CLINICAL STUDY

Monthly CERA Treatment Maintains Stable Hemoglobin Levels in Routine Clinical Practice of Peritoneal Dialysis Patients

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Abstract

Data on routine use of continuous erythropoietin receptor activator (CERA) in peritoneal dialysis patients are scarce. This study aimed to assess the efficacy of CERA administered once monthly in maintaining stable Hb levels in patients on peritoneal dialysis under routine medical practice. This was a 12-month, observational, prospective and multicenter study. A total of 83 patients with anemia secondary to chronic kidney disease (CKD) on peritoneal dialysis for more than 3 months, on once-monthly subcutaneous CERA treatment, were followed up over a period of 1 year. Efficacy evaluation included Hb levels, mean time in which the Hb level was maintained within target range, CERA doses and number of dose changes. Median Hb level (interquartile range [IQR]) remained stable during the evaluation period [11.8 / 6 1.4 g/dL at baseline, 11.8 / 6 1.4 g/dL at month 6 and 11.8 / 6 1.5 g/dL at month 12 (p > 0.05)]. The median (IQR) time of Hb level maintained within target range (11 – 13 mg/dL) was 6 (4 – 10) months. Ferritin, transferrin saturation index, and Fe were also stable and well maintained during the 12 months (p > 0.05). CERA mean dose (SD) was [115.4 (56.2) μg baseline; 117.2 (58.5) μg 6 months; 126.0 (65.9) μg 12 months (p = 0.127)]. The mean number of CERA dose changes per patient during the study was 1.6 (SD 1.3). Serious adverse events were not related to CERA treatment. The results suggest that once-monthly CERA successfully corrects anemia and maintains stable Hb levels within the recommended target range on peritoneal dialysis under routine medical practice.

Keywords: anemia, CERA, hemoglobin, methoxy polyethylene glycol-epoetin beta, peritoneal dialysis

INTRODUCTION

Anemia, due to the decrease in erythropoiesis-stimulating agent (ESA) synthesis by the damaged kidney, is a common condition in patients with chronic kidney disease (CKD), and contributes to morbidity and mortality, (mainly of cardiovascular origin) and reduces the quality of life in these patients. Anemia is of paramount importance in the general management of patients receiving regular peritoneal dialysis. Treatment with conventional ESA to manage anemia in CKD patients needs frequent administrations, changes of doses, and close monitoring of hemoglobin (Hb) concentrations. Increasing the administration intervals of ESAs represents an opportunity to improve the efficiency of anemia management in patients with CKD and to ameliorate the quality of life of patients through saving frequent punctures.

A first continuous erythropoietin receptor activator (CERA) methoxy polyethylene glycol-epoetin beta (Mircera®) provides correction of anemia and stable control of Hb levels at extended administration intervals with a unique pharmacologic profile and a long half-life (139 h after subcutaneous administration in patients who are on peritoneal dialysis. Numerous randomized Phase
III trials demonstrated that CERA administered once every 4 weeks effectively maintains Hb levels stable in patients with CKD on dialysis and offers similar or superior efficacy compared with shorter-acting ESAs as maintenance therapy. Recent studies have also proved that dialysis patients can be successfully converted from epoetin or darbepoetin-α to monthly CERA maintenance therapy. However, only a low proportion of those patients were on peritoneal dialysis. As a consequence, these randomized studies do not provide real evidence concerning the efficacy and safety of the use of CERA in patients on peritoneal dialysis in day-to-day clinical practice. Few trials have analyzed CERA efficacy exclusively in peritoneal dialysis patients, and few of them had been conducted in routine clinical conditions. Noninterventional studies may provide complementary information on the effectiveness of CERA in real-life conditions. The aim of this study was to evaluate the efficacy of once-monthly CERA administration maintaining stable Hb levels in CKD patients on peritoneal dialysis, under routine medical practice.

PATIENTS AND METHODS

We have performed a 12-month, observational, prospective and multicenter study under routine medical practice, in Catalonia, an Autonomous Community of Spain. The study was conducted in 112 adult patients (≥18 years of age) with anemia secondary to CKD who had been receiving peritoneal dialysis for more than 3 months and treated with once-monthly subcutaneous CERA [Mircera® (methoxy polyethylene glycol-epoetin beta); F. Hoffmann-La Roche Ltd., Basel, Switzerland], at least 1 month before to start data collection.

This nonintervention nature study was carried out between September 2008 and December 2009, with patients from eight Catalan Hospitals and was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization of Good Clinical Practice guidelines and local Ethics Committees. All study participants provided their written informed consent to collect clinical data.

CERA was dosed according to the decision of the clinician and not given by protocol. However, a target of Hb level was established within the range of international guidelines. Patients were monitored once every 2 months. Results from basal, 6 months, and 12 months are shown.

Cause of CKD, doses of prior ESAs administered, starting dose of CERA and types of peritoneal dialysis were recorded. Systolic blood pressure (SBP) and diastolic blood pressure (DBP), adequacy of dialysis (Kt/V), and laboratory parameters as transferrin saturation index (TSI), Hb, iron (Fe) status, ferritin, B12 vitamin, C-reactive protein (CRP), albumin, cholesterol, and doses of CERA were assessed throughout the study. Hb was considered to have remained stable when the Hb level was within the Hb target range (11–13 g/dL) at consecutive visits.

Efficacy assessment included Hb levels, the average of patients who reached the target Hb (11–13 g/dL), the mean number of CERA dose modifications per patient during the study, the proportion of patients who maintain the Hb level within the target range and mean time in which the Hb level was maintained within this target range. Serious adverse events information was collected throughout the whole observation period.

Patient characteristics were described by means and standard deviations for quantitative variables and by the distributions of absolute and relative frequencies for qualitative variables. Tests were two-tailed with a significance level of 5%. Data were analyzed using SAS statistical software. To determine possible relationships, Spearman’s rho test was calculated between the CERA dose, Hb level, and clinical parameters.

RESULTS

Study Population

A total of 112 patients were included in the study but only 83 (74.1%) of these remained over the whole study period and were evaluable. The reasons for premature withdrawal and/or exclusion from the analysis of the remaining 29 (25.9%) patients were kidney transplantation (n = 8), transfer to hemodialysis (n = 8), death (n = 1), refractory anemia (n = 1), renal function recovery (n = 2), did not meet inclusion/exclusion criteria (n = 2), did not have Hb records (n = 3), lost to follow-up (n = 2), protocol violation (n = 1), and administrative problem (n = 1) (Figure 1).

Patient characteristics at baseline and the etiology of the renal disease are summarized in Table 1. The majority of patients were men (59.0%); the mean age was 57.8 years. Glomerulonephritis was the main cause of CKD (24.1%); 59 (71.1%) patients received peritoneal dialysis as first treatment option, 12 (14.5%) had previously received hemodialysis treatment, and 12 (14.5%) had kidney graft failure and returned to dialysis.

Almost all patients (89.1%) had previously received other ESA therapy before CERA treatment [53 (71.62%) darbepoetin-α (42.5 ± 24.3 μg/week),

![Figure 1. Causes of withdrawal from the study.](image)
At baseline, 52 (62.7%) patients were receiving automated peritoneal dialysis (APD), 26 (31.3%) continuous ambulatory peritoneal dialysis (CAPD), and 5 (6.0%) nighttime intermittent peritoneal dialysis (NIPD).

### Efficacy Evaluation

Table 3 shows the evolution of the anemia parameters. Statistically significant differences were not observed in the course of the 12-month study. The mean Hb levels in ESA naïve patients remained stable and within the recommended target range during the study, 11.8 ± 1.9 g/dL (p = 0.309). Patients converted from other ESA also presented stable Hb levels within the target range, irrespective of the frequency of administration of previous ESAs, 11.8 ± 1.5 g/dL (p = 0.622). In the total study population, the mean and median Hb levels were well maintained at nearly 12 g/dL during the evaluation period (p = 0.780) (Table 3).

With regard to the average of patients within the target Hb range (11–13 g/dL), at the different visits were shown not statistically significant differences (59.0%, baseline; 56.6%, 6 months; 44.6%, 12 months; p = 0.323).

The median [interquartile range (IQR)] time in which the Hb level was maintained within the target range (11–13 mg/dL) was 6 months. About 45.8% of the patients succeeded in maintaining their Hb levels within 11–13 g/dL during 8 months or more than 8 months, and 10% of the patients maintained it throughout the 12 months of the study.

B12 vitamin, Fe, Ferritin, and TSI were stable and well maintained during the 12 months (p < 0.05, Table 3).

### Table 1. Clinical and sociodemographic characteristics.

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>(N = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male), n (%)</td>
<td>49 (59.0)</td>
</tr>
<tr>
<td>Age, mean (SD), year</td>
<td>57.8 (16.0)</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>26.4 (4.9)</td>
</tr>
<tr>
<td>Cause of CKD, n (%)</td>
<td>20 (24.1)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>19 (22.9)</td>
</tr>
<tr>
<td>Vascular nephropathy</td>
<td>12 (14.5)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>12 (14.5)</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>7 (8.4)</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>8 (9.6)</td>
</tr>
<tr>
<td>Hereditary disease</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Systemic disease</td>
<td>2 (2.4)</td>
</tr>
</tbody>
</table>

Note: SD, standard deviation; BMI, body mass index; CKD, chronic kidney disease.

### Table 2. Starting CERA doses according to previous ESA treatment.

<table>
<thead>
<tr>
<th>Previous ESA</th>
<th>N (%)</th>
<th>Starting CERA doses median (IQR) (µg/month)</th>
<th>CERA doses according to SPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoetin &lt;8000 IU/week</td>
<td>50 (60.2)</td>
<td>100 (75–100)</td>
<td>120</td>
</tr>
<tr>
<td>Darbepoetin-α &lt;40 µg/week</td>
<td>18 (21.6)</td>
<td>150 (100–200)</td>
<td>200</td>
</tr>
<tr>
<td>Epoetin &gt;16,000 IU/week</td>
<td>6 (7.2)</td>
<td>200 (137–250)</td>
<td>360</td>
</tr>
<tr>
<td>Native</td>
<td>9 (10.8)</td>
<td>87.5 (75–112.5)</td>
<td></td>
</tr>
</tbody>
</table>

Note: SPC, summary of product characteristic; IQR, interquartile range.

### Table 3. Evolution of the anemia parameters.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb, mean (SD) [95% CI], g/dL</td>
<td>11.8 (1.4) [11.6–12.2]</td>
<td>11.8 (1.4) [11.5–12.1]</td>
<td>11.8 (1.5) [11.4–12.1]</td>
</tr>
<tr>
<td>(N = 83) Native (N = 10)</td>
<td>10.5 (0.6) [10.1–11.0]</td>
<td>11.2 (1.0) [10.4–12.0]</td>
<td>11.8 (1.9) [10.4–13.3]</td>
</tr>
<tr>
<td>Hb previous ESA, mean (SD) [95% CI], g/dL (N = 73)</td>
<td>11.9 (1.5) [11.6–12.3]</td>
<td>11.9 (1.4) [11.6–12.2]</td>
<td>11.8 (1.5) [11.4–12.1]</td>
</tr>
<tr>
<td>&lt;8000 IU/week or &lt;40 µg/week</td>
<td>12.1 (1.4) [11.7–12.6]</td>
<td>12.2 (1.3) [11.8–12.5]</td>
<td>11.9 (1.4) [11.5–12.3]</td>
</tr>
<tr>
<td>8000–16,000 IU/week or 40–80 µg/week</td>
<td>11.7 (1.4) [11.0–12.3]</td>
<td>11.2 (1.6) [10.4–12.0]</td>
<td>11.2 (1.6) [10.4–12.0]</td>
</tr>
<tr>
<td>&gt;16,000 IU/week or &gt;80 µg/week</td>
<td>11.3 (1.8) [9.4–13.2]</td>
<td>11.8 (0.7) [11.0–12.5]</td>
<td>12.3 (1.4) [10.9–13.8]</td>
</tr>
<tr>
<td>Vitamin B12, mean ± SD, pmol/L (N)</td>
<td>463.2 ± 156.3 (30)</td>
<td>481.2 ± 215.6 (69)</td>
<td>415.4 ±146.2 (38)</td>
</tr>
<tr>
<td>Fe, mean ± SD, mmol/L (N)</td>
<td>12.4 (5.2) (64)</td>
<td>12.9 (5.5) (60)</td>
<td>12.2 (4.8) (19)</td>
</tr>
<tr>
<td>Ferritin, mean ± SD, ng/mL (N)</td>
<td>231.2 ± 213.8 (70)</td>
<td>238.1 ± 247.0 (66)</td>
<td>223.4 ± 146.8 (64)</td>
</tr>
<tr>
<td>TSI, % ± SD (N)</td>
<td>27.2 ± 12.7 (35)</td>
<td>26.5 ± 9.9 (33)</td>
<td>26.5 ± 9.9 (37)</td>
</tr>
</tbody>
</table>

Notes: SD, standard deviation; Hb, hemoglobin; TSI, transferrin saturation index.

p-Values between visits were not statistically significant (>0.05) for all parameters.

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DISCUSSION

ESAs are necessary in most CKD patients on dialysis to maintain Hb levels, preventing anemia complications and ameliorating both the quality and the expectancy of life. Different ESAs have been used in the last few years. CERA has been demonstrated effective in maintaining stable Hb levels by once-monthly administration in dialysis patients with CKD in numerous randomized studies. However, most of the subjects in those were on hemodialysis. Few trials have analyzed CERA efficacy exclusively in peritoneal dialysis patients, and few of them were conducted in routine clinical conditions.

Results from this observational study indicate that once-monthly CERA maintains stable levels of Hb within the recommended target range, under routine clinical conditions, in patients on peritoneal dialysis. During the 12-month evaluation period, Hb levels remained stable, with a low number of CERA dose changes.

The mean number of CERA dose changes during the study was 1.6 in a 12-month period. This result was higher than reported in a historical cohort study; the reason may be the presence of naïve patients in a titration period in our study. Previous studies conducted in hemodialysis patients reported a mean CERA dose change of nearly 2.12,14

Dose changes have been related to fluctuations in Hb. Several studies have reported that Hb levels frequently fluctuate over time in patients treated with ESAs.17,20–23 Fluctuation in serum Hb have been linked to poor patient outcomes.22 The longer half life of CERA may offer a small advantage in reducing the degree of Hb variability, possibly because of fewer dose changes per patient.17

Although Hb fluctuations are smaller in patients on peritoneal dialysis compared with those on hemodialysis, our findings, as other authors have also
reported, underline the difficulty of maintaining Hb levels within the narrow range of the guideline recommendations over long periods of time. Thus, the mean time of maintained stable Hb levels within range (11–13 g/dL) in our study was 6.3 months. In the historical cohort study in peritoneal patients, above mentioned, 31.6% of patients in the CERA group had stable serum Hb with no fluctuations during the 12 months, but only 26 patients were treated with CERA. In our study, 10% of the patients succeeded in maintaining Hb levels within the target range throughout the study. Different authors had estimated that only 5% of patients who are on hemodialysis have Hb between 11–12 g/dL persistently remain within that range for 6 months.

Monthly administration of CERA is becoming more widely adopted, so it is important to assess whether the efficacy observed in the controlled trial setting is matched when dosing is adjusted at the clinician’s prescription. Due to the nonintervention nature of this study, treatment patterns were entirely according to the physician’s clinical judgment. The required doses are lower in peritoneal dialysis than in hemodialysis patients due to better adequacy of dialysis and lower hematological losses in the capillary filters. In clinical practice, lower and better stratification of the initial CERA dosage has been proved compared with the doses recommended in the SPC. The information provided by the present study suggests that CERA is effective even at dose levels lower than the dosage recommended by SPC. So, mean Hb levels remained close to 12 g/dL over the whole evaluation period. Regarding this issue, the prescription of CERA doses below recommended values has been reported in several studies and it was considered effective in maintaining Hb levels in CKD patients not on dialysis.

In peritoneal dialysis patients, the need for frequent punctures could diminish their quality of life and increase the loss of adherence to treatment. The prolonged half-life of CERA could be beneficial in preventing these problems in peritoneal dialysis patients. ESAs are administered commonly via subcutaneous injections in patients on peritoneal dialysis, and different authors have reported that subcutaneous administration of CERA is significantly less painful than darbepoetin-α. Therefore, CERA offers the advantage of monthly dosing, which provides a lower pain burden, avoids repeated controls at the hospital, and may improve patient compliance.

Some limitations should be borne in mind. Among them, the observational design of the study implies potential confounding factors. One of these was that the treatment pattern was entirely according to the physician’s clinical judgment and not determined by protocol. So, the decisions to initiate CERA, the initial dose, and subsequent dose adjustments were made at the discretion of the physician. It is therefore not certain that the treatment pattern was the same for all patients. Furthermore, this study included patients treated with once-monthly subcutaneous CERA during at least 1 month prior to start of data collection, so some patients could be still in the period of stabilization of their Hb levels during the first months of the study.

Randomized clinical trials employ restrictive criteria. However, these conditions do not reflect conditions in actual clinical practice. Observational studies assess the use of a drug in real conditions, providing complementary data. The information provided by the present study suggests that CERA is effective, even at dose levels lower than the dosage recommended by SPC, and maintains stable Hb levels within the recommended target range in peritoneal dialysis under routine medical practice conditions.

In conclusion, the fact that mean Hb levels were maintained stable over 1 year with a monthly dose of CERA, allows us to conclude that CERA may be an effective treatment of anemia in patients with end-stage renal failure on chronic peritoneal dialysis treatment in routine clinical practice.

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