Shifting Darbepoetin Alpha to Subcutaneous Methoxy Polyethylene Glycol-Epoetin Beta of Similar Doses and Extended Dose Intervals Effectively Maintains Hemoglobin Concentrations in Peritoneal Dialysis Patients

Ming-Hsien Tsai¹, Yu-Wei Fang¹, and Jyh-Gang Leu¹, ²

¹Division of Nephrology, Department of Internal Medicine, Shin-Kong Wu Ho-Su Memorial Hospital
²Fu-Jen Catholic University School of Medicine, Taipei, Taiwan, Republic of China

Abstract

BACKGROUND: Methoxy polyethylene glycol-epoetin beta is a continuous erythropoietin receptor activator (CERA) that provides stable control of blood hemoglobin levels at extended administration intervals in patients with chronic kidney disease. The purpose of this single-center case study is to assess whether patients on peritoneal dialysis (PD) can be successfully switched from previous darbepoetin alfa treatment to CERA with extended dose intervals.

METHODS: Selective PD patients receiving regular darbepoetin alfa therapy were switched to monthly or bimonthly CERA injections. Data of blood biochemical tests and dialysis adequacy before and after 6 months of CERA treatment were analyzed to evaluate the effect on hemoglobin maintenance.

RESULTS: Fifteen PD patients (mean age: 50.4 years; men: 9, women: 6) were enrolled for this study. Mean baseline and evaluation-period hemoglobin levels were similar (10.2 ± 0.66 vs. 10.1 ± 1.35 g/dL, P = 0.450). No change in blood hemoglobin levels and biochemical or dialysis adequacy parameters before and after 6 months of CERA treatment was noted. The dosages of darbepoetin alfa (1.51 μg/kg/month) and CERA (1.59 μg/kg/month) used for erythropoiesis were similar. The average monthly cost of darbepoetin alfa (NT$ 4337 ± 1069) and CERA (NT$ 4775 ± 728) also showed no significant difference.

CONCLUSIONS: PD patients receiving regular darbepoetin alfa treatment could be safely switched to CERA injection of similar dosage levels at extended dose intervals. Large-scale studies are needed to confirm our observation.

KEY WORDS: peritoneal dialysis, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta, anemia, end-stage renal disease

Introduction

Anemia is common in patients with chronic kidney disease (CKD). Correction of anemia with erythropoiesis-stimulating agents (ESAs) improves patient’s outcome and quality of life (1, 2). Four types of ESAs, including epoetin alfa, epoetin beta, darbepoetin alfa, and methoxy polyethylene glycol-epoetin beta (continuous erythropoietin receptor activator; CERA) are available in the market. The intravenous half-life is 8 hours for epoetin alfa and beta (3), 25 hours for darbepoetin alfa (4), and 134 hours for CERA (5). ESAs with longer half-lives provide greater advantage and convenience in anemia treatment for both dialysis and nondialysis patients with CKD (6).

In Taiwan, patients on peritoneal dialysis (PD) usually visit their doctors and nurses once a month.
Home ESA injections are inconvenient for PD patients, thus leading frequently to treatment non-compliance. Replacing shorter half-life ESAs with weekly-injected darbepoetin alfa successfully maintains blood hemoglobin (Hb) levels and enhances compliance in PD patients (7, 8). However, weekly injection is still inconvenient, also resulting in non-compliance and injection complications in many PD patients. Monthly injection with longer half-life ESAs has been considered to improve patient care.

CERA is an ESA made by adding a large water-soluble polyethylene glycol moiety to epoetin beta (9), leading to a higher molecular weight (60 kDa) and a longer half-life (130 hours). Clinical trials have shown that once-monthly CERA administration is effective in maintaining blood Hb levels after switching from recombinant human EPO (rHuEPO) or darbepoetin alfa therapy (10, 11). Once-monthly intravenous administration of CERA is better than once-monthly darbepoetin alfa in maintaining blood Hb levels in hemodialysis patients (12). The long-term safety profile of CERA is also comparable to that of the other ESAs (13). In this study, we evaluated the effect of CERA on PD patients after switching from darbepoetin alfa therapy.

Materials and Methods

We reviewed the charts of patients on PD at Shin-Kong Wu Ho-Su Memorial Hospital from December 2009 to December 2011. Eighty-two PD patients with regular darbepoetin alfa therapy had been switched to CERA treatment during that period. During the 6-months of darbepoetin alfa therapy before CERA treatment, patients were excluded for the following reasons: [1] less than 3 years on PD (13 patients) for eliminating the effect of residual renal function on erythropoietin production; [2] intravenous EPO administration route (4 patients); [3] insufficient data due to irregular follow-up (4 patients) (4 patients); [4] Hb levels not maintained between 9.0 and 12.0 g/dL (3 patients); [5] history of blood transfusion (6 patients), massive blood loss (5 patients), systemic infection (9 patients), malignancy (0 patients), New York Heart Association (NYHA) class III or IV congestive heart failure (2 patients), uncontrolled hyperparathyroidism (2 patients), hematological disorders (1 patient), or inflammatory disorders such as systemic lupus erythematosus (0 patients).

After CERA therapy, the patients were excluded if they did not persist for at least 6 months because of any reason (11 patients). Only 22 patients fitted these criteria, and 7 were further excluded because of major diseases (1 exit site infection, 1 peritonitis, 1 pneumonia, 1 acute pancreatitis, and 3 gastrointestinal bleeding) during CERA therapy. Finally, 15 patients qualified for analysis. All 15 patients had received regular subcutaneous CERA injection for 24 weeks. The conversion rate and dose intervals were decided by the attending physician to maintain Hb levels between 9.0 g/dL and 12.0 g/dL. This study has been approved by the Institutional Review Board of the Shin-Kong Wu Ho-Su Memorial Hospital.

Statistical Analysis

Baseline data, including blood Hb levels, serum iron profile, biochemical parameters, monthly cost, and Kt/V values, were collected before and after 6 months of CERA treatment. Data before and after CERA treatment were compared using Wilcoxon signed ranks tests because data were not normally distributed. Generalized estimating equation (GEE) method with working correlation matrix of first-order autoregressive (AR1) was employed to evaluate the association between monthly serum Hb levels and different ESA treatment periods in our study. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using SPSS software v 20.0 (IBM Inc., Chicago, IL, USA).

Results

Fifteen patients, 9 men and 6 women, with an average age of $50.4 \pm 13.1$ years were included for data analysis. There were 6 patients receiving renin-angiotensin system blockade during the entire study period. CERA administration maintained stable
CERA Effectively Maintains PD Patients’ Hemoglobin Level at Extended Intervals

C.E.R.A. Effectively Maintains PD Patients’ Hemoglobin Level at Extended Intervals

Blood Hb levels during the 6 months of treatment (Fig. 1). Hb levels before (10.2 ± 0.66 g/dL) and after 6 months (10.1 ± 1.35 g/dL) of CERA treatment showed no difference (P = 0.450). There was no change in serum albumin, iron profile, and other biochemical parameters before and after 6 months of CERA treatment (Table 1). In addition, there was no change in the parameters of dialysis adequacy, such as Kt/V (2.0 vs 2.1, P = 0.570) and weekly creatinine clearance (51.0 ± 13.5 vs. 48.3 ± 13.4 L/week/1.73 m², P = 0.370). Residual renal function was significantly lower after 6 months of CERA administration probably due to progressive deterioration of kidney function (0.10 ± 0.10 vs. 0.06 ± 0.07, P = 0.005; Table 1). The change was too small and hence can be ignored. The dosages of darbepoetin alfa (1.51 μg/kg/month) and CERA (1.59 μg/kg/month) used for erythropoiesis were similar (P = 0.363; Table 1). The average monthly cost of darbepoetin alfa (NT$ 4,337 ± 1,069) and CERA (NT$ 4,775 ± 728) also showed no significant difference (P = 0.156). Five patients received CERA (100 μg) treatment bimonthly, and their Hb levels showed higher variation (Fig. 2).

Discussion

This is the first study that compares the effects of CERA and darbepoetin alfa of similar monthly dosages on PD patients. The effect of CERA on renal anemia has been shown in several previous studies. A study in Taiwan reported that monthly subcutaneous CERA administration provided better correction of renal anemia than epoetin beta or darbepoetin alfa in PD patients (14). Another study in the United Kingdom showed that CERA provided less variability of Hb levels than epoetin beta in PD patients because of a longer half-life and fewer dose changes (15). However, no total monthly dosages or cost were

Table 1. Difference in data collected before and after use of C.E.R.A.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.2 ± 0.7</td>
<td>10.1 ± 1.4</td>
<td>0.450</td>
</tr>
<tr>
<td>Kt/V (total)</td>
<td>2.01 ± 0.3</td>
<td>2.07 ± 0.4</td>
<td>0.570</td>
</tr>
<tr>
<td>Kt/V (renal)</td>
<td>0.10 ± 0.10</td>
<td>0.06 ± 0.07</td>
<td>0.005</td>
</tr>
<tr>
<td>WCcrCl (L/week/1.73 m²)</td>
<td>51.0 ± 13.5</td>
<td>48.3 ± 13.4</td>
<td>0.370</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.0 ± 0.3</td>
<td>4.1 ± 0.2</td>
<td>0.166</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>13.3 ± 2.3</td>
<td>13.5 ± 2.1</td>
<td>0.348</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>67.9 ± 18.1</td>
<td>68 ± 14.6</td>
<td>0.910</td>
</tr>
<tr>
<td>Ionized calcium (mg/dL)</td>
<td>5.1 ± 0.4</td>
<td>5.1 ± 0.4</td>
<td>0.551</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>6.0 ± 1.3</td>
<td>6.1 ± 1.5</td>
<td>0.660</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>19.0 ± 7.0</td>
<td>20.3 ± 6.6</td>
<td>0.292</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>20.2 ± 8.4</td>
<td>21.6 ± 6.03</td>
<td>0.271</td>
</tr>
<tr>
<td>iPTh (pg/mL)</td>
<td>174.57 ± 108.0</td>
<td>208 ± 148</td>
<td>0.650</td>
</tr>
<tr>
<td>Aluminum (μg/L)</td>
<td>4.6 ± 3.1</td>
<td>6.8 ± 7.7</td>
<td>0.245</td>
</tr>
<tr>
<td>Ferritin (ng/dL)</td>
<td>322 ± 179.7</td>
<td>355 ± 191.0</td>
<td>0.865</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>32 ± 18.8</td>
<td>34 ± 15.8</td>
<td>0.244</td>
</tr>
<tr>
<td>RAS blockade (No/total)</td>
<td>6/15</td>
<td>6/15</td>
<td>n/a</td>
</tr>
<tr>
<td>EPO dose (μg/kg/per month)</td>
<td>1.5 ± 0.5</td>
<td>1.6 ± 0.4</td>
<td>0.363</td>
</tr>
<tr>
<td>Cost (NT$/per month)</td>
<td>4337 ± 1069</td>
<td>4775 ± 728</td>
<td>0.156</td>
</tr>
</tbody>
</table>

AST, aspartate aminotransferase; ALT, alanine aminotransferase; iPTh, intact parathyroid hormone; RAS, renin angiotensin system.
compared in those two studies.

In this research, CERA and darbepoetin alfa of similar dosages showed similar effects in correcting anemia in PD patients. No change in serum albumin levels, aluminum levels, iron profile, other biochemical parameters, Kt/V, and weekly creatinine clearance was noted during the evaluation period. These results indicate that PD patients without hematological or inflammatory disorders may be successfully and safely switched from darbepoetin alfa administration to CERA of similar dosage levels. The high price is usually a major factor in delayed CERA usage. In our study, the average monthly cost of CERA was only slightly higher than that of darbepoetin alfa. Once-monthly injection makes CERA much more convenient and acceptable to most patients and medical staff.

The effect of CERA in patients on CKD and hemodialysis had been evaluated in many previous studies. Initiation with CERA injection once a month (1.2 μg/kg, approximately 100 μg/month) was proven effective in correcting renal anemia for nondialysis patients with CKD (16). Hb levels remained stable during routine use of CERA (17). Subcutaneous injection of CERA (1.2 μg/kg every 4 weeks) and darbepoetin alfa (0.45 μg/kg every week or 0.75 μg/kg every 2 weeks) maintained similar blood Hb levels in patients with CKD (18). In hemodialysis patients, once-monthly CERA was effective and well tolerated when used in routine clinical practice with lower intra-individual variability and fewer dose adaptations compared with other ESAs (19, 20). CERA was found to be as safe as conventional epoetins (11) and maintained stable Hb levels in dialysis patients converting directly from epoetin 1 to 3 times/week (10). Achieving tight Hb control with few dose adjustments at extended administration intervals may offer benefits for patients and resource management (10).

According to the regulations of the national health insurance program in Taiwan, an Hb level between 10 g/dL and 11 g/dL is the target for anemia correction in patients with CKD. ESA treatment should be stopped if Hb levels are beyond this range. Most patients reached this target with 100 μg CERA once monthly. However, there are 5 patients receiving subcutaneous CERA injections bimonthly with good response to CERA. Hb levels in these patients showed higher fluctuation during the evaluation period. Bi-monthly CERA combined with monthly short-acting ESA injection may be a good choice for these patients to decrease cost while maintaining stable Hb levels.

Our study has some limitations. Retrospective observation was used, and the results may be affected by certain confounders. The number of patients was small and may decrease the statistical power. The lack of a control group also lowers the reliability of our conclusion. However, strict inclusion criteria were employed to eliminate the confounder effect. GEE method was utilized to evaluate the correlation between monthly serum Hb levels and ESA treatment. There was no difference in Hb levels between darbepoetin alfa and CERA for the same administration period. Large-scale studies are needed to evaluate the long-term effects and safety of CERA in PD patients.

In conclusion, PD patients receiving regular darbepoetin alfa treatment could be safely switched to CERA injection of similar dosage levels at extended dose intervals. Reducing injection frequency offers significant advantages for both patients and healthcare workers. However, dosage titration is more difficult with CERA than with other short-acting ESAs. Oral administration of ESAs should be the goal of future drug development.

References


