

Continuous Erythropoietin Receptor Activator (C.E.R.A.) Treatment of Renal Anemia in Patients with Chronic Kidney Disease: A Two-Year Observational Study

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Abstract

Objective: To evaluate once-monthly continuous erythropoiesis receptor activator (C.E.R.A.) in patients with chronic kidney disease (CKD) for two years under standard conditions.

Methods: In a non-interventional study, C.E.R.A. was administered according to local practice in patients with dialysis dependent or non-dialysis dependent CKD.

Results: 206 patients were evaluable to month 24. In the dialysis dependent and non-dialysis dependent patients who had received ESA therapy prior to study entry, Hb remained stable from baseline to the end of the study: mean (SD) change was -0.3 (1.5) g/dL (n=148) and 0.3 (1.6) g/dL (n=33), respectively. The mean (SD) dose of C.E.R.A. was 114 (78) µg in dialysis dependent patients and 97 (71) µg in non-dialysis dependent patients at baseline, remaining virtually unchanged during the study (109 (76) µg and 99 (68) µg). During the two-year study, dialysis dependent and non-dialysis dependent patients received a mean of 6.1 and 4.3 dose changes, respectively. Discontinuation due to adverse events was rare (2.9%).

Conclusions: Once-monthly C.E.R.A. is effective and convenient in dialysis dependent and non-dialysis dependent patients with renal anemia under routine conditions for at least two years, and requires few dose changes. C.E.R.A. was well-tolerated with a good safety profile over the two-year study period.

Keywords: Anemia; C.E.R.A.; Chronic kidney disease; Dialysis; Non-dialysis; Efficacy

Introduction

Renal anemia is highly prevalent in patients with chronic kidney disease (CKD), particularly in the more severe stages as erythropoiesis declines [1]. It is associated with increased risk of end-stage renal disease [2], cardiovascular events [3] and death [2], as well as significantly reducing patients' quality of life [4]. Hemoglobin (Hb) control in patients with CKD centers on erythropoiesis-stimulating agent (ESA) therapy [5], but the short half-lives of conventional ESAs, such as epoetin alfa and epoetin delta, necessitate relatively frequent dosing (one to three times a week). The impact on patients and for the healthcare system, and the fact that frequent ESA administration may contribute to increased Hb fluctuation [5], led to the investigation of agents with longer dosing intervals. Darbepoetin alfa was developed, with a half-life of approximately 25 hours when administered intravenously, and more recently the continuous erythropoiesis receptor activator (C.E.R.A.) was introduced, which has a half-life of more than 100 hours [6]. As a result, C.E.R.A. can be given once a month during the maintenance phase of management [7].

A series of randomized trials has confirmed the efficacy of once-monthly C.E.R.A. in maintaining stable Hb in patients with CKD, either requiring dialysis [8-10] or non-dialysis dependent [11]. Management of renal anemia outside the confines of a controlled trial, however, is not subject to protocol-stipulated visit schedules or Hb-triggered dose changes, and covers all patients instead of the somewhat selected populations enrolled in clinical studies. The efficacy of C.E.R.A. under trial conditions cannot necessarily be assumed to apply under routine conditions, therefore, and several large-scale observational studies have been undertaken to address this question. These have consistently confirmed the effectiveness and tolerability of once-monthly C.E.R.A. in maintaining target Hb levels in dialysis-dependent patients with CKD [12-14], non-dialysis dependent patients with CKD [14-17] and

renal transplant patients [15,18,19], either following previous ESA therapy or in ESA-naïve patients. No 'real-world' study, however, has followed patients beyond one year, and long-term data are lacking.

We describe here an observational study in which patients with dialysis-dependent or non-dialysis dependent CKD with renal anemia were managed with monthly administration of C.E.R.A. under standard conditions and followed for up to two years.

Methods

Study design

This was a non-interventional, 24-month study undertaken during September 2010 to April 2014 at specialist nephrology centers in Germany. Patients provided written informed consent prior to study entry. The trial met the criteria for a non-interventional trial stipulated by the Germany Medicines Act, and the relevant health authorities were notified.

Recruitment and C.E.R.A. administration

All patients with dialysis-dependent stage 5 CKD or non-dialysis dependent stage 4 CKD for whom the treating physician had decided to manage renal anemia with C.E.R.A. were eligible for inclusion in the study. All patients were required to be at least 18 years of age with a life

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expectancy of more than 12 months in the opinion of the investigator, and pregnant females were excluded.

At least 100 nephrology centers in Germany were to take part in the study to provide a representative sample. A minimum of five patients were to be enrolled per center with the aim of recruiting a representative sample, with a maximum of 15 to avoid over-representation of any center in the study population. To ensure that adequate numbers of patients with either CKD stage 4 or 5 were recruited, enrollment was capped for either stage once 700 patients had been recruited. C.E.R.A. was initiated and dosed as per the clinical judgement of the managing physician.

Data collection

Data were submitted electronically by the contributing physicians and checked by an independent contract research organization for completeness, plausibility and adverse events, with data clarified as required by the physician.

Baseline data documentation included demographics, dialysis scheme (if applicable), previous ESA therapy during the 16 weeks prior to study entry (if applicable), reason for change to C.E.R.A. (if applicable), Hb levels during preceding 16 weeks, and laboratory values. At subsequent standard clinic visits, information was recorded on C.E.R.A. administration, requirement for dialysis and dialysis scheme (if applicable), laboratory values, and adverse events and serious adverse events, including causal relationship to C.E.R.A. treatment. Serious adverse events were defined as adverse events considered fatal or life-threatening, which necessitated hospitalization or extension of hospitalization, resulted in permanent or serious disability or invalidity, or which were regarded as clinically significant.

Data analysis

The main target variables were Hb values during the 24-month study period, and the proportion of patients within prespecified Hb target ranges (11–12, 10–12, 11–13 and 10–13 g/dL) throughout the study. These variables are presented with 95% confidence interval (CI) values. Subgroup analyses were preplanned to assess the homogeneity of the therapeutic effect of C.E.R.A. (i) in patients who were dialysis dependent or non-dialysis dependent at baseline and (ii) in patients who were or were not receiving ESA therapy (including C.E.R.A.) during the 16 weeks prior to study entry.

The analysis plan specified that a minimum of 100 patients should be available per subgroup, since the percentage of responders could then be estimated with a precision of at least 10% (i.e. half the width of the 95% CI was $\leq 10\%$). Accordingly, a population size of 800 to 1,000 patients was planned to ensure that even in small subpopulations (e.g. 10–15% of the full population) meaningful conclusions could be drawn.

All analyses were descriptive in nature. Three efficacy populations were predefined. Efficacy and C.E.R.A. dosing data are shown here from the month 24 efficacy population, defined as all patients with at least one Hb level recorded at the end of the full study period, defined as any Hb value within the period month 22 to month 24. Safety analyses are based on all patients who received at least one dose of C.E.R.A.

Results

Study population

In total, 1,085 patients were recruited to the study at 95 centers. At least one dose of C.E.R.A. was documented in 978 patients (the safety

population). Supply problems with C.E.R.A. during the time period of the study meant that many centers had to discontinue C.E.R.A. treatment and ended patients' participation in the study, such that only 245 completed the 24-month study (Figure 1). In total, 206 patients provided at least one Hb level at the end of the full study period i.e. during months 22 to 24 (Figure 1) and all dosing and efficacy data are based on this subpopulation.

Baseline characteristics are summarized in Table 1. The mean age was 63.8 years. Slightly more than half the patients were male (54.9%) and virtually all patients were Caucasian (99.0%). The majority of patients had received ESA therapy in the 16 weeks prior to study entry {(181/206 (87.6%))}. In total, 164 patients were receiving dialysis at time of study entry. The subpopulations of dialysis dependent patients (n=11) and non-dialysis dependent patients (n=9) who were ESA-naïve at study entry were considered too small for meaningful analysis. Prior ESA therapy was slightly more frequent in the dialysis dependent cohort {148/164 (90.2%)} than the non-dialysis dependent group {33/42 (78.6%)}.

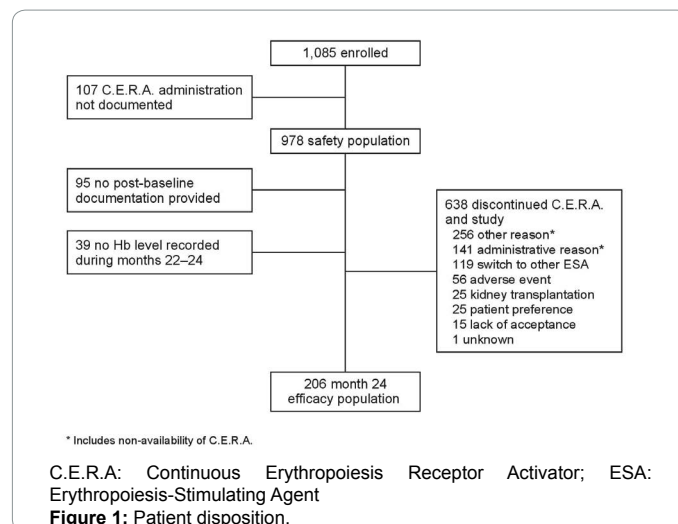
C.E.R.A. therapy

At baseline, the mean (SD) C.E.R.A. dose was 111 (76) μg . When the mean dose was calculated over the entire 24-month study period, it was virtually unchanged from baseline {107 (75) μg }. The dose remained stable in both the dialysis dependent and non-dialysis dependent subgroups, with slightly higher dosing in dialysis dependent patients (Table 2). The mean (SD) time between doses across all patients was 29 (6) days (median 30 days).

During the 24-month study period patients received a mean (SD) of 5.7 (3.9) C.E.R.A. dose changes (median 5, range 0–18) (month 24 efficacy population). Patients not on dialysis required slightly fewer dose changes {4.3 (2.9)} than those on dialysis {6.1 (4.1)}. The mean number of dose increases {2.7 (2.0)} and dose decreases {3.0 (2.2)} to month 24 was not markedly different.

Hb level

Hb level showed little change during the 24-month study either overall, or within the dialysis dependent and non-dialysis dependent subpopulations (Table 3). Overall, mean (SD) Hb was 11.5 (1.1) g/dL at baseline and 11.4 (1.2) g/dL at month 24, a change of -0.1 (1.6) g/dL. In the patients who had received ESA therapy (including C.E.R.A.)



	Total (n=206)
Age, years	63.8 (14.2)
Male gender, n (%)	113 (54.9)
Caucasian, n (%)	204 (99.0)
Dialysis-dependent at study entry	164 (79.6)
Time since start of dialysis, years	4.5 (4.1) ^a
ESA therapy in 16 weeks prior to study entry, n (%)	
None	20 (9.7)
Any	181 (87.6)
Missing	5 (2.4)

Table 1: Baseline characteristics (month 24 efficacy population) Continuous variables are shown as mean (SD).^aFor the 164 patients on dialysis at study entry

	Dialysis dependent (n=164)	Non-dialysis dependent (n=42)	All patients (n=206)
C.E.R.A. dose at baseline, µg			
Mean (SD)	114 (78)	97 (71)	111 (76)
Median (range)	100 (15-360)	75 (30-360)	95 (15, 360)
C.E.R.A. dose during the 24-month study period, µg			
Mean (SD)	109 (76)	99 (68)	107 (75)
Median (range)	81 (15-353)	82 (26-329)	82 (15, 354)
C.E.R.A. dose changes per patient during the 24-month study period			
Mean (SD)	6.1 (4.1)	4.3 (2.9)	5.7 (3.9)
Median (range)	6 (0, 18)	4 (0, 13)	5 (0, 18)

Continuous variables are shown as mean (SD). C.E.R.A.- Continuous Erythropoietin Receptor Activator; SD- Standard Deviation

Table 2: C.E.R.A. therapy (month 24 efficacy population).

prior to study entry, there was again only a minor change in Hb level from baseline to month 24 {mean -0.3 (1.5) g/dL in dialysis dependent patients and 0.3 (1.6) g/dL in non-dialysis dependent patients} (Table 3).

The proportion of patients within the pre-defined Hb windows 11–12, 10–12, 11–13 and 10–13 g/dL was 38.7%, 58.1%, 65.4% and 84.8% at month 1, respectively. During the subsequent 24 months, the proportion of patients with a Hb level of 11–12 g/dL was in the range 30.8–48.2%; for 10–12 g/dL it was 53.1–68.8%; for 11–13g/L it was 51.0–64.9%, and for 10–13g/dL it was 70.3–85.3%.

Over any six-month period during the 24-month study, the mean maximum intra-individual fluctuation in Hb levels from mean (defined as the maximum difference from individual mean Hb during the six-month period) ranged from 0.9 g/dL to 1.0 g/dL. The maximum fluctuation was ≤1.0 g/dL in between 53% and 65% of patients.

Safety

Adverse events were reported in 241 patients in the safety population (241/978; 24.6%), most frequently death (n=21), pneumonia (n=17, including 12 'pneumonia', 3 'bronchopneumonia', 1 'lobar pneumonia' and 1 'pneumonia chlamydial'), fall (n=12), myocardial infarction (n=11) and cardiac failure (n=10). Forty patients had one or more adverse events with a suspected relation to C.E.R.A., most frequently overdose (n=4), myocardial infarction, Hb decreased, hypertension and fall (three patients each). Serious adverse events occurred in 172 patients (17.6%), 34 of whom experienced one or more serious adverse

Patient population	N	Hb at baseline, g/dL	Hb at month 24 ^a , g/dL	Change from baseline to month 24 ^a g/dL
All patients	206	11.5 (1.1)	11.4 (1.2)	-0.1 (1.6)
Dialysis dependent				
All patients	164	11.6 (1.1)	11.4 (1.3)	-0.2 (1.5)
ESA prior to study entry	148	11.7 (1.1)	11.4 (1.3)	-0.3 (1.5)
Non-dialysis dependent				
All patients	42	11.2 (1.2)	11.5 (1.3)	0.3 (1.6)
ESA prior to study entry	33	11.4 (1.2)	11.6 (1.4)	0.3 (1.6)

^aLast value recorded during months 22 to 24 ESA- Erythropoiesis-Stimulating Agent; Hb- Hemoglobin

Table 3: Mean (SD) Hb values to month 24 (month 24 efficacy population).

event with a suspected relation to C.E.R.A. (3.5%). In 28 patients in the safety set (2.9%), C.E.R.A. was discontinued due to adverse events.

In the safety population, 411/978 patients (42.0%) were receiving one or more iron supplements. Mean (SD) serum ferritin was similar at baseline {464 (377)ng/mL} and month 24 {484 (416) ng/mL}. There was a small rise in transferrin saturation (TSAT) {26.3 (9.9) % at baseline, 32.2 (10.5) % at month 24}. Mean (SD) levels of C-reactive protein were 11.2 (13.5) mg/L and 10.1 (11.0) mg/L at baseline and month 24, respectively.

Discussion

This large non-interventional study demonstrates that in an unselected population of patients with dialysis dependent or non-dialysis dependent CKD, once-monthly C.E.R.A. maintains stable Hb levels to at least two years under standard conditions. This was achieved with a median of only five dose changes over two years' follow-up. These findings extend those of previous observational studies which used a similar methodology but followed patients for no more than one year [12-17]. C.E.R.A. was well tolerated over the two-year study with no new safety signals.

Maintaining Hb levels within the desired target range is extremely challenging in patients with severe CKD [20,21]. Natural variations in Hb levels caused by concurrent events such as acute illness are compounded by the effect of exogenous ESA therapy. Episodic administration of ESA agents artificially stimulates an acute erythropoietic response, in contrast to the natural condition of continuous low-level synthesis of endogenous erythropoietin. This provokes a peak in the Hb levels that can prompt the clinician to reduce or miss the next ESA dose, often until Hb declines to below the minimum acceptable level, when the dose is reintroduced or increased again, leading to marked oscillation in Hb levels [22]. Additionally, depletion of iron stores in response to ESA-stimulated erythropoiesis can occur, leading to hyporesponsiveness and further fluctuations in Hb levels, compounding the Hb fluctuation associated with frequent ESA administration [5]. Encouragingly, in the current series, the maximum intra-individual fluctuation in Hb over any six-month period during the study was ≤1 g/dL in between 53% and 65% of patients. Consistent with this, the proportion of patients with Hb level within pre-defined Hb windows showed no marked change over the 24-month study.

The fact that few C.E.R.A. dose changes were required during the 24-month study – a median of six in dialysis dependent patients and four in non-dialysis dependent patients – suggests that the oscillation between overly high Hb level and then a downwards effect due to

ESA dose adjustment may be relatively infrequent using long-acting C.E.R.A.

Discontinuation of C.E.R.A. due to adverse events was rare over the 24-month study (2.9%). This proportion was comparable with that seen in shorter observational studies ranging from six to 12 months, in which between 0.4% and 4.5% of patients stopped C.E.R.A. as a result of adverse events [12,13,15,19], indicating that tolerability is sustained over the long term.

Certain limitations of the study should be considered. First and foremost, supply problems for C.E.R.A. during the study period meant that many centers did not receive C.E.R.A. and had to revert to other ESA therapies. As a result, although the planned population size of 800 to 1,000 patients was successfully recruited, only approximately a fifth of patients provided Hb data to month 24 and formed the analysis population for the efficacy data presented here. Efficacy analyses were therefore based primarily on this smaller subgroup. This high discontinuation rate also undermines adverse event reporting, since the proportions of patients experiencing adverse events or discontinuations due to adverse events were calculated using the safety population, not those who completed follow-up. Moreover, safety reporting in an observational study does not include completion of a detailed clinical report form about adverse events at all study visits as is the case in controlled, interventional trials, so even with higher follow-up rates the adverse event incidences documented in observational studies can only be regarded as indicative.

Conclusion

In this series, once-monthly C.E.R.A. maintained Hb stability in patients with dialysis dependent or non-dialysis dependent CKD over a 24-month period under standard conditions. Particularly for non-dialysis dependent patients, less frequent administration with fewer clinical visits and reduced intravenous access is to be welcomed. Moreover, from a management perspective, a previous observational international analysis of dialysis dependent patients managed under clinical practice conditions found that once-monthly treatment with C.E.R.A. required 76–89% less staff time than shorter-acting ESA therapies [23,24]. Few C.E.R.A. dose changes were required and the safety profile of C.E.R.A. was good over the two-year study. Despite the limited final population size, once-monthly ESA therapy using C.E.R.A. appears to be effective and convenient.

Conflicts of interest

Jan Galle has received speaker's honoraria from Amgen, Novartis, Abbott, USB and FMC, and consultancy fees from PHV, Amgen, FMC and Roche.

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Appendix: Study Investigators

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