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Review Article

Maintenance of Stable Hemoglobin Levels and Improvement of Iron Utilization in Hemodialysis Patients after Switching from Short to Long Acting Erythropoiesis Stimulating Agents

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Abstract

Background: Several studies have clearly shown the effectiveness of administering monthly doses of continuous erythropoietin receptor activator (C.E.R.A.) in treatment of hemodialysis (HD) patients. However, the appropriate doses of C.E.R.A. corresponding with the previously used treatment with EASs are not well known in Japanese HD patients.

Aim: The objective of this study was to describe dose equivalence and hemoglobin (Hb) stability in a cohort of unselected HD patients who were switched from epoetin alfa or beta or darbepoetin alfa to C.E.R.A..

Methods: This was a multicenter, observational, prospective study in patients aged >18 years who switched from epoetin alfa or beta or darbepoetin alfa to C.E.R.A. and were undergoing HD for 9 months (screening, titration, and evaluation phases). The corresponding dose was referred from the previous studies and dose of C.E.R.A. was adjusted to maintain Hb within 0.5g/dL of baseline during the titration phases. Hb level variability was calculated as one standard deviation.

Results: Of 289 patients, 284 patients started C.E.R.A. therapy (previous treatment: epoetin alfa or beta, 136 patients (47.9%); darbepoetin alfa, 148 patients (52.1 %)). No changes were observed in Hb levels throughout the study. After conversion, the erythropoiesis-stimulating agent (ESA) dose decreased significantly in patients previously treated with epoetin alfa or beta, but not with darbepoetin alfa. Besides, erythropoietin resistance index (ERI) was significantly decreased in patients previously treated with epoetin alfa or beta but not with darbepoetin alfa. In contrast, although hemoglobin level variability was similar in both groups of epoetin alfa or beta and C.E.R.A., there was a significant difference between darbepoetin and C.E.R.A. (0.675 vs. 0.560, P=0.02). Transferrin saturation (TSAT) was significantly increased after the start of C.E.R.A. therapy in patients regardless of previous ESAs treatment, although there were no changes in levels of serum ferritin in all patients.

Conclusion: This single-arm, open-label, multicenter clinical study validated the proposed dose of C.E.R.A. for maintenance of appropriate Hb levels after switching from the previously administered ESAs in Japanese HD patients and found that stable Hb levels were successfully maintained after conversion.
In addition, conversion to C.E.R.A. decreased ERI compared with epoetin alfa or beta and reduced variability of Hb levels compared with darbepoetin. Besides it is conceivable that C.E.R.A. treatment results in long term improvement of iron metabolism.

Keywords: Anemia; Darbepoetin; Epoetin Alfa or Beta; Transferrin Saturation (TSAT); Ferritin; Erythropoietin Resistance Index; Hb Cycling

Introduction

The introduction of erythropoiesis-stimulating agents (ESAs) improved the treatment strategy for anemia in patients with end-stage renal disease (ESRD). However, treatments with ESAs have occasionally been reported to result in fluctuation of hemoglobin (HB) levels in patients receiving hemodialysis (HD). This was attributed to the relatively short half-life, e.g., up to 9 hours for epoetin alfa or beta and approximately 25 hours for darbepoietin alfa [1]. This limitation in clinical practice needs a potential ESA with a longer half-life. A continuous erythropoietin receptor activator (C.E.R.A.) is the first compound of a novel class of ESAs with a long half-life (approximately 130 hours) demonstrated by pharmacokinetic studies [2]. Recently, it was clearly demonstrated that the efficacy of C.E.R.A. was compatible to shorter-acting ESAs, when given monthly to HD patients during the maintenance phase [3]. Although the Anemia Working Group of European Renal Best Practice recommends a monthly dosing schedule for C.E.R.A. [4-6], there have been few studies in Japan examining dose adjustments when switching from epoitin alfa or beta and darbepoietin alfa to C.E.R.A.. The primary objective of this study was to validate the proposed dose of C.E.R.A. after switching from ESAs in unselected Japanese chronic HD patients in the "real world of in-center HD". Secondary objectives included studies of erythropoietin resistance index (ERI) and iron metabolism.

Methods and Subjects

This was an observational, prospective study conducted in multi- institutional dialysis units, in Saitama Medical University, Saitama, Japan. Data were collected from October 2011 to December 2012. The main inclusion criteria were patients aged >18 years who met the following criteria: (1) continuous HD three times a week for at least 12 weeks prior to study entry with Kt/V>1.2 (single pool); (2) Hb level >10 g/dL and <13 g/dL; (3) intravenous or subcutaneous maintenance epoetin alfa or beta or darbepoetin alfa with a constant dose interval during the 3 months prior to study entry; (4) serum ferritin >100 ng/mL and transferrin saturation (TSAT) >20% during the 12 weeks prior to study entry and confirmed during the screening phase. Patients with pregnancy, lactation, allergic to erythropoietin, hematological malignancy, neoplasm, amyloidosis, severe systemic infection, active bleeding tendency, and major surgery within the previous 6 months were excluded. With monthly measurements of hemoglobin (Hb) levels, the C.E.R.A. dose was adjusted during the titration phase of the initial 3 months to a target Hb level within +0.5 g/dL of the baselines at the discretion of the investigators. Hb level variability was calculated as one standard deviation. The conversion rates for erythropoietin alfa or beta were decided according to the recommendation of clinical practice guideline of the Japanese Society for Dialysis Therapy [7]. For example, Epoietin alfa or beta of 180 IU/week and over was converted to C.E.R.A. 1 μg/month. The manufacturer's recommendations for C.E.R.A. dosing in patients who were currently receiving darbepoetin alfa are shown in the Appendix. The study protocol was conducted in accordance with the Helsinki Declaration and the guidelines for Good Clinical Practice. The study protocol was approved by the ethics committee of each participating center. Institutional review board committee approval was obtained for investigation on human subjects.

Statistical Analysis

Data are provided as mean + standard deviation. Changes from baseline at post-baseline visits were evaluated using paired t-test or Wilcoxon signed-rank test. Changes in continuous variables over time were evaluated using repeated-measures analysis of variance with the Dunnett test. All analyses were performed using JMP software (version 10; SAS Institute, Cary, NC, USA).

Results

There were 289 evaluable HD patients. Of the 289 patients, 274 patients started C.E.R.A. therapy. They had been treated previously with epoetin alfa or beta, 126 or 46% and with darbepoetin alfa, 148 or 54%. Patients' characteristics are summarized in Table 1. The underlying renal diseases in the patients treated with epoetin alfa or beta and darbepoetin alfa respectively, were: a) diabetes mellitus (DM), 61 or 47% and 61 or 41.2%; b) chronic glomerulonephritis 31 or 22.8% and 25 or 22.2%; c) hypertensive nephrosclerosis, 15 or 11% and 15 or 10.2%; d) polycystic kidney diseases, 4 or 4.4% and 6 or 5.5%; and e) others, 23 or 16.9% and 31 or 20.9%.

Table 1. Characteristics of patients

Characteristic	Epoetin alfa or beta	Darbepoetin alfa
Age (years), mean (SD)	66.0 ± 13.0	67.4 ± 11.4
Male/female	91/45	89/59
Underlying renal disease (%)		
Diabetic Nephropathy	61(44.9)	61 (41.2)
Chronic glomerulonephritis	31 (22.8)	33 (22.2)
Nephrosclerosis	15 (11.0)	15 (10.2)
Polycystic kidney diseases	6 (4.4)	8 (5.5)
Others	23 (16.9)	31 (20.9)

Values expressed as mean ±SD.

Hb levels over time

The mean Hb levels remained stable throughout the study and no significant changes in mean and median monthly values of Hb were observed through the follow-up period (Figures 1A and 1B) (Tables 2A and 2B).

Figure 1A. Changes in hemoglobin levels before and after switching from epoetin alfa or beta to C.E.R.A. There were no changes in hemoglobin levels throughout the study.

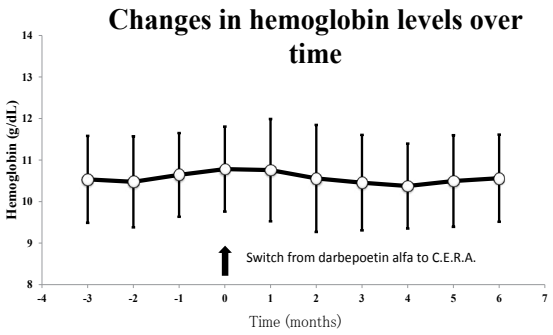

Figure 1A

Figure 1B. Changes in hemoglobin levels before and after switching from darbepoetin alfa to C.E.R.A. There were no changes in hemoglobin levels throughout the study.

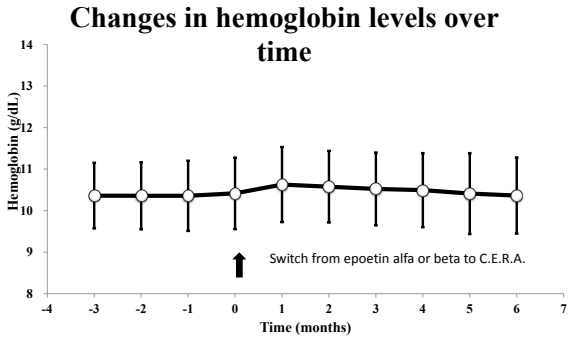

Figure 1B

Table 2A. Values of Hemoglobin, doses of ESAs, ferritin and TSAT in screening, titration and evaluation phases in patients previously.

	Screening	Titration	Evaluation
Hb（g/dL）	10.5±1.1	10.6±1.2	10.4±1.1
Doses（μg/month）	126.2±82.6	120.5±53.6	122.8±59.0
Percentage of iron supplementation（%）	18.3	22.6	21.5
eERI	12.3±8.7	11.7±5.8	12.2±6.5
Ferritin (ug/L)	172.1±176.5	161.6±155.8	170.0±205.3
TSAT (%)	23.9±11.9	30.9±13.7*	27.9±12.2*

Values are expressed as mean ± SD.

*P<0.05 vs. values in screening phase.

Table 2B. Values of Hemoglobin, doses of ESAs, ferritin and TSAT in screening, titration and evaluation phases in patients previously treated with epoetin alfa or beta.

	Screening	Titration	Evaluation
Hb（g/dL）	10.4±0.8	10.6±0.9*	10.4±0.9
Doses (ug/month)	125.7±70.2	103.9±39.4*	105.3±50.8*
Percentage of iron supplementation（%）	13.8	19.6	15.1
eERI	12.4±7.3	10.0±4.0*	10.4±5.4*
Ferritin (ug/L)	97.1±91.0	110.4±93.2	105.3±95.8
TSAT (%)	24.1±10.1	28.8±12.6*	28.7±11.9*

Values are expressed as mean ± SD.

*P<0.05 vs. values in screening phase.

1) Erythropoiesis Resistance index

Erythropoietin resistance index (ERI), defined as the total weekly erythropoietin dose per kg of body weight, and divided by the patient's Hb level, expressed as units per kg per g/dl) There were no changes in ERI in patients who were switched from darbepoetin to C.E.R.A. However, significant changes were noted in ERI in patients who were switched from epoetin alfa or beta to C.E.R.A. in both titration and evaluation phases (P<0.05). (Tables 2A and 2B)

Iron metabolism

The percentage of patients who needed iron supplementation did not change in both groups after entering the study. Serum levels of ferritin showed no changes after switching from the previous ESAs to C.E.R.A. However, TSAT after study entry was significantly increased in patients who were switched from the previous ESAs. (Tables 2A and 2B)

The doses of C.E.R.A.

The doses of C.E.R.A. did not change in patients treated with darbepoetin alfa, but significantly decreased in patients treated with epoetin alfa or beta (P<0.05). (Tables 2A and 2B)

Variability of Hemoglobin levels

Although the variability of hemoglobin levels was similar for both epoetin alfa or beta and C.E.R.A., there was a significant difference between darbepoetin and C.E.R.A. (0.675 vs. 0.560, P=0.02) (Tables 3A and 3B).

Figure 2A. Changes in TSAT (transferrin saturation) levels before and after switching from darbepoetin alfa to C.E.R.A.
There were significant increases in TSAT levels after the start of C.E.R.A. administration.

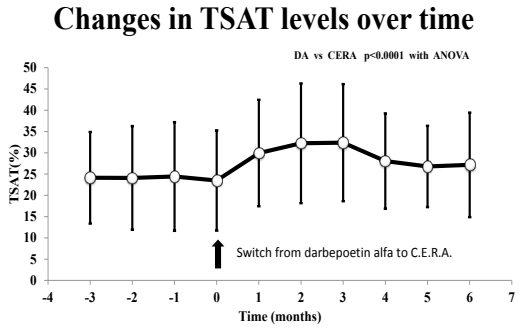

Figure 2A

Figure 2B. Changes in TSAT levels before and after switching from epoetin alfa to C.E.R.A.
There were significant increases in TSAT levels after the start of C.E.R.A. administration.
Values are mean + SD.

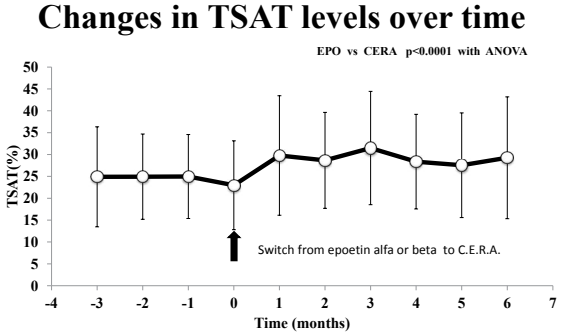

Figure 2B

Table 3A. Hemoglobin variability level (Darbepoetin alfa vs. C.E.R.A.)

	1SD	P value	
Darbepoetin alfa	0.675	P=0.37	
C.E.R.A. I	0.618		P=0.022
C.E.R.A. II	0.560	P=0.37	

Table 3B. Hemoglobin variability level (Epoetin alfa or vs. C.E.R.A.)

	1SD	P value	
Darbepoetin alfa	0.675	P=0.37	
C.E.R.A. I	0.618		P=0.022
C.E.R.A. II	0.560	P=0.37	

Safety

Six patients died during the 9-month study. These deaths were neither directly associated with administration of ESAs nor conversion to C.E.R.A. Twelve patients were admitted to hospitals with various reasons. Sixteen patients were discontinued for various reasons that were not related to treatment with ESAs.

Discussion

This single-arm, open-label, multicenter clinical study of HD patients examined the dose of C.E.R.A. for maintaining appropriate Hb levels after switching from the previously administered ESAs. It was clearly demonstrated that monthly C.E.R.A. administration offered good control of Hb levels. Similar results were observed regardless of whether patients had previously received epoetin alfa, beta or delta, or darpoetin alfa, both in terms of remaining within target Hb range and the requirement for dose modifications after conversion to C.E.R.A. In STRIATA (Stabilizing haemoglobin TaRgets in dialysis following IV C.E.R.A. Treatment for Anaemia), a multicenter, open-label randomized phase III study [3], stable Hb levels were successfully maintained in patients on HD who were converted directly to intravenous C.E.R.A. from darbepoetin alfa. Also, results from randomized, multicenter, active-control, and phase III studies demonstrated that patients previously maintained on short-acting ESA could be successfully converted to a once-monthly dose of C.E.R.A. In these studies, Hb levels remained stable from baseline through the titration and evaluation periods [5,6]. In addition, in this study, patterns of iron utilization as indicated by the levels of serum ferritin and TSAT were examined before and after switching from previously administered ESAs to C.E.R.A. After switching, C.E.R.A. significantly increased TSAT without changes in levels of serum ferritin, indicating that iron may be more efficiently utilized than with the previous treatments with ESAs.

In the present study, the monthly doses of C.E.R.A. were significantly different between the patients previously treated with epoetin alfa or beta and those with darbepoetin alfa, although there were no differences in patients' characteristics between the two groups. With respect to patients' responses, the only difference was in levels of serum ferritin which were significantly higher in patients who received darberpoetin alfa than epoetin alfa or beta. This might have some influences after conversion. In both groups, after the start of C.E.R.A., no changes in serum ferritin were seen despite significant increases in TSAT. In the STRIATA study [3], when C.E.R.A. and darberpoetin alfa were compared after a relatively longer term administration no differences were seen between the two groups. In their study, C.E.R.A. was administered once every 2 weeks instead of a month and darbepoetin alfa once a week.

The dose reduction may reflect the conversion rate, because corresponding doses with darbepoetin alfa were set up with narrower increments than those of epoetin alfa or beta. Or it

cannot be denied that some other unknown reason may exist for the difference between the two groups. For example, patients who needed three doses of ESAs had shorter HD duration than those given a single dose of C.E.R.A. Moreover, these patients might have minor infections or other systemic problems influencing ESAs doses [8]. At present, an explanation for the difference in reduction of doses of C.E.R.A. in patients who were previously treated with epoetin alfa or beta is not known. Recently, Sasaki et al. [9] suggested that C.E.R.A. potentially had more sustained effects than epoetin on reducing hepcidin levels and thus increase iron availability. Subsequently, Jonckheere et al. [10] reported that in HD patients a marked drop was observed in ferritin as well as in TSAT within 10 days after the start of C.E.R.A. administration. Similar findings after C.E.R.A. dosing were also noted by Kakimoto-Shino et al [11] in which serum hepcidin levels were decreased within one week and accompanied with decreases in ferritin and TSAT levels. Compared with these previous studies, TSAT was measured in the present study at least 3 months after the start of C.E.R.A. administration and its levels were significantly increased. Combining these findings, it is suggested that after administering C.E.R.A. erythropoiesis is strongly stimulated in the early phase and eventually the effects on erythropoiesis works with less demand for iron. However, more data for the long term effects on iron metabolism following C.E.R.A. administration will need to be gathered. In the present study, the required doses of C.E.R.A. were essentially the same for patients with and without diabetes. (Data not shown). A similar finding was recently reported by Hirai et al. [12]. Previously, the Hb cycle has been a focus of discussion in patients receiving EASs, and the influence of different ESAs on hemoglobin has shown variable results [13,14]. In the present study, the variability of hemoglobin levels was similar in both epoetin alfa or beta and C.E.R.A. groups, although there was a significant difference between darbepoetin and C.E.R.A. The basis for these findings remains to be clarified.

The major findings of this study are as follows:
a) The primary advantage of using C.E.RA. over darboetin alfa and epoetin alfa or beta was in successfully extending the dosing in unselected populations of eligible patients. The extension of the dosing is considered a critically important difference.

b) Secondarily, it is believed that the estimated time savings derived from reductions in frequency of drug dosing could benefit clinical practice, facilitating greater efficiency of anemia management, and enabling healthcare providers to devote more time to other aspects of patient care.

One of the limitations of this study is the single-arm study design. A single cohort study set-up was considered appropriate since the trial aimed to examine the effectiveness of conversion to a once-monthly dose of C.E.R.A. based on local decision-making at a large number of nephrology centers. Second, biomarkers for evaluation of iron metabolism such as hepcidin and reticulocyte-hematocrit were not measured. Finally, the study period was relatively short to evaluate the effects of ESA on iron metabolism.

In conclusion, this single-arm, open-label, multicenter clinical study validated the proposed dose of C.E.R.A. for maintenance of appropriate Hb levels in Japanese HD patients after switching from the previously administered ESAs in real world.

Moreover, it is possible that C.E.R.A. treatment results in a long term improvement of iron metabolism.

Appendix Corresponding doses of C.E.R.A.to Darbepoetin alfa

Darbepoetin alfa (μg/week)	C.E.R.A. (μg/month)
15	50
15-30	100
30-40	100
40-80	200
80	250

Lists of Participants (Saitama Renal Anemia Group)

Name	Institution
Aoki Hiroaki	Ogose Medical Clinic
Suzuki Hiromichi	Saitama Medical University
Naofumi Ikeda	Sayama Jin Clinic
Sugahara Souichi	Oka Hospital
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Kanagawa Seiichi	Tsurugashimaekimae Clinic
Ooshima Jouji	Kubojima Clinic
Tomita Tetsuya	Kamino Clinic
Ootsuka Keiichi	Ooshima Clinic
Matsumura Osamu	Musashiranzan Hospital
Yoshida Akira	Wakabanaika Clinic
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Okamura Yuima	Okamurakinen Clinic
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