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ORIGINAL ARTICLE

Artificial Kidney/Dialysis

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 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 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.

Keywords Continuous erythropoiesis receptor activator · Epoetin beta pegol · Hemoglobin · Hemodialysis · Anemia

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

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levels with greater reliability than Q4W administration [6], enabling reduction of CERA dose [7, 8], improving iron use efficiency [7, 9], 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 [10].

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 [11]. 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 [12–14]. 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 (10–60 μg) to CERA Q2W between July 21, 2014 and April 1, 2016; (3) had been receiving intravenous DA Q1W (10–60 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 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 15–20 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 (10.0–12.0 g/dL), based on the blood test data described below.

Following the JSDT guideline recommendations for the management of renal anemia [15], 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 a dialysis indicator (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 1–3, 4–6, 7–9, and 10–12 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 1–3, 4–6, 7–9, and 10–12 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 μg/week) or a high dose (30, 40, or 60 μg/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 ± 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.

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
Kt/V	1.73 ± 0.29

Data are expressed as the mean ± standard deviation, or as the number

Hb hemoglobin, *TSAT* transferrin saturation, *CRP* C-reactive protein

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 indicator, 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 and 62.8 ng/dL, and mean TSAT ranged between 13.9 and 19.9%.

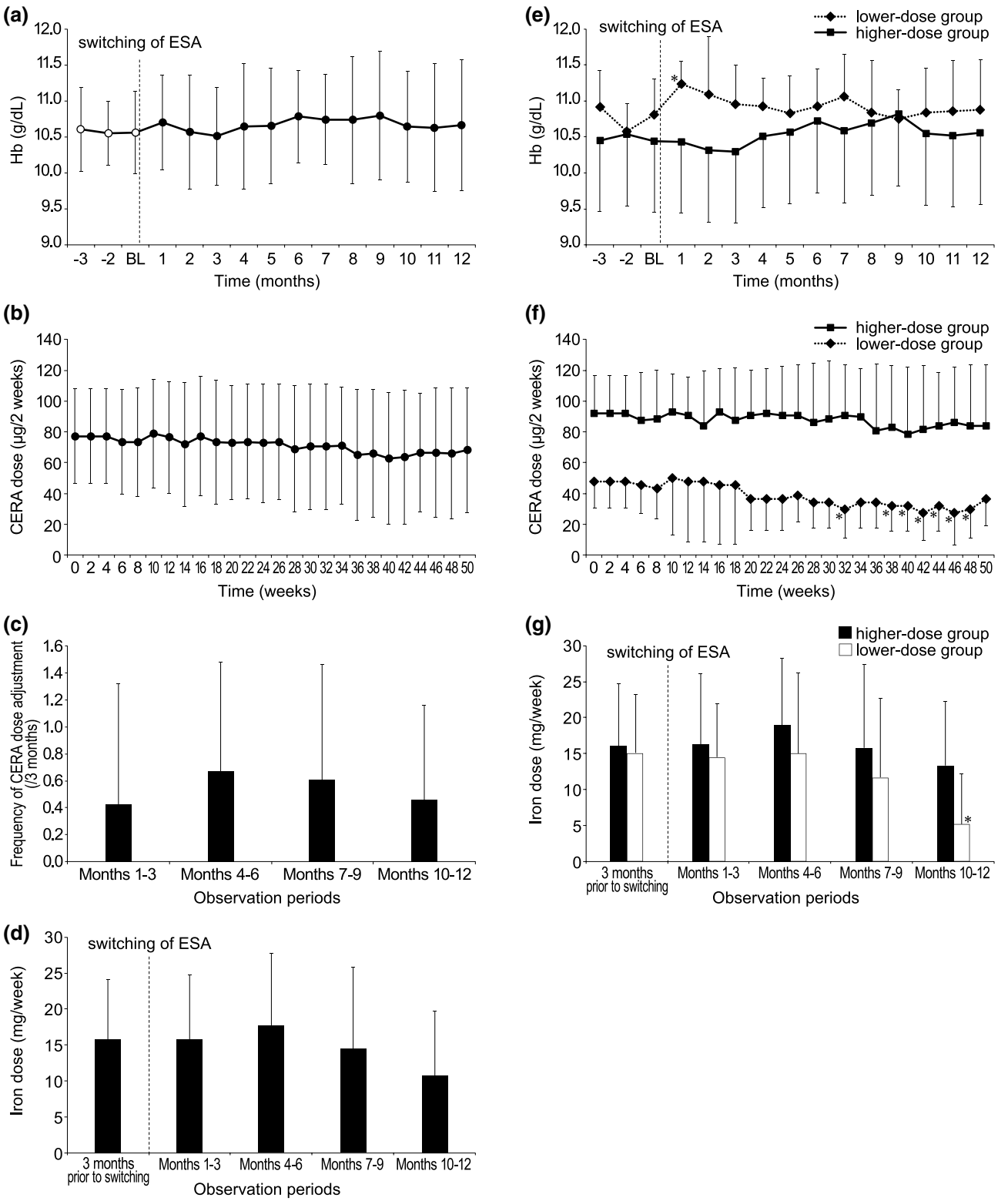
Table 2 Temporal changes in parameters prior to and following ESA switching in all patients ($n=33$)

	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
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

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

*$p<0.05$ vs. baseline



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

Figure 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.

◂**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**–**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 ± standard deviation. *$p<0.05$ vs. baseline. *BL* baseline

When converted to one dose/2 weeks, the mean DA dose prior to the switch was 65.2 ± 29.8 μg/2 weeks. The mean CERA dose at the switch was 77.3 ± 30.8 μg/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 μg/2 weeks at 12 weeks, 73.5 ± 38.0 μg/2 weeks at 26 weeks, 65.9 ± 41.8 μg/2 weeks at 38 weeks, and 68.2 ± 40.6 μg/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 1–3, 8 times/14 times in months 4–6, 9 times/11 times in months 7–9, and 9 times/6 times in months 10–12. The number of dose adjustments per patient was 0.42 ± 0.90 times in months 1–3, 0.67 ± 0.82 times in months 4–6, 0.61 ± 0.86 times in months 7–9, and 0.45 ± 0.71 times in months 10–12, 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 1–3, 17.7 ± 10.0 mg/week in months 4–6, and 14.5 ± 11.4 mg/week in months 7–9, with no significant change occurring throughout these periods. However, a tendency to decrease was evident in months 10–12, 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.

Figure 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 μg/2 weeks in the low-dose group and 80.9 ± 23.5 μg/2 weeks in the high-dose group. The mean CERA doses at the switch were 47.7 ± 17.5 μg/2 weeks in the low-dose group and 92.0 ± 24.9 μg/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 10–12, 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 10–12 ($p<0.05$). 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 (Fig. S1a). 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 (Fig. S1b).

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 10–12 ($r_S=0.71$, $p<0.05$; Fig. S2). The change in TSAT during the 12 months following the switch

was not significantly correlated with the change neither in CERA dose nor in iron dose 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 [11]. 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 [16, 17]. 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 [18]. Although CERA greatly reduces blood hepcidin-25 levels after administration, its concentration is known to rise again 2 weeks later [19]. CERA Q2W suppresses hepcidin-25 in a more sustained manner than Q4W, improving iron metabolism and permitting more effective iron use in erythropoiesis [9]. 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 [20, 21], infection [20, 21], and death [22], 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 [23]; 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 2763 institutions in the United States found that the greater the frequency of Hb monitoring and ESA dose adjustment, the lower the Hb variability [24]. 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 [25]. 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 2–4 months, when determining the frequency of ESA dose adjustment [26]. Following this, Lines et al. reported that long-term stable Hb levels within the target range were achieved by keeping a minimum interval of 2 months between ESA dose adjustments in the algorithm for the management of anemia with DA [27].

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, 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 4.5–7.1 months.

The hemodialysis patients in this study had lower mean serum ferritin (range 43.9–62.8 ng/dL) and TSAT levels

(range 13.9–19.9%). These results implied that the study population had persistent iron deficiency before switching to CERA and during CERA administration. The underlying cause of the iron deficiency was attributed to the adoption of the following iron replacement protocol.

In this study, following the JSDT guideline recommendations for the management of renal anemia [15], the criteria for initiating iron replacement were as follows: serum ferritin level of < 100 ng/mL and TSAT of < 20%. However, with regard to the intravenous iron dose and its administration frequency, 40 mg was administered once a week, and the policy procedure recommended the assessment of patients after the 5-week course had been completed. Therefore, the administration frequency of one course was lower than that recommended in the JSDT guidelines [15]. As a result, the mean weekly iron dose for each 3-month period before switching to CERA and during CERA administration was comparatively low, ranging from 10.7 to 17.7 mg/week.

This iron replacement protocol focused on the prevention of cardiovascular diseases and infection associated with intravenous iron administration [28]. However, previous observational studies demonstrated that iron deficiency with TSAT ≤ 20% was associated not only with hyporesponsiveness to ESA [29], but also with adverse clinical outcomes [30, 31] in hemodialysis patients. To establish an optimal iron replacement therapy for hemodialysis patients with low TSAT, which suggests decreased efficiency of iron use, further studies are needed, comprehensively taking into consideration the long-term prognosis and safety of patients as well as the effectiveness of this therapy in treating iron deficiency and ESA hyporesponsiveness.

In the subgroup analysis, 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.

There were several limitations in this study. First, this study used a small size, resulting in relatively high standard deviations of the data and limiting the clear understanding of the results, especially in the subgroup analysis. Second, 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. Third, 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 4.5–7.1 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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Author 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.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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