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Long-term safety and effectiveness of a continuous erythropoietin receptor activator (CERA) in patients with renal anemia: a prospective, observational, multicenter study

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Abstract

Background: This observational study investigated the safety and effectiveness of continuous erythropoietin receptor activator in patients with renal anemia in Japan.

Methods: Patients were enrolled between August 2011 and November 2015 and followed for up to 1 year. Outcomes were analyzed according to disease stage (not receiving dialysis, on hemodialysis, on peritoneal dialysis).

Results: Three thousand six hundred eighty-four patients were enrolled (1678 not receiving dialysis, 1605 on hemodialysis, 392 on peritoneal dialysis, and 9 other). Study treatment was well tolerated with no new safety concerns; adverse drug reactions were reported in 3.06%, 4.19%, and 4.46% of patients. Study treatment improved or maintained hemoglobin levels in 54.05–77.27% of patients, including erythropoiesis stimulating agent-naïve responders (hemoglobin ≥10.0 g/dL and hemoglobin increase ≥ 1.0 g/dL until week 24) and erythropoiesis-stimulating agent-switched responders (hemoglobin 10.0–12.0 g/dL at week 48).

Conclusions: This study shows the safety and effectiveness of long-term continuous erythropoietin receptor activator for renal anemia.

Keywords: Chronic kidney disease, Continuous erythropoietin receptor activator, Dialysis, Methoxy polyethylene glycol-epoetin beta, Anemia

Background

Renal anemia in patients with chronic kidney disease (CKD) is primarily due to decreased ability of the kidneys to produce erythropoietin [1, 2]. Erythropoiesis-stimulating agents (ESAs) are common agents for the treatment of renal anemia. ESAs act by promoting the proliferation of red blood cells by stimulating the erythropoietin receptor. Methoxy polyethylene glycol-epoetin beta (International Nonproprietary Name), a continuous erythropoietin receptor activator (CERA, Mircera®; F. Hoffmann-La Roche, Ltd.), is characterized as the longest acting of the currently available ESAs. In comparison with recombinant human erythropoietin (rHuEPO), when administered subcutaneously, the plasma half-life of CERA is 6–7 times longer, and when administered intravenously, the plasma half-life is 15–19 times longer [3–5]. Therefore, CERA once every 4 weeks as outpatient treatment was developed for the management of anemia in patients with CKD not on dialysis (ND) and those on peritoneal dialysis (PD), which improves treatment convenience for these patients. In patients on hemodialysis (HD), it is expected that decreased frequency of drug administration may improve safety by reducing the risk of administration errors and the risk of infections in patients and healthcare staff.

The results of Japanese phase 3 studies reported in 2011 demonstrated that CERA is very effective in managing

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anemia and maintaining adequate hemoglobin levels 18–24 weeks after initiation of treatment in patients with CKD ND [6], ESA-naïve patients with renal anemia on HD [7], and patients with renal anemia on PD [8]. In a study conducted in Japan, in which 23 medical facilities helped investigate the effectiveness and safety of continuous ESA administration, switching to CERA following treatment with rHuEPO resulted in maintenance of hemoglobin levels within the reference range after 42–48 weeks of treatment in about 60% of patients [9].

This prospective, observational, post-marketing study aimed to investigate the effectiveness and safety of CERA in Japanese patients with renal anemia in a real-world setting, including ESA treatment-naïve patients on PD (which have not been previously evaluated in clinical studies). This study also aimed to investigate the potential relationship between the rate of hemoglobin increase with CERA and the occurrence of treatment-related adverse events (which has not previously been fully examined in clinical studies), as well as the optimal dose of CERA when switching from other ESAs.

Methods

Study design and patients

A nationwide, prospective, observational, multicenter study was conducted between August 2011 and November 2015 in Japan (Japanese University Hospital Medical Information Network registry code: UMIN000023966). Patients were included if they were initiating CERA for the treatment of renal anemia. Patients with any grade of renal anemia were eligible for inclusion; however, patients with CKD who were planning to start dialysis treatment were enrolled only if CERA was initiated at least 8 weeks before the start of dialysis, whereas patients who were already receiving dialysis were enrolled if they planned to receive CERA for at least 1 year. CERA was administered as per the prescribing information and patients were followed for up to 1 year after the initiation of CERA treatment.

To attempt to reduce patient selection bias, patients were registered by attending physicians via a central electronic data capture (EDC) system. To prevent selection bias based on patient baseline hemoglobin levels, the registration period was limited to the time from 14 days prior to CERA treatment to 14 days after the start of CERA treatment. Furthermore, to reduce institution selection bias, patients from any medical institution were eligible for enrolment provided they met study inclusion criteria.

This study was conducted at institutions under contract in accordance with the Good Post-Marketing Study Practice regulations (GPSP) from the Ministry of Health, Labor, and Welfare in Japan. If necessary, the study protocol was approved by the ethics committee at each institution in accordance with institutional standards. In the present study, informed consent was not required according to the GPSP, although it was obtained from some patients depending on the rules and regulations of the institutions involved.

Outcomes

Safety and effectiveness outcomes were analyzed in different disease stages (ND, HD, and PD patients).

Safety endpoints included the incidence of adverse events and adverse drug reactions (ADRs), which were classified using the Medical Dictionary for Regulatory Activities Version 20.0, as well as the change in hemoglobin levels, changes in the dosage and administration of CERA over the study period, and the relationship between changes in hemoglobin levels and the occurrence of adverse events often related to changes in hemoglobin (vascular access thrombosis, hypertension including hypertensive encephalopathy, cardiovascular disease, cerebral hemorrhage, and thromboembolism including pulmonary embolism). These adverse events were evaluated by checklist in the case report form. In addition, the data used for the diagnosis for each patient, such as their New York Heart Association classification, computed tomography and magnetic resonance imaging test results etc., and clinical symptoms, were collected and reviewed. These adverse events were also analyzed in patients with hemoglobin measurements on the day prior to the adverse event and assessed as the rate of increase in hemoglobin immediately before the onset of an adverse event compared with hemoglobin levels in the 8 weeks prior to the onset of the adverse event.

The effectiveness endpoint was anemia response rate. Response rates were defined as the proportion of patients who achieved hemoglobin levels of ≥ 10.0 g/dL and an increase in hemoglobin of ≥ 1.0 g/dL until week 24 (ESA treatment-naïve patients) or the proportion of patients with hemoglobin levels of 10.0–12.0 g/dL at week 48 (patients who switched ESA treatment).

Hemoglobin level testing (frequency, type of assay) was conducted per standard clinical practice at the participating institutions. In addition, these levels were measured at enrolment into the study and at week 48.

Statistical analysis

Based on the incidence of hypertension, cardiovascular events, and thrombotic events observed in the main phase 3 Japanese study [7], a total of 3250 patients were planned to be enrolled. This would allow detection of adverse events associated with increased hemoglobin levels in at least one, two, or four or more patients (with a 95% confidence interval), respectively.

Continuous variables are expressed as means and standard deviations. Frequency tables were generated for categorical or qualitative variables and the data are presented

as the *n* (%). All statistical analyses were performed by using SAS Release 9.2 (SAS Institute, Cary, NC, USA).

Results

Patients

Between August 1, 2011, and November 30, 2015, data from 3377 patients at 419 institutions were collected. Of these, 3345 patients were included in the safety analysis set, while 32 patients were excluded (Fig. 1). The reasons for the exclusion were enrollment-related violations ($n = 31$) and CERA treatment failure ($n = 2$).

The disease stages of 3345 patients in the safety analysis set were ND in 1599 patients, HD in 1408 patients, PD in 336 patients, and "other" in 2 patients, the latter being one patient reported with "unknown type of renal replacement therapy" and the other patient with "peritoneal dialysis plus hemodialysis (concomitant therapy at the time of introduction)".

A further 191 patients were excluded from the effectiveness analysis; one patient was excluded because they received CERA off-label and 190 were excluded because of insufficient hemoglobin measurements. A total of 3154 patients were included in the effectiveness analysis (Fig. 1).

The patient characteristics were relatively similar between ND, HD, and PD patients, with the exception of baseline hemoglobin levels and transferrin saturation (TSAT) (Table 1). The mean age of patients was 72.02, 65.76, and 62.63 years in the ND, HD and PD patient groups, respectively. The main primary disease in each of the patient groups was diabetic nephropathy and chronic glomerulonephritis. The percentage of patients with a history of ESA treatment in each of the patient groups was 50.59%, 91.19%, and 78.27%, respectively, and the most frequent reason for switching to CERA was insufficient improvement of anemia.

CERA was given every 4 weeks in 75.48% (1207/1599 patients) of ND patients, 80.68% (1136/1408 patients) of HD patients, and 82.14% (276/336 patients) of PD patients.

During the observation period, iron supplements were given to 19.82% of ND patients ($n = 317$; oral administration in 263 patients and intravenous administration in 58 patients), 33.45% of HD patients ($n = 471$; oral administration in 42 patients and intravenous administration in 435 patients), and 21.72% of PD patients ($n = 73$; oral administration in 61 patients and intravenous administration in 15 patients).

The changes in TSAT and ferritin levels during the observation period according to disease stage and history of switching of ESA are shown in Additional file 2. The standard deviation (SD) was large at each time point, and no specific trends in changes were noted.

Blood transfusion was performed in 3.12%, 4.68%, and 3.27% of ND, HD, and PD patients, respectively, during the period from 6 months prior to treatment to the end of the observation period.

The administration of iron supplements and blood transfusions was at the discretion of the treating physician. Since the iron administration period and type of iron supplements varied among patients, we did not analyze the

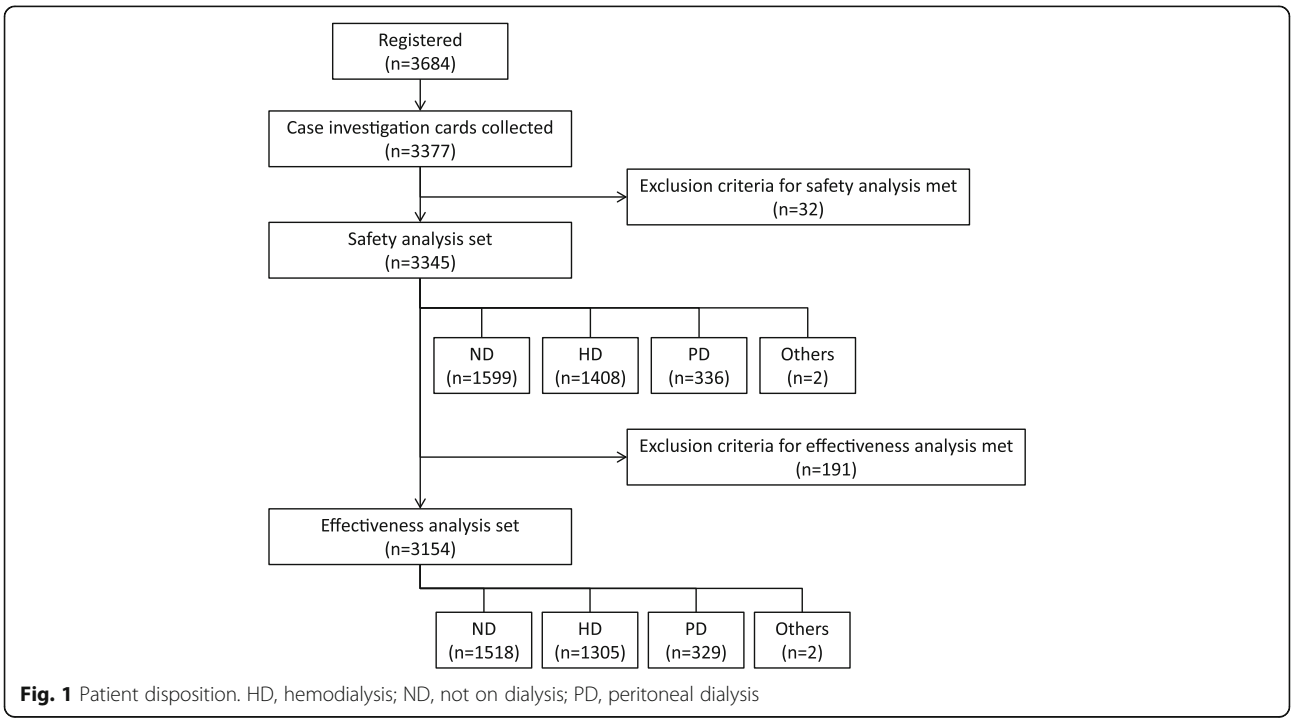


Fig. 1 Patient disposition. HD, hemodialysis; ND, not on dialysis; PD, peritoneal dialysis

Table 1 Baseline characteristics and demographics

Characteristic	Disease stage			Total patient population (*n*)
	ND (*n* = 1599)	HD (*n* = 1408)	PD (*n* = 336)	
Age, years	72.02 ± 12.78	65.76 ± 12.64	62.63 ± 13.50	3345
Male, *n* (%)	875 (54.72)	866 (61.50)	216 (64.28)	3345
Primary diagnosis, *n* (%)				
Chronic glomerulonephritis	390 (24.39)	524 (37.21)	113 (33.63)	1027
Diabetic nephropathy	551 (34.45)	529 (37.57)	123 (36.60)	1205
Nephrosclerosis	417 (26.07)	158 (11.22)	47 (13.98)	622
Other	240 (15.00)	197 (13.99)	53 (15.77)	490
Previous ESA therapy, *n* (%)				
Any	809 (50.59)	1284 (91.19)	263 (78.27)	2357
Erythropoietin	286 (17.88)	664 (47.15)	32 (9.52)	982
Darbepoetin α	523 (32.70)	620 (44.03)	231 (68.75)	1375
Duration of dialysis, years	–	6.78 ± 7.06	2.18 ± 2.47	
Hb, g/dL	9.68 ± 1.12	10.27 ± 1.18	10.15 ± 1.28	3191
eGFR, mL/min/1.73 m^2	18.55 ± 11.82	–	5.56 ± 2.81	
Serum creatinine, mg/dL	3.43 ± 2.12	–	9.21 ± 3.32	
Albumin, g/dL	3.66 ± 0.55	3.65 ± 0.42	3.29 ± 0.49	2837
Ferritin, ng/mL	162.75 ± 188.51	144.38 ± 179.77	159.45 ± 126.12	1636
TSAT, %	28.91 ± 13.20	25.38 ± 11.72	34.54 ± 13.34	1508

All values are presented as mean ± standard deviation unless otherwise stated
eGFR estimated glomerular filtration rate, *ESA* erythropoietin-stimulating agent, *Hb* hemoglobin, *HD* hemodialysis, *ND* not on dialysis, *PD* peritoneal dialysis, *TSAT* transferrin saturation

Table 2 Treatment-related adverse events

	Disease stage					
	ND (*n* = 1599)		HD (*n* = 1408)		PD (*n* = 336)	
	ADRs, *n* (%)	SADRs, *n* (%)	ADRs, *n* (%)	SADRs, *n* (%)	ADRs, *n* (%)	SADRs, *n* (%)
Any	49 (3.06)	21 (1.31)	59 (4.19)	35 (2.48)	15 (4.46)	6 (1.78)
Number of cases that had ≥ 2 ADRs						
Hypertension	15 (0.93)	0	16 (1.13)	1 (0.07)	5 (1.48)	0
Increased BP	1 (0.06)	0	4 (0.28)	0	1 (0.29)	0
IDA	4 (0.25)	0	3 (0.21)	0	0	0
Anemia	2 (0.12)	2 (0.12)	10 (0.71)	10 (0.71)	2 (0.59)	2 (0.59)
Cerebral infarction	1 (0.06)	1 (0.06)	4 (0.28)	4 (0.28)	0	0
Shunt occlusion	1 (0.06)	1 (0.06)	5 (0.35)	5 (0.35)	0	0
Cerebral hemorrhage	0	0	2 (0.14)	2 (0.14)	0	0
Subdural hematoma	2 (0.12)	2 (0.12)	0	0	0	0
Diabetic nephropathy	2 (0.12)	2 (0.12)	0	0	0	0
Increased Hb	2 (0.12)	0	0	0	0	0
Decreased platelets	2 (0.12)	0	1 (0.07)	1 (0.07)	0	0
Decreased appetite	0	0	2 (0.14)	2 (0.14)	0	0

ADRs adverse drug reactions, *BP* blood pressure, *Hb* hemoglobin, *HD* hemodialysis, *IDA* iron deficiency anemia, *ND* not on dialysis, *PD* peritoneal dialysis, *SADRs* serious adverse drug reactions

dose of iron supplements or changes in TSAT and ferritin levels according to the presence/absence of iron administration.

Safety

Adverse events

Overall, 3.06%, 4.19%, and 4.46% of ND, HD, and PD patients experienced ADRs with CERA (Table 2). The most common ADRs were hypertension (reported in 0.93%, 1.13% and 1.48% of ND, HD, and PD patients, respectively) and anemia (0.12%, 0.71%, and 0.59%, respectively).

Serious ADRs were reported in 1.31%, 2.48%, and 1.78% of ND, HD, and PD patients, respectively. In the HD patient group, one patient developed serious hypertension, but the event resolved without further treatment. During CERA treatment, none of the patients developed malignant tumors or pure red cell aplasia (including suspected pure red cell aplasia) due to this drug.

Fourteen patients (0.41%) had ADRs that led to death. Additional file 1 gives demographic and clinical characteristics of these patients, as well as the ADR and other relevant details relating to their death. Six patients died from hemorrhage-related events: two from cerebral hemorrhage, one from pulmonary alveolar hemorrhage, one from subdural hematoma, one from aortic aneurysm rupture, and one from thalamic hemorrhage. In four of these patients, it was reported that besides CERA treatment, factors such as the primary disease, medical history, and complications may have been related to the death. The other two patients who experienced a hemorrhage-related event had several complications: one patient had aplastic anemia, cardiac hypertrophy, and hypertension, while the other had cerebral infarction and hypertension.

Relationship between changes in hemoglobin levels and adverse events

The rate of increase in hemoglobin levels did not appear to influence the incidence of AEs experienced by any treatment group; no specific adverse events were more common in patients who had an increase in hemoglobin of > 0.5 g/dL/week compared with patients with an increase in hemoglobin of ≤0.5 g/dL/week (Table 3). Furthermore, in patients with cardiovascular disease, no relationship was observed between the occurrence of cardiovascular adverse events and hemoglobin levels measured immediately before the onset of the adverse events.

Table 3 Increases in hemoglobin levels immediately before the onset of adverse events

Types of AEs	Disease stage	Rate of increase in hemoglobin level immediately before onset of AEs (g/dL/week)				
		<− 0.5	≥ − 0.5 and < − 0.3	≥ − 0.3 and ≤ 0.3	> 0.3 and ≤ 0.5	> 0.5
Overall patients	ND	161	370	1522	477	212
	HD	155	419	1367	423	119
	PD	43	138	330	153	71
All AEs	ND	7 (4.34)	3 (0.81)	48 (3.15)	2 (0.41)	2 (0.94)
	HD	1 (0.64)	2 (0.47)	64 (4.68)	7 (1.65)	1 (0.84)
	PD	1 (2.32)	3 (2.17)	14 (4.24)	2 (1.30)	0 (0.00)
Vascular access thrombosis	ND	–	–	1 (0.06)	–	–
	HD	–	1 (0.23)	8 (0.58)	1 (0.23)	–
	PD	–	–	–	–	–
Hypertension	ND	–	–	21 (1.37)	–	1 (0.47)
	HD	–	1 (0.23)	28 (2.04)	1 (0.23)	–
	PD	–	2 (1.44)	8 (2.42)	2 (1.30)	–
Cardiovascular disease	ND	4 (2.48)	2 (0.54)	21 (1.37)	2 (0.41)	1 (0.47)
	HD	1 (0.64)	–	15 (1.09)	2 (0.47)	1 (0.84)
	PD	–	1 (0.72)	6 (1.81)	–	–
Cerebral hemorrhage	ND	1 (0.62)	1 (0.27)	3 (0.19)	–	–
	HD	–	–	7 (0.51)	2 (0.47)	–
	PD	–	–	1 (0.30)	–	–
Thromboembolism	ND	2 (1.24)	–	5 (0.32)	–	–
	HD	–	1 (0.23)	22 (1.60)	3 (0.70)	–
	PD	1 (2.32)	–	1 (0.30)	–	–

AEs adverse events, *Hb* hemoglobin, *HD* hemodialysis, *ND* not on dialysis, *PD* peritoneal dialysis

Relationship between changes in CERA frequency and dose and adverse events

During the study period, the frequency of CERA administration was changed from once every 4 weeks to once every 2 weeks in 139 patients, and from once every 2 weeks to once every 4 weeks in 152 patients. In all patient groups (ND, HD, and PD patients), the rate of adverse events with onset at least 8 weeks after a change in administration frequency of CERA did not exceed the frequency of adverse events observed before the change. During the study period, the dose of CERA was increased by one step in 442 patients and by two or more steps in 135 patients. In all patient groups, the rate of adverse events did not exceed the rate of adverse events before the change in CERA dose.

CERA dosing after switching from ESAs

Among patients who switched from rHuEPO to CERA, the most frequent dose and administration schedule was erythropoietin < 4500 IU/week to CERA 100 μg/4 weeks in ND patients (22.72% of patients), erythropoietin ≥ 4500 IU/week to CERA 150 μg/4 weeks in HD patients (23.04%), and erythropoietin < 4500 IU/week to CERA 100 μg/4 weeks in PD patients (15.62%; Table 4).

Among patients who switched from darbepoetin alfa to CERA, the most frequent dose and administration schedule was darbepoetin alfa ≥ 30 and < 40 μg/week to CERA 100 μg/4 weeks in ND patients (10.51% of patients), darbepoetin alfa ≥ 40 and < 60 μg/week to CERA 150 μg/4 weeks in HD patients (9.51%), and darbepoetin alfa ≥ 30 and < 40 μg/week to CERA 150 μg/4 weeks in PD patients (12.12%; Table 4).

Changes in hemoglobin

In all patients, a gradual increase in hemoglobin was observed after initiating CERA, reaching a steady state at approximately 8 weeks. There was no significant difference in the dose of CERA required to achieve steady state hemoglobin in any patient group.

Among patients who were treatment-naïve and receiving PD at study initiation ($n = 73$), hemoglobin levels gradually increased after initiating CERA and reached steady state after 16 weeks (Fig. 2). No major changes in hemoglobin levels were observed between reaching steady state at week 16 and week 52.

Among patients who switched from erythropoietin (Fig. 3) or darbepoetin alfa (Fig. 4) to CERA treatment, hemoglobin levels stabilized after approximately 8 weeks of treatment in all patient groups. No major changes in hemoglobin levels were observed from initiation of treatment until 52 weeks of treatment.

During treatment with CERA, 23 patients changed the route of administration from intravenous to subcutaneous injection and 70 patients changed the route of administration from subcutaneous to intravenous injection. In all patients who switched the route of CERA administration during the study, no rapid changes in CERA dosage or hemoglobin levels were observed.

During the study, 12 ND patients started dialysis and continued CERA throughout. In these patients, mean hemoglobin levels were 9.47, 9.64, and 9.44 g/dL at 12 weeks before dialysis was initiated, at the start of dialysis, and at 12 weeks after dialysis was initiated, respectively. Mean administered doses were 112.5, 115.9, and 120.0 μg/4 weeks at 12 weeks before dialysis was initiated, at the start of dialysis, and at 12 weeks after dialysis was initiated, respectively (Fig. 5).

Effectiveness

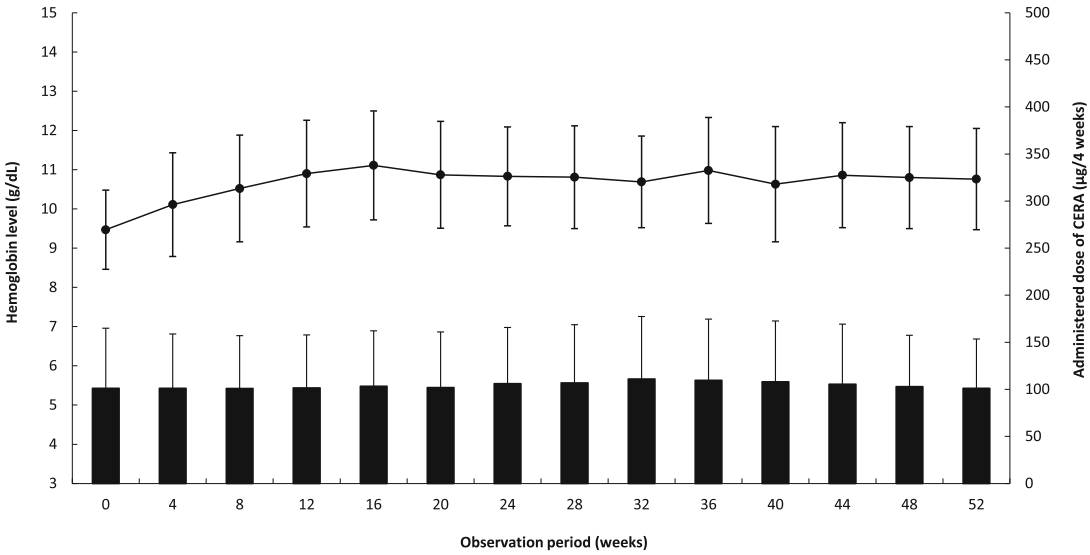
Anemia response rates

In the three patient groups, anemia response rates ranged from 54.05 to 77.27% (Table 5). Anemia response rates in ESA treatment-naïve patients were 65.04% ($n = 441$), 54.05% ($n = 60$), and 77.27% ($n = 51$) in the ND, HD, and PD patient groups, respectively. In patients who switched

Table 4 Top 3 most common CERA dosage/administration schedules when switching from erythropoietin-stimulating agent

	ND	HD	PD
1	EPO < 4500 IU/wk. → 100 μg/4 wks (65/286; 22.72%)	EPO ≥4500 IU/wk. → 150 μg/4 wks (153/664; 23.04%)	EPO < 4500 IU/wk. → 100 μg/4 wks (5/32; 15.62%)
2	EPO < 4500 IU/wk. → 50 μg/4 wks (31/286; 10.83%)	EPO ≥4500 IU/wk. → 100 μg/4 wks (124/664; 18.67%)	EPO ≥4500 IU/wk. → 100 μg/4 wks (5/32; 15.62%)
3	EPO ≥4500 IU/wk. → 150 μg/4 wks (29/286; 10.13%)	EPO < 4500 IU/wk. → 100 μg/4 wks (67/664; 10.09%)	Others → 100 μg/4 wks (5/32; 15.62%)
1	DA ≥30 and < 40 (μg/wk) → 100 μg/4 wks (55/523; 10.51%)	DA ≥40 and < 60 (μg/wk) → 150 μg/4 wks (59/620; 9.51%)	DA ≥30 and < 40 (μg/wk) → 150 μg/4 wks (28/231; 12.12%)
2	DA ≥15 and < 20 (μg/wk) → 100 μg/4 wks (51/523; 9.75%)	DA ≥20 and < 30 (μg/wk) → 100 μg/4 wks (45/620; 7.25%)	DA ≥30 and < 40 (μg/wk) → 100 μg/4 wks (21/231; 9.09%)
3	DA ≥15 and < 20 (μg/wk) → 50 μg/4 wks (49/523; 9.36%)	DA ≥60 (μg/wk) → 200 μg/4 wks (44/620; 7.09%)	DA ≥15 and < 20 (μg/wk) → 100 μg/4 wks (14/231; 6.06%)

DA darbepoetin alfa, *EPO* erythropoietin, *wk.* week



Weeks	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Hemoglobin level, n	71	64	64	62	55	53	49	51	50	46	53	50	48	49
Administered dose of CERA, n	73	70	70	62	58	59	55	53	54	51	52	50	46	42

Fig. 2 Changes in mean hemoglobin levels (line graph with closed circles) among ESA treatment- naïve patients on peritoneal dialysis. Bar graph represents mean dose of continuous erythropoietin receptor activator (CERA) administered; error bars represent ± 1 standard deviation

from erythropoietin, anemia response rates were 68.12% ($n = 109$), 69.92% ($n = 279$), and 60.00% ($n = 12$) in the ND, HD, and PD patient groups, respectively. In patients who switched from darbepoetin alfa, anemia response rates were 61.13% ($n = 162$), 66.84% ($n = 256$), and 67.80% ($n = 99$), in the ND, HD, and PD patient groups, respectively.

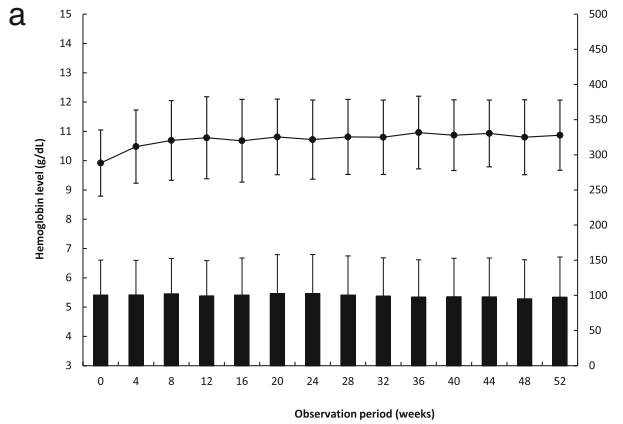
Discussion

This prospective, observational study investigated the safety and effectiveness of long-term treatment with CERA under routine clinical conditions, including hospitals and outpatient clinics, in Japanese patients with renal anemia. To our knowledge, this is the first study investigating the use of CERA in routine clinical practice in Japan in all subsets of patients that may receive this treatment, including patients who are ESA treatment-naïve, patients who have switched from a previous ESA, and patients also receiving HD or PD. The results of this study show that CERA was well tolerated, with no unexpected safety or tolerability issues reported. ADRs were reported in 3.06%, 4.19%, and 4.46% of ND, HD, and PD patients, respectively. The most common ADRs were hypertension (0.93%, 1.13%, and 1.48%, respectively) and anemia (0.12%, 0.71%, and 0.59%, respectively). During the observational period, CERA maintained hemoglobin levels in the target range, and treatment response was high in all patient groups, including patients who switched from a previous ESA.

The incidence and type of ADRs with CERA in this study are similar to those that were seen in the pivotal clinical study of CERA in Japanese patients [10]. Furthermore, the safety profile of CERA in this study was similar to that of other existing ESAs available in Japan [10] and therefore did not require any new safety measures. However, it is important to note that hypertension was the most common adverse event reported with CERA and, as serious adverse events such as hypertensive encephalopathy have also been reported in other studies of CERA [6–8], this study again highlights the importance of monitoring patients receiving CERA who develop hypertension.

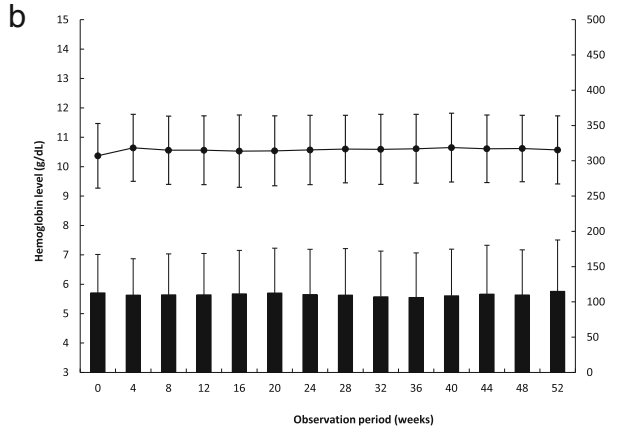
In the present study, 14 patients (0.41%) had ADRs that led to death, with six of these deaths being due to hemorrhage-related events. While a causal relationship between the ADRs leading to death and the administration of CERA could not be ruled out in any of the cases, a causal relationship between the administration of CERA and deaths related to hemorrhage in this study could not be established. In any case, the mortality rate in this study is similar to the mortality rate resulting from all ADRs that occurred in studies with CERA, which is 0.5% [10].

In the 2008 Japanese Society for Dialysis Therapy (JSDT) Guidelines for Renal Anemia in Chronic Kidney Disease, it was suggested that an increase in hemoglobin at a rate of > 0.5 g/dL per week might lead to an increased risk of the onset of adverse



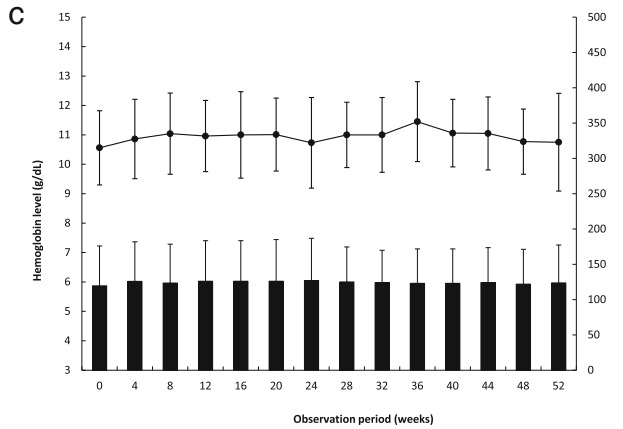
	Week 0	Week 24	Week 52
Hemoglobin level (g/dL)	9.92 ±1.13	10.72 ±1.35	10.87 ±1.20
Administered dose of CERA (μg/4 weeks)	100.38 ±49.90	102.53 ±55.59	97.44 ±57.22

Weeks	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Hemoglobin level, n	276	223	223	205	199	192	184	178	175	157	164	155	138	144
Administered dose of CERA, n	286	266	254	244	231	255	212	210	203	197	188	182	177	148



	Week 0	Week 24	Week 52
Hemoglobin level (g/dL)	10.37 ±1.10	10.57 ±1.18	10.57 ±1.16
Administered dose of CERA (μg/4 weeks)	112.63 ±54.65	110.40 ±64.26	114.89 ±72.80

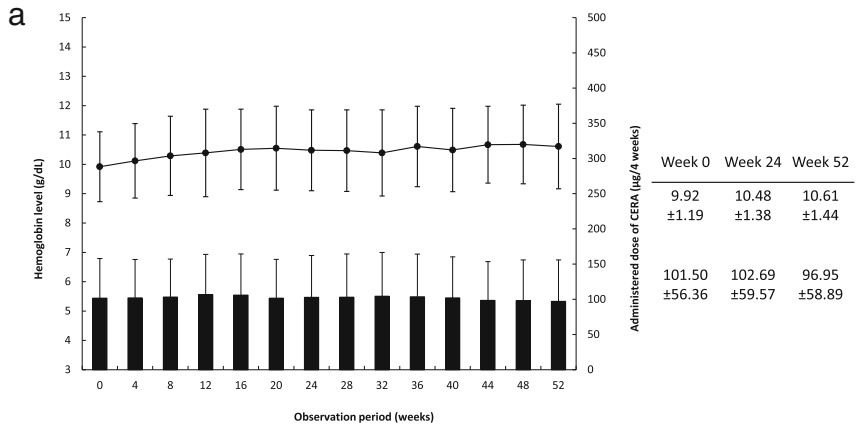
Weeks	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Hemoglobin level, n	602	622	596	598	543	551	501	500	500	548	579	472	468	458
Administered dose of CERA, n	662	649	638	618	573	567	562	549	533	516	491	477	464	423



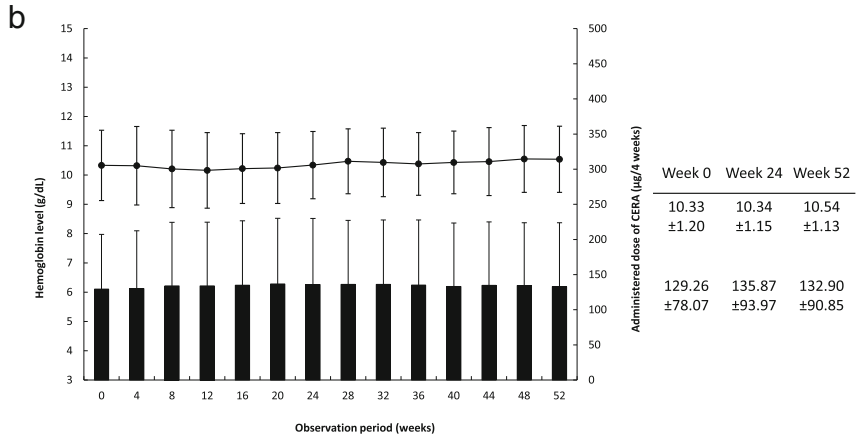
	Week 0	Week 24	Week 52
Hemoglobin level (g/dL)	10.56 ±1.26	10.73 ±1.54	10.75 ±1.66
Administered dose of CERA (μg/4 weeks)	119.53 ±56.34	126.78 ±60.06	123.68 ±53.66

Weeks	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Hemoglobin level, n	31	29	24	26	22	26	23	21	23	20	18	18	20	24
Administered dose of CERA, n	32	31	30	29	29	29	28	26	25	24	24	23	23	19

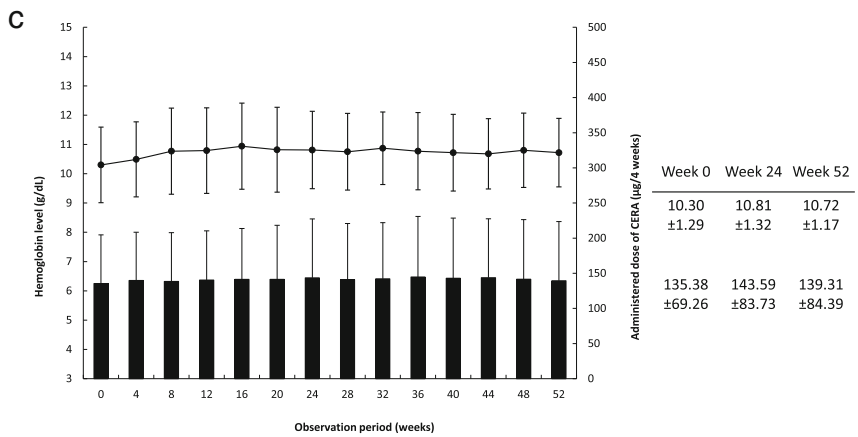
Fig. 3 Changes in mean hemoglobin levels (line graph with closed circles) following a switch from erythropoietin treatment in **a** patients not on dialysis, **b** patients on hemodialysis, and **c** patients on peritoneal dialysis. Bar graph represents mean dose of continuous erythropoietin receptor activator (CERA) administered; error bars represent ± 1 standard deviation



Weeks	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Hemoglobin level, n	502	394	396	343	367	339	336	310	295	272	268	274	254	258
Administered dose of CERA, n	522	493	471	445	428	412	385	378	364	347	327	316	300	253

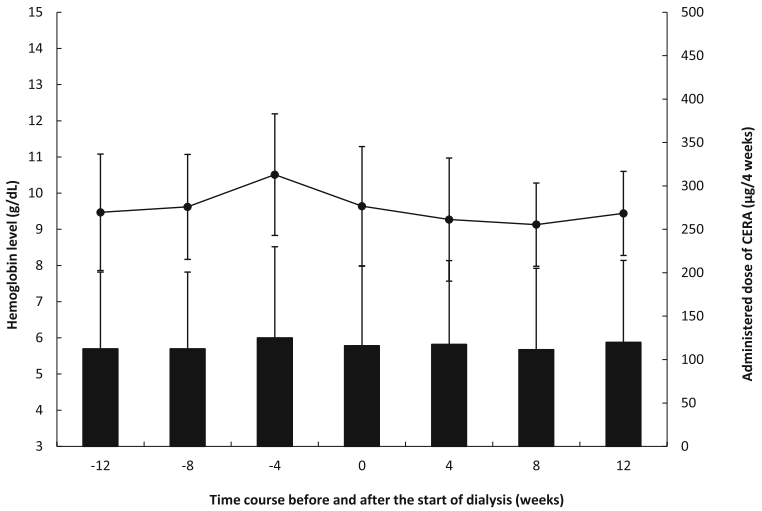


Weeks	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Hemoglobin level, n	591	571	569	542	474	480	456	431	453	454	440	453	432	397
Administered dose of CERA, n	620	612	593	553	539	515	508	496	484	477	458	448	434	374



Weeks	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Hemoglobin level, n	229	207	183	197	171	170	171	167	159	160	161	153	151	149
Administered dose of CERA, n	231	225	216	208	201	197	196	189	183	178	169	162	155	131

Fig. 4 Changes in mean hemoglobin levels (line graph with closed circles) following a switch from darbepoetin alfa in **a** patients not on dialysis, **b** patients on hemodialysis, and **c** patients on peritoneal dialysis. Bar graph represents mean dose of continuous erythropoietin receptor activator (CERA) administered; error bars represent ± 1 standard deviation



Weeks	-12	-8	-4	0	4	8	12
Hemoglobin level, n	12	12	12	12	12	12	12
Administered dose of CERA, n	12	12	11	11	10	11	10

Fig. 5 Changes in mean hemoglobin levels (line graph with closed circles) among patients not on dialysis at baseline who started dialysis during the study ($n = 12$). Bar graph represents mean dose of continuous erythropoietin receptor activator (CERA) administered; error bars represent ± 1 standard deviation

events [11]. Therefore, this observational study investigated the relationship between the rate of increase in hemoglobin and the frequency of the onset of adverse events. This study confirmed the results published by Hirakata and colleagues [10] by showing that there was no relationship between the rate of change of hemoglobin and the rate of adverse events reported with CERA. In addition, switching treatment from other ESAs to CERA was smooth, without associated acute changes in hemoglobin levels or significant dose changes. It was therefore considered that appropriate use and dose administration according to patient condition led to stable maintenance of hemoglobin levels. The dose of CERA at the time of switching from darbepoetin alfa (Table 4) was similar to the findings of a previous study [12].

The effectiveness results of the present study confirm and expand on the current knowledge of the use of CERA in Japanese patients with CKD-related anemia

Table 5 Anemia response rate

	ND	HD	PD
Treatment-naïve patients			
N	678	111	66
Response rate[†], *n* (%; 95% CI)	441 (65.04; 61.32–68.63)	60 (54.05; 44.33–63.55)	51 (77.27; 65.30–86.68)
No effect, *n* (%)	237 (34.95)	51 (45.94)	15 (22.72)
Patients switched from EPO			
N	160	399	20
Response rate[‡], *n* (%; 95% CI)	109 (68.12; 60.30–75.25)	279 (69.92; 65.16–74.38)	12 (60.00; 36.05–80.88)
No effect, *n* (%)	51 (31.87)	120 (30.07)	8 (40.00)
Patients switched from DA			
N	265	383	146
Response rate[†], *n* (%; 95% CI)	162 (61.13; 54.97–67.03)	256 (66.84; 61.87–71.53)	99 (67.80; 59.58–75.29)
No effect, *n* (%)	103 (38.86)	127 (33.15)	47 (32.19)

[†]Effectiveness: cases in which Hb levels reached ≥ 10.0 g/dL, and Hb levels increased by ≥ 1.0 g/dL until week 24
[‡]Effectiveness: cases in which Hb levels were maintained within a range between 10.0 to 12.0 g/dL at week 48
DA darbepoetin alfa, *EPO* erythropoietin, *Hb* hemoglobin, *HD* hemodialysis, *ND* not on dialysis, *PD* peritoneal dialysis

[6–8]. In this study, 65.04% of ESA-naïve patients who were not on dialysis maintained hemoglobin for 24 weeks, which suggests that the effect observed in the clinical study translates to clinical practice. Further, the hemoglobin levels observed in the 12 patients who initiated dialysis during the observational period further support the results of the clinical study, which indicated that no sudden decreases in hemoglobin during the hemodialysis initiation period are observed in patients receiving CERA [6, 13, 14].

In a study in Japanese PD patients with renal anemia receiving CERA, 88.9% of the patients successfully maintained hemoglobin levels of 10–12 g/dL at 48 weeks [8]. The results of the present study support these findings. Furthermore, while the previous study only included PD patients who switched from an ESA to CERA [8], the observational study reported here also included PD patients who were ESA-naïve and supports the use of CERA in this patient population.

In a study in Japanese HD patients with CKD-related anemia who were ESA-naïve, 91.7% of patients had an improvement in their anemia (defined as hemoglobin of ≥10 g/dL and an increase in hemoglobin of ≥ 1.0 g/dL until week 26) with CERA treatment [7]. In contrast, the anemia response rate seen in HD patients in this study was 54.05%. This difference in response rates may be explained by differences in study designs. The previous study only included patients with hemoglobin levels < 10 g/dL and patients had a mean hemoglobin level at baseline of 7.98 g/dL [7], which was much lower than the baseline mean hemoglobin levels of patients in the present study (9.60 g/dL). Due to the higher baseline hemoglobin levels in this study, 27 of the 51 patients in whom treatment was not effective did not reach the benchmark of an increase in hemoglobin of ≥ 1 g/dL (although an increase in hemoglobin level to ≥ 10 g/dL was reached at least once up until 24 weeks after initiation of treatment), and therefore treatment was judged not to be effective. In other words, in this observational study, the anemia response rate might appear low compared with the previous study because the patients' state of anemia at the initiation of treatment was considered mild. Moreover, the 2015 JSDT guidelines recommend iron supplementation in patients with ferritin levels of < 100 ng/mL or TSAT of ≤ 20% [15], and in the present study, the percentage of patients with ferritin levels of < 100 ng/mL and TSAT < 20% at initiation of treatment was 40.00% and 27.27% respectively. The high proportion of patients who required iron supplementation may have affected the results of this study. In the present study, among patients who switched to CERA from other ESAs, the rate of anemia response was approximately 60–70% in all patient groups. In addition, the reason for switching to CERA was "insufficient improvement in anemia" in ≥ 70% of ND and PD patients. The rate of anemia response in these patients was ≥ 60%, which was similar to the rate of anemia response in other patient groups.

There are some limitations to this study, mainly due to the non-interventional methods employed in the observational period. All patients with CKD-related anemia were included, with no exclusion criteria based on laboratory findings. The study did not have a comparator group and there was no intervention during the study period with regard to the dosage and administration route of CERA. While these limitations in the design of this study do not allow for exact determination of the safety and effectiveness of CERA in specific patient populations, we believe the study reflects what is seen in routine clinical practice and we believe the results of this study are generalizable to the broader CKD-related anemia population.

Conclusions

The results of this prospective, observational study confirm the safety and effectiveness of long-term treatment with CERA in Japanese patients with CKD and renal anemia in routine clinical practice, including ND, HD, and PD patients. No new safety concerns were reported, even in patients who switched treatment from other ESAs, and CERA effectively improved and maintained hemoglobin levels over the study period.

Additional file

Additional file 1: ADRs leading to death. This table gives demographic and clinical characteristics of patients with an ADR whose outcome was death, and includes relevant details relating to their death. (DOCX 43 kb)

Additional file 2: TSAT and ferritin levels, by disease stage and prior treatment. These tables provide baseline, week 24 and 52 TSAT and ferritin levels according to disease stage and history of ESA administration. (DOCX 23 kb)

Abbreviations

ADR: Adverse drug reaction; CERA: Continuous erythropoietin receptor activator; CKD: Chronic kidney disease; EDC: Electronic data capture; ESA: Erythropoiesis stimulating agents; GPSP: Good Post-Marketing Study Practice; HD: Hemodialysis; JSDT: Japanese Society for Dialysis Therapy; ND: Not on dialysis; PD: Peritoneal dialysis; rHuEPO: Recombinant human erythropoietin; TSAT: Transferrin saturation

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
HT, AM, RH, and TI contributed to the data analysis and interpretation. HK and YU contributed to the study design and data analysis and interpretation. All authors approved the final version of the manuscript.

Ethics approval and consent to participate
This study was conducted at institutions under contract in accordance with the Good Post-Marketing Study Practice regulations from the Ministry of Health, Labor, and Welfare in Japan. If necessary, the study protocol was approved by the ethics committee at each institution in accordance with institutional standards. Informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Competing interests
HT is an employee of Chugai Pharmaceutical; HK is an employee of Chugai Pharmaceutical; AM is an employee of Chugai Pharmaceutical; TI is an employee of Chugai Pharmaceutical; RH is an employee of Chugai Pharmaceutical; YU is an employee of Chugai Pharmaceutical.

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References
1. Eschbach JW, Adamson JW. Anemia of end-stage renal disease (ESRD). Kidney Int. 1985;28:1–5.
2. Kazmi WH, Kausz AT, Khan S, Abichandani R, Ruthazer R, Obrador GT, et al. Anemia: an early complication of chronic renal insufficiency. Am J Kidney Dis. 2001;38:803–12.
3. Macdougall IC, Robson R, Opatrna S, Liogier X, Pannier A, Jordan P, et al. Pharmacokinetics and pharmacodynamics of intravenous and subcutaneous continuous erythropoietin receptor activator (C.E.R.a.) in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2006;1:1211–5.
4. Macdougall IC, Gray SJ, Elston O, Breen C, Jenkins B, Browne J, et al. Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients. J Am Soc Nephrol. 1999;10:2392–5.
5. Halstenson CE, Macres M, Katz SA, Schnieders JR, Watanabe M, Sobota JT, et al. Comparative pharmacokinetics and pharmacodynamics of epoetin alfa and epoetin beta. Clin Pharmacol Ther. 1991;50:702–12.
6. Yuzawa Y, Hotta O, Suzuki H, Oishi T, Mochizuki T, Wakasa M, et al. Effect of hemoglobin maintenance of subcutaneous or intravenous C. E. R. a (continuous erythropoietin receptor activation) in chronic kidney disease patients not on dialysis. Jpn Pharmacol Ther. 2011;39:S55–68.
7. Watanabe Y, Itami N, Hashimoto N, Kurosawa A, Ueki K, Irie Y, et al. Clinical efficacies of C. E. R. A. (continuous erythropoietin receptor activator) administered intravenously to epoetin (EPO) naïve renal anemia patients on hemodialysis: phase III study. Jpn Pharmacol Ther. 2011;39:S21–30.
8. Hiramatsu M, Hotta O, Masakane I, Suzuki H, Mochizuki T, Nishizawa Y, et al. Effect of haemoglobin (Hb) maintenance of subcutaneous (SC) or intravenous (IV) C.E.R.a. (continuous erythropoietin receptor activator) in renal anemia patients on peritoneal dialysis. Jpn Pharmacol Ther. 2011; 39:S69–78.
9. Tsuruta Y, Itami N, Hashimoto N, Masakane I, Kurosawa A, Miyazaki S, et al. Switching and maintenance study of intravenous C. E. R. A. (continuous erythropoietin receptor activator) after switching from rHuEPO in hemodialysis patients. Jpn Pharmacol Ther. 2011;39(Suppl 1):S31–42.
10. Hirakata H. Safety profile of C.E.R.a. (continuous erythropoietin receptor activator) clinical studies for the CKD patients with renal anemia. Kidney Dial. 2011;70:964–70.
11. Tsubakihara Y, Nishi S, Akiba T, Hirakata H, Iseki K, Kubota M, et al. 2008 Japanese Society for Dialysis Therapy: guidelines for renal anemia in chronic kidney disease. Ther Apher Dial. 2010;14:240–75.
12. Kuwahara M, Mandai S, Kasagi Y, Kusaka K, Tanaka T, Shikuma S, et al. Responsiveness to erythropoiesis-stimulating agents and renal survival in patients with chronic kidney disease. Clin Exp Nephrol. 2015;19:598–605.
13. Yoshiya Y, Tsukuda M, Shoji H, Yasufuku T. Effectiveness of continuous erythropoietin receptor activator (C.E.R.a.) on renal anemia treatment at induction phase of renal dialysis.[article in Japanese]. Rinsho Toseki. 2013;29:1413–5.
14. Kawahara K, Minakuchi J, Yokota N, Suekane H, Tsuchida K, Kawashima S. Treatment of renal anaemia with erythropoiesis-stimulating agents in predialysis chronic kidney disease patients: haemoglobin profile during the 6 months before initiation of dialysis. Nephrology (Carlton). 2015;20 Suppl 4:29–32.
15. Yamamoto H, Nishi S, Tomo T, Masakane I, Saito K, Nangaku M, et al. 2015 Japanese Society for Dialysis Therapy: guidelines for renal anemia in chronic kidney disease. Ren Replace Ther. 2017;3:36.