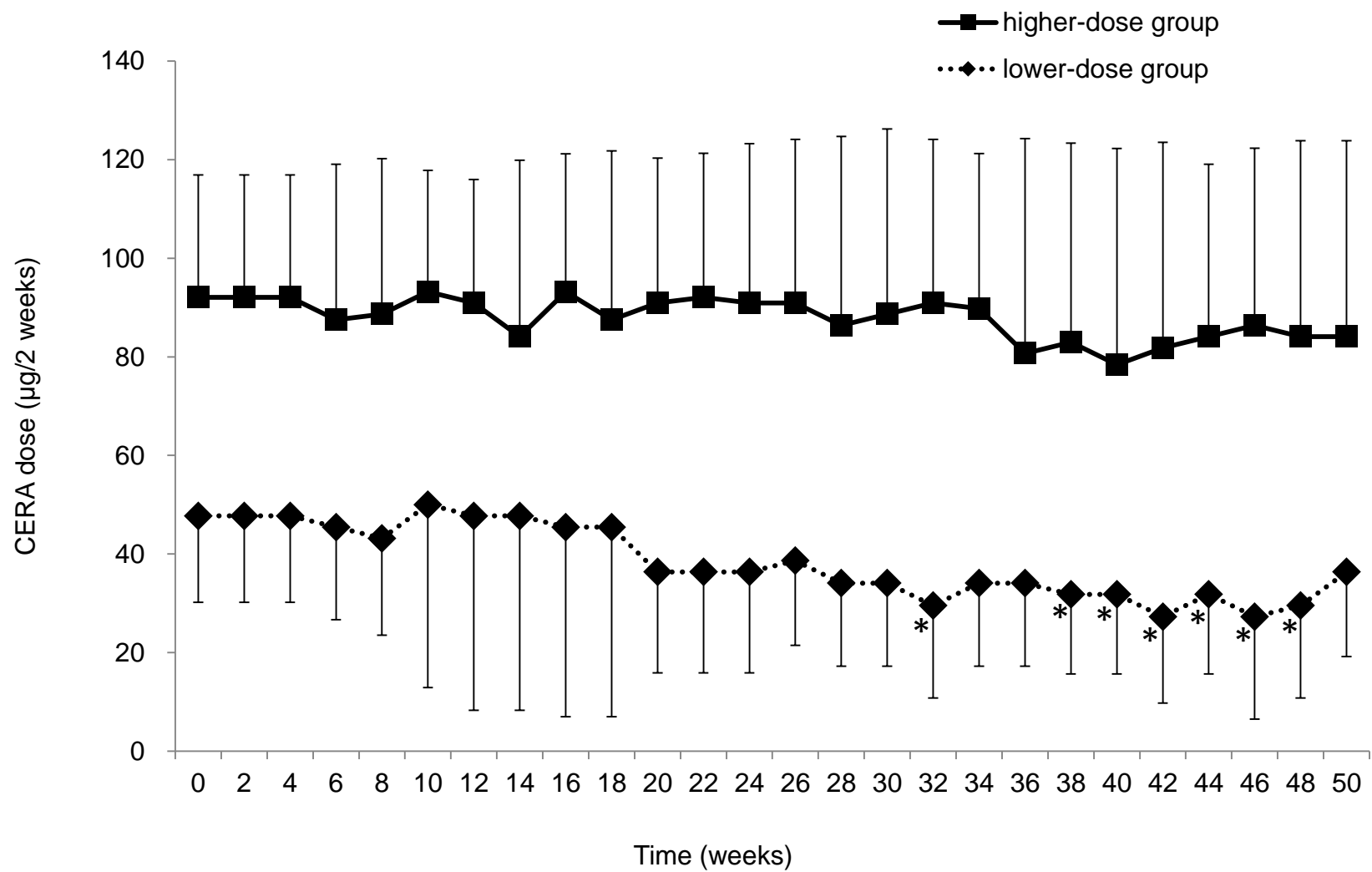


Fig. 1f

(g)

■ higher-dose group

□ lower-dose group

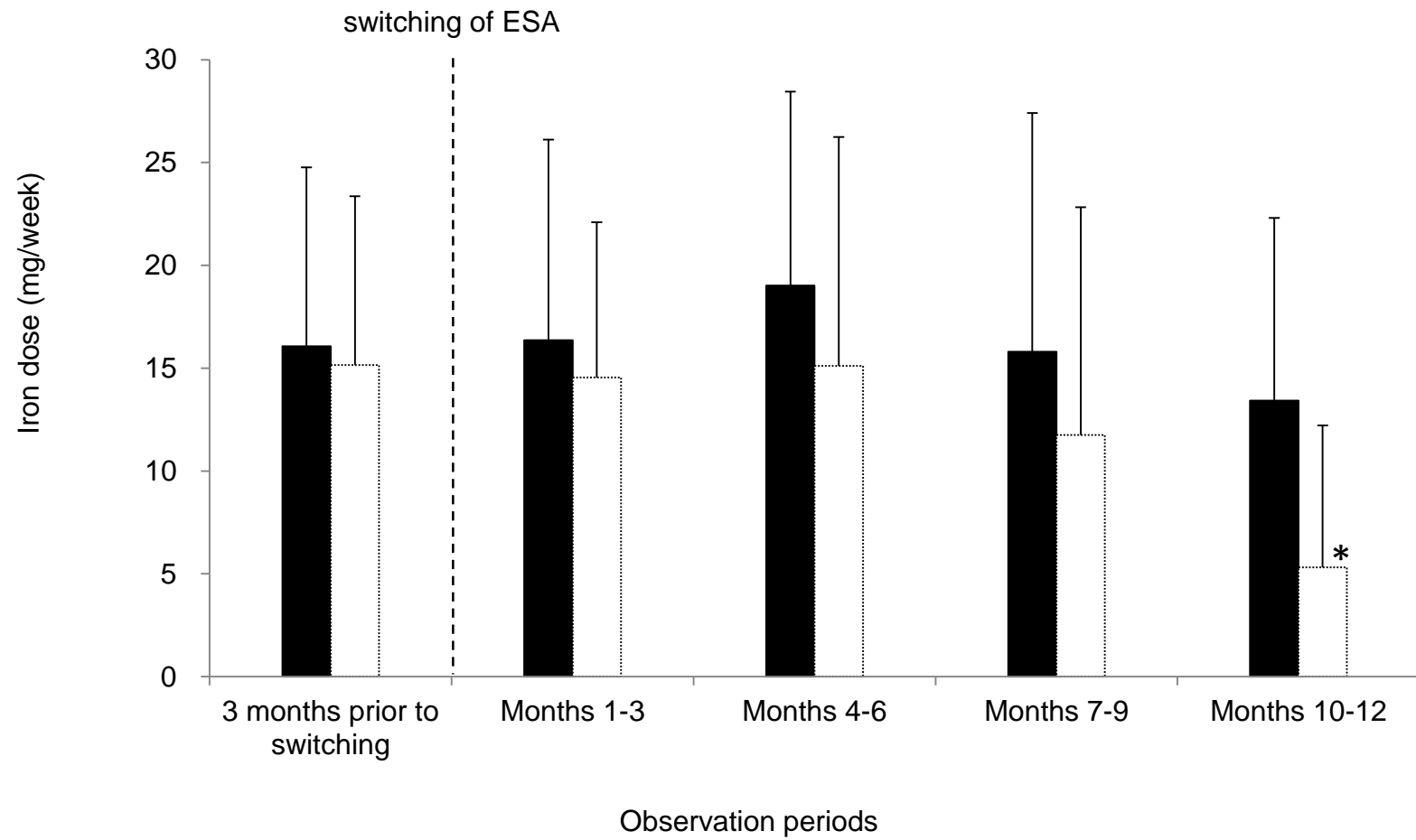


Fig. 1g

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Manuscript title: Long-term maintenance of hemoglobin levels in hemodialysis patients treated with bi-weekly epoetin beta pegol switched from darbepoetin alfa: A single-center, 12-month observational study in Japan

Author's names: Toru Kawai, Yoshie Kusano, Kyouko Yamada, Chikako Ueda, Atsushi Kawai, Takao Masaki

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