C.E.R.A. once every 4 weeks in patients with chronic kidney disease not on dialysis: The ARCTOS extension study

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Abstract

C.E.R.A., a continuous erythropoietin receptor activator is approved for the treatment of anemia in patients with chronic kidney disease (CKD). The ARCTOS (administration of C.E.R.A. in CKD patients to treat anemia with a twice-monthly schedule) phase 3 study demonstrated the efficacy and safety of C.E.R.A. in correcting anemia when administered once every 2 weeks (Q2W) subcutaneously in patients with CKD not on dialysis. We assessed the feasibility and long-term safety of converting patients who responded to treatment with C.E.R.A. Q2W to C.E.R.A. once every 4 weeks (Q4W) during a 24-week extension period. After the core ARCTOS study period (28 weeks), 296 patients entered the 24-week extension period. At week 29, patients who responded to C.E.R.A. Q2W during the core period were rerandomized to receive subcutaneous C.E.R.A. Q2W or Q4W. Patients in the comparator arm could receive darbepoetin alfa once weekly or Q2W. Dosage was adjusted to maintain hemoglobin (Hb) between 11 and 13 g/dL. Mean Hb levels remained stable in all groups, and were comparable at the end of the extension period (mean [standard deviation], C.E.R.A. Q2W, 11.92 [0.90] g/dL; C.E.R.A. Q4W, 11.70 [0.86] g/dL; darbepoetin alfa, 11.89 [0.98] g/dL). Mean within-patient standard deviation values for Hb were also comparable in all groups (0.66, 0.62, and 0.65 g/dL for C.E.R.A. Q2W, C.E.R.A. Q4W and darbepoetin alfa, respectively). All treatments were well tolerated. Subcutaneous C.E.R.A. Q4W is safe and effective in maintaining stable Hb levels in patients with CKD not on dialysis following correction with subcutaneous C.E.R.A. Q2W.

Key words: Anemia, C.E.R.A., chronic kidney disease, hemoglobin

INTRODUCTION

Anemia is a common complication of chronic kidney disease (CKD) that results primarily from inadequate erythropoietin production by the damaged kidney. It develops early in the course of CKD, and is seen even among patients with mild-to-moderate CKD (creatinine clearance \( \leq 70 \text{ mL/min} \) for men and \( \leq 50 \text{ mL/min} \) for women).1 Recent estimates indicate that anemia is present in nearly half of all patients with CKD, increasing in prevalence and severity as kidney function deteriorates.2 Anemia is associated with poor outcomes, and contributes to the increased morbidity and mortality associated with CKD.3,4

The use of erythropoiesis-stimulating agents (ESAs) for the management of renal anemia ameliorates symptoms of anemia, is associated with improvements in quality of life and overall well-being5 and possibly slows the decline of
renal function.\textsuperscript{6} However, less than a third of patients with CKD who have anemia receive ESA treatment before they progress to end-stage renal disease.\textsuperscript{7-10} The low usage of ESAs in patients who are not yet on dialysis may in part be attributed to the need for frequent dosing when short-acting ESAs such as epoetin are used.\textsuperscript{11} Newer ESAs which can be dosed less frequently may improve the management of anemia in these patients.

C.E.R.A., a continuous erythropoietin receptor activator, is approved for the treatment of anemia in patients with CKD. C.E.R.A. has a longer half-life than other ESAs (\(\sim 130\) hours following intravenous or subcutaneous administration),\textsuperscript{12-15} allowing extended dosing intervals of once every 2 weeks (Q2W) for anemia correction, and once monthly for maintenance treatment.\textsuperscript{16}

The ARCTOS (administration of C.E.R.A. in CKD patients to treat anemia with a twice-monthly schedule) study was designed to assess the efficacy of C.E.R.A. in correcting anemia in ESA-naïve patients with CKD not on dialysis.\textsuperscript{17} The study demonstrated that C.E.R.A. given subcutaneously Q2W corrected anemia in these patients, with efficacy and safety similar to that of darbepoetin alfa.\textsuperscript{17} We have analyzed the feasibility and long-term safety of converting those patients who responded to Q2W C.E.R.A. treatment in the ARCTOS study to C.E.R.A. once every 4 weeks (Q4W) during a 24-week extension phase.

**MATERIALS AND METHODS**

**Study design and patients**

The rationale, design, and outcomes of the ARCTOS study have been published previously.\textsuperscript{17} In brief, ARCTOS was an open-label, randomized, multicenter, darbepoetin alfa-controlled, parallel-group phase 3 study which examined the efficacy of C.E.R.A. Q2W for correcting anemia in patients with CKD not on dialysis. The study randomized 324 ESA-naïve patients (aged \(\geq 18\) years) with CKD stage 3 (creatinine clearance 30–59 mL/min) or stage 4 (creatinine clearance 15–29 mL/min) not on dialysis, adequate iron status (defined as serum ferritin \(\geq 100\) ng/mL or transferrin saturation \(\geq 20\%\) [or percentage of hypochromic red blood cells (RBCs) \(< 10\%\)]), and hemoglobin (Hb) 8 to 11 g/dL at baseline, to treatment with subcutaneous C.E.R.A. Q2W or subcutaneous darbepoetin alfa once weekly (QW) during an 18-week correction period followed by a 10-week evaluation period (core treatment period). Patients were excluded from the study if there was expected rapid progression of CKD (e.g., a creatinine clearance decrease of \(> 20\%\) within 12 weeks) or need for dialysis therapy within 6 months of the start of the study. If a patient required emergency or regular dialysis (hemodialysis or peritoneal dialysis) due to worsening renal function, the patient was to be kept in the study, where possible, until the final visit. Patients were also excluded if they had received ESA therapy within 12 weeks before screening, or if they had overt bleeding that necessitated transfusion within 8 weeks of the start of screening or during the screening period; C-reactive protein \(> 15\) mg/L; or life expectancy <12 months.

At the end of the core treatment period (week 28), patients who responded to C.E.R.A. (defined as an increase in Hb \(\geq 1.0\) g/dL vs. baseline and Hb \(\geq 11\) g/dL without blood transfusion during the first 28 weeks after the first dose) were eligible to continue treatment, and were randomized at week 29 to receive subcutaneous C.E.R.A. either Q2W or Q4W for an additional 24-week extension period (weeks 29–53) to assess long-term safety. Patients who responded to darbepoetin alfa QW in the core period could receive darbepoetin alfa QW or Q2W during the extension period, at the discretion of the investigating nephrologists. Hemoglobin levels were to be maintained between 11 and 13 g/dL during the extension period. Dose adjustments were performed no more than Q4W, unless safety concerns dictated otherwise, as previously described.\textsuperscript{17} Patients in the C.E.R.A. treatment group who remained on the Q2W schedule received the same dose as at week 27, and patients randomized to the Q4W schedule received a dose that was double the week 27 dose. Patients in the darbepoetin alfa group who remained on the QW schedule received the same dose as at week 28, and patients on the Q2W schedule received a dose that was double the week 28 dose.

**Assessments**

Patients were scheduled for assessments Q4W during the extension period. Hemoglobin, blood pressure, and heart rate were measured at each assessment and at the final visit, while iron parameters were assessed every 8 weeks and at the final visit. Anti-C.E.R.A. and antierthropoietin antibody testing was carried out at week 37 and at the final visit; other laboratory parameters were also assessed at these two visits. Adverse events (AEs), iron administration and RBC transfusions were recorded throughout the extension period.

**Data analysis**

Hemoglobin values over time were analyzed descriptively in the intent-to-treat (ITT [all patients randomized]) pop-
ulation. Dose of study medication over time and the number of dose changes were analyzed descriptively in the safety population (all patients who received at least 1 dose of study medication and had a safety follow-up). In response to queries from Health Authorities, the proportion of patients maintaining stable Hb within \pm 1 g/dL of the response value was analyzed in the ITT population. Within-patient variability of Hb, defined as the intra-individual standard deviation (SD) of Hb, was analyzed after week 36 in the ITT population. The incidence of RBC transfusions was also summarized and the groups compared using descriptive statistics. Group summary statistics were provided for safety parameters.

RESULTS

Patients

Of the 324 patients randomly assigned to receive treatment during the 28-week core period (C.E.R.A. Q2W, n=162; darbepoetin alfa QW, n=162), 158 in the C.E.R.A. group and 156 in the darbepoetin alfa group responded to treatment (Figure 1). A total of 145 responders in the C.E.R.A. group were rerandomized to C.E.R.A. Q2W (73 patients) and C.E.R.A. Q4W (72 patients), including 1 patient in each group who received treatment for the extension period, but who withdrew before day 201 (defined as the cut-off for the start of the extension period). A total of 151 responders in the darbepoetin alfa group entered the extension period.

Mean (SD) Hb levels were similar in both treatment groups at week 28, before patients were rerandomized (C.E.R.A. Q2W, 12.2 [1.14] g/dL; darbepoetin alfa QW, 12.1 [1.11] g/dL). Iron parameters were also similar in both treatment groups at week 28 (median [interquartile range (IQR)] transferrin saturation, C.E.R.A., Q2W, 27.7% [21.0–35.0]; darbepoetin alfa QW, 24.0% [19.9–29.9]; median [IQR] ferritin, C.E.R.A. Q2W, 223 ng/mL [133–326]; darbepoetin alfa, 236 ng/mL [136–375]).

All 296 randomized patients who entered the extension period were eligible for the ITT and safety populations. In total, 275 patients completed the extension period (C.E.R.A. Q2W, n=68; C.E.R.A. Q4W, n=68; and darbepoetin alfa, n=139, Figure 1).

Nineteen patients were withdrawn from the study during the extension treatment period: 4 patients in the C.E.R.A. Q2W group, 3 in the C.E.R.A. Q4W group, and 12 in the darbepoetin alfa group. Reasons for withdrawal were AE (C.E.R.A. Q4W, n=1; darbepoetin alfa, n=4), death (C.E.R.A. Q2W, n=2; C.E.R.A. Q4W, n=1;...
and darbepoetin alfa, n=4), refusal of treatment (C.E.R.A. Q2W, n=1; darbepoetin alfa, n=3), kidney transplantation (n=1 for C.E.R.A. Q2W and Q4W), and loss to follow-up (darbepoetin alfa, n=1). No patients were withdrawn due to lack of efficacy.

Demographic data are summarized in Table 1. During the extension period, 109 patients (37%) received iron supplementation: 28 (38%) in the C.E.R.A. Q2W group, 26 (36%) in the C.E.R.A. Q4W group, and 55 (36%) in the darbepoetin alfa group. The most commonly received supplements were iron sucrose (14%, 15%, and 14% patients, respectively), ferrous sulfate (11%, 10%, and 11%, respectively), and ferrous gluconate (7%, 6%, and 5%, respectively). Most of the patients in each group had C-reactive protein levels ≤ 10 mg/L at the start of the extension period (C.E.R.A. Q2W, 82%; C.E.R.A. Q4W, 90%; and darbepoetin alfa, 85.4%) and at the end of the extension period (C.E.R.A. Q2W, 81%; C.E.R.A. Q4W, 79.3%; and darbepoetin alfa, 86.9%).

Efficacy

Table 2 shows that mean Hb levels remained stable in all treatment groups during the extension period. Mean Hb levels were maintained within ± 1 g/dL of the response value for 55 (76.4%) of the 72 patients given C.E.R.A. Q2W; 50 (70.4%) of the 71 patients given C.E.R.A. Q4W; and 103 (68.2%) of the 151 patients given darbepoetin alfa. Mean within-patient SD values for Hb were also comparable in all treatment groups (mean [SD] values, 0.66 [0.45] g/dL, 0.62 [0.41] g/dL, and 0.65 [0.42] g/dL for C.E.R.A. Q2W, C.E.R.A. Q4W, and darbepoetin alfa, respectively) (Figure 2).

The numbers of patients receiving at least 1 RBC transfusion in the C.E.R.A. Q2W, C.E.R.A. Q4W, and darbepoetin alfa groups were 2 (2.7%), 0 (0%), and 4 (2.6%), respectively. Median doses of trial medication remained stable in all groups during the extension period (Table 3).

Safety

The incidence of AEs was similar in the 3 treatment groups: at least 1 AE was experienced by 67%, 64%, and 66% of patients in the C.E.R.A. Q2W, C.E.R.A. Q4W, and darbepoetin alfa groups, respectively. The most commonly reported AEs are listed in Table 4. Most were mild

<table>
<thead>
<tr>
<th>C.E.R.A. Q2W</th>
<th>C.E.R.A. Q4W</th>
<th>Darbepoetin alfa QW/Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>Hb (g/dL)</td>
<td></td>
</tr>
<tr>
<td>Week 32</td>
<td>71</td>
<td>12.00 (1.33)</td>
</tr>
<tr>
<td>Week 36</td>
<td>70</td>
<td>12.00 (1.33)</td>
</tr>
<tr>
<td>Week 40</td>
<td>66</td>
<td>11.84 (1.11)</td>
</tr>
<tr>
<td>Week 44</td>
<td>71</td>
<td>11.81 (1.03)</td>
</tr>
<tr>
<td>Week 48</td>
<td>70</td>
<td>11.83 (0.97)</td>
</tr>
<tr>
<td>Week 52</td>
<td>68</td>
<td>11.92 (0.90)</td>
</tr>
</tbody>
</table>

C.E.R.A. = continuous erythropoietin receptor activator; Hb = hemoglobin; QW = once weekly; Q2W = once every 2 weeks; Q4W = once every 4 weeks; SD = standard deviation.

Table 1 Demographic data for patients entering the extension period (intent-to-treat population)

<table>
<thead>
<tr>
<th></th>
<th>C.E.R.A. Q2W (n=73)</th>
<th>C.E.R.A. Q4W (n=72)</th>
<th>Darbepoetin alfa QW/Q2W (n=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>30 (41)</td>
<td>30 (42)</td>
<td>74 (49)</td>
</tr>
<tr>
<td>Mean (SD) age (year)</td>
<td>63.9 (13.8)</td>
<td>63.5 (14.9)</td>
<td>66.9 (12.8)</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>77</td>
<td>65</td>
<td>83</td>
</tr>
<tr>
<td>Black</td>
<td>15</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td>Oriental</td>
<td>7</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>10</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>90</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Geographic region (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>26</td>
<td>42</td>
<td>35</td>
</tr>
<tr>
<td>Outside</td>
<td>74</td>
<td>58</td>
<td>65</td>
</tr>
</tbody>
</table>

C.E.R.A. = continuous erythropoietin receptor activator; QW = once weekly; Q2W = once every 2 weeks; Q4W = once every 4 weeks; SD = standard deviation.
or moderate in intensity. Only 1 AE (chills: C.E.R.A. Q2W group) was considered to be related to study medication.

The incidence of serious AEs was 15%, 15%, and 20% in the C.E.R.A. Q2W, C.E.R.A. Q4W, and darbepoetin alfa groups, respectively; none were considered to be treatment related.

Nine patients died during the extension period: 2 in the C.E.R.A. Q2W group, 1 in the C.E.R.A. Q4W group, and 6 in the darbepoetin alfa group (including 1 patient who died after the end of the extension period [day 375], and 1 patient who chose to discontinue dialysis and continue with comfort care—this patient died 8 days after last treatment). None of the deaths were considered to be treatment related.

Iron parameters were well maintained in all treatment groups. No anti-C.E.R.A. antibodies were detected in any patient. One patient in the darbepoetin alfa group had nonneutralizing anterythropoietin antibodies. There were no clinically relevant changes in vital signs or laboratory parameters during the study.

**DISCUSSION**

The ARCTOS extension study has shown that subcutaneous C.E.R.A. Q4W effectively maintained Hb levels within a target range of 11 to 13 g/dL in patients with CKD not on dialysis following correction with subcutaneous C.E.R.A. Q2W. Furthermore, analysis of within-patient variability showed a similar degree of Hb control in all treatment groups. None of the patients in the C.E.R.A. Q4W group required transfusions. C.E.R.A. was also well tolerated, with an AE profile typical of this patient population.

These data add to those of other C.E.R.A. phase 3 studies by providing further evidence of the safety and efficacy of C.E.R.A. Q4W in patients with CKD. In the previously published maintenance studies, patients receiving epoetin once weekly to 3 times weekly (QW to TIW) were converted directly to C.E.R.A. Q4W. The 2 studies, which were designed to demonstrate noninferiority of C.E.R.A. Q4W compared with epoetin QW to TIW, showed that C.E.R.A. Q4W maintained stable Hb levels as effectively as epoetin QW to TIW. The present study demonstrates that patients can be converted from C.E.R.A. Q2W correction treatment to C.E.R.A. Q4W maintenance treatment without compromising efficacy or safety.

The use of Q4W dosing regimens with other ESAs has been investigated in patients with CKD not on dialysis. Provenzano et al. examined the efficacy of fixed doses of epoetin alfa given up to Q4W in patients who had previously received epoetin alfa. While the mean final Hb level in the Q4W group was statistically noninferior compared with the QW treatment group, the follow-up period in this study was short (16 weeks). In other studies, conversion of patients with CKD not on dialysis from...
Q2W darbepoetin alfa maintenance dosing to Q4W darbepoetin alfa has been shown to be effective in selected patients; only those stable on Q2W maintenance dosing were converted to Q4W administration. In 1 of the studies, the efficacy criterion was less stringent (proportion of patients maintaining mean Hb ≥ 10 g/dL during the evaluation period [weeks 21–33]) than in the current study.

Despite the adverse consequences of anemia on the well-being of the anemic patient, treatment remains inadequate in patients not yet on dialysis. An obstacle to optimal anemia management in this patient group has been the need for frequent dosing of short-acting ESAs. A more convenient dosing regimen which does not compromise efficacy may improve patient compliance, and improved compliance may in turn help improve outcomes. With fewer clinic visits and fewer injections, less frequent ESA administration is not only preferred by patients with CKD not on dialysis over more frequent dosing, but also has the potential to reduce health care resource utilization.

In summary, the ARCTOS extension study demonstrates the efficacy and long-term safety of C.E.R.A. administered Q4W in patients with CKD not on dialysis following anemia correction with C.E.R.A. Q2W. Thus, C.E.R.A. has the potential to optimize anemia management in this patient group.

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