

## EFFICACY AND SAFETY OF CONTINUOUS ERYTHROPOIETIN RECEPTOR ACTIVATOR (CERA) IN PATIENTS OF CHRONIC RENAL FAILURE WITH ANEMIA

H.K. AGGARWAL<sup>1</sup>, DEEPAK JAIN<sup>2</sup>, KAMAL VERMA<sup>3</sup>

<sup>1</sup>Sr. Professor & Head Med. IV, Division of Nephrology, <sup>2</sup>Assistant Professor, Medicine, <sup>3</sup>Resident, Medicine, Department of Medicine, Division of Nephrology, Pt. B.D. Sharma University of Health Sciences, Rohtak 124001, Haryana, India  
Email: jaindeepakdr@gmail.com

Received: 6 July 2011, Revised and Accepted: 16 Aug 2011

### ABSTRACT

**Introduction:** Continuous Erythropoietin Receptor Activator (CERA) is a new agent for treatment of anemia with extended administration interval in patients who have Chronic kidney disease (CKD). Preclinical and phase I and phase II studies have demonstrated that CERA has unique pharmacological properties, acting differently than Erythropoietin (Epoetin) at the erythropoietin receptor level, with long serum half life (134 hr after intravenous and 139 hr after subcutaneous administration) and low clearance. These half life values are considerably longer than those reported in healthy volunteers for epoetin alpha (6.8 hrs (iv) and 19.4 hrs (s.c.) and epoetin beta (8.8 h (iv) and 24.2 hr (sc) and upto 5 times longer than those reported for darbepoetin alpha. CERA is equally efficacious when given intravenously or subcutaneously.

**Material and methods:** It was a prospective study of six months duration which included 30 adult predialysis patients of chronic kidney disease with anemia. Each patient acted as his own control. After enrolment in the study, each patient was subjected to detailed physical examination and investigations. CERA was administered in a dose of 50 µg subcutaneously once every fortnightly for initial two months. Thereafter, CERA was administered once monthly for the next 4 months. Patients were followed up every fortnightly. Complete haemogram, Packed cell volume (PCV) and Renal Function Tests including GFR were carried out at each visit. Ferroketic studies were carried out at baseline and at the end of study.

**Results:** There was significant rise of hemoglobin concentration at 2 months i.e.  $11.04 \pm 0.34$  g/dl from base line  $8.94 \pm 0.53$  g/dl ( $p < 0.01$ ). Also when CERA was administered once monthly after initial fortnightly dosing, levels of Hb continued to be maintained at 4 months ( $10.90 \pm 0.37$  g/dl), & at 6 months ( $10.79 \pm 0.41$  g/dl) respectively which was statistically significant ( $p < 0.05$ ). Similarly there was significant rise in the PCV.

**Conclusions:** The observations of the present study reveal that there was a significant improvement in various hematological parameters in predialysis patients of CKD after administration of CERA. The haemoglobin cycling was not observed even after decreasing the frequency of administration of CERA.

**Keywords:** Erythropoietin receptor activator, CERA, CKD.

### INTRODUCTION

Anemia is an almost universal complication of Chronic kidney disease (CKD) and contributes considerably to the reduced quality of life in these patients. Renal anemia is typically normocytic normochromic. It is observed as early as stage 3 CKD and is almost universal by stage 4 CKD. Anemia of chronic kidney disease is primarily due to insufficient production of glycoprotein hormone erythropoietin<sup>1</sup>

Recombinant human erythropoietin (rHuEPO) has been the most important break through in treating anemia of CKD. Erythropoietin was approved by Food and Drug Administration (FDA) in 1989<sup>2,3</sup>. By the early to mid - 1990s, the majority of dialysis and nondialysis CKD patients with anaemia were receiving erythropoietin therapy. The benefits of erythropoietin therapy resonated among patients and providers alike: preventing blood transfusion, improving quality of life, improving survival and reducing cardiovascular complications including heart failure and Left ventricular hypertrophy (LVH).

Hemoglobin levels in individuals with chronic kidney disease fluctuate frequently above or below the recommended target levels within short periods of time even though calculated mean hemoglobin remains within the target range of 11 to 12g/dl. NKF - KDOQI working group reformulated its recommendations by stating that the Hb target in patients receiving Erythropoiesis stimulating agents (ESAs) should generally be 11-12g/dl and not >13g/dl because possibility of causing harm weighs more heavily than potential of improving the quality of life and decreasing transfusions.<sup>4</sup> Both pharmacologic features and dosing of erythropoiesis stimulating agents may lead to cyclic pattern of hemoglobin levels within the recommended range. As a consequence, patients may risk increased hospitalization and mortality, because both low and high hemoglobin levels are

associated with increased cardiovascular events and death. Hemoglobin variability (cycling) is the fluctuation of hemoglobin above or below the target range over time. Hence hemoglobin variability is the extent to which multiple measured hemoglobin values differ from each other within a given time span, whereas the calculated mean of all hemoglobin levels may still remain within the target range.<sup>5</sup> ESA therapy produces short, intermittent, nonbiologic burst of plasma erythropoietin availability. The result can be a rising and falling of hemoglobin in a cyclic pattern that varies from patient to patient. This is in contrast to untreated, healthy individuals, in which hemoglobin levels are maintained within a narrow range by close regulation of oxygen sensing, erythropoietin producing and erythropoietic system.<sup>6</sup>

Therefore the development of novel agent that corrects anemia effectively maintains stable Hb levels and allows less frequent administration may reduce the burden of anemia management for both patients and physicians. Continuous Erythropoietin Receptor Activator (CERA) is a new agent for treatment of anemia with extended administration interval in patients who have CKD.

CERA, a continuous erythropoietin receptor activator, is a novel agent that provides correction of anemia and stable control of Hb level at extended administration intervals.<sup>7</sup> Preclinical and phase I and phase II studies demonstrate that CERA has unique pharmacological properties, acting differently than Erythropoietin (Epoetin) at the erythropoietin receptor level,<sup>8</sup> with long serum half life (134 hr after iv and 139 hr after subcutaneous administration in patient) and low clearance.<sup>7-9</sup> These half life values are considerably longer than those reported in healthy volunteers for epoetin alpha (6.8 hrs (iv) and 19.4 hrs (s.c.) and epoetin beta (8.8 h (iv) and 24.2 hr (sc))<sup>10</sup> and upto 5 times longer than those reported for darbepoetin alpha.<sup>11</sup> CERA is equally efficacious when given intravenously or subcutaneously.

## MATERIAL AND METHODS

It was a prospective study which included 30 adult predialysis patients of chronic kidney disease with anemia, attending kidney and dialysis clinic at Pt. B.D. Sharma PGIMS, Rohtak. The patients were administered continuous erythropoietin receptor activator (CERA) as detailed below. The duration of study was for six months and was duly approved by institutional ethical committee. The following inclusion and exclusion criteria were taken.

### Inclusion criteria

1. Patient between 18-65 years of age
2. Chronic renal anaemia (Hb concentration 8.0 g/dl – 10.0 g/dl)
3. No prior erythropoiesis stimulating agent (ESA) therapy.

### Exclusion criteria

1. Uncontrolled hypertension (systolic blood pressure (SBP) 170mmHg or above) and diastolic blood pressure (DBP 100 mm Hg or above)
2. Significant acute or chronic bleeding
3. Active malignant disease
4. Congestive heart failure (NYHA IV)
5. Patients on maintenance dialysis

Each patient acted as his own control. Each patient was administered CERA in a dose of 50 µg subcutaneously once every fortnightly for initial two months. Thereafter, CERA was administered once monthly for the next 4 months. Each patient received iron, vitamin B12 and folic acid supplementation. Iron was administered in a dose of 100 mg (iron sucrose) in intravenous infusion (100ml normal saline) at each visit. The dose of Folic acid was 5mg/day and that of vitamin B12 was 1000 µg/day. Patients were followed every fortnightly and were evaluated for the adverse effects like hypertension; diarrhea; constipation; headache and peripheral edema and the following investigations were carried out at each visit i.e. complete haemogram including PCV, Reticulocyte count and Renal Function Tests including GFR. Ferrokinetic studies were carried out at baseline and at the end of study. Responses of improvement in Hematological parameters were seen in comparison with baseline parameters by using Student's t-test. Statistical significance was assumed at p value of less than 0.05.

## RESULTS

The mean age of patients were yrs. Majority of the patients (13) were between 40-59 years of age. 9 patients were in the age group 20-39 years and 8 patients were in the age group 60 and above. Among 30 patients, 17 were males and 13 were female patients. Most common cause of CKD in patients enrolled in our study was diabetes mellitus (12 patients) followed by Chronic

glomerulonephritis (10 patients), Hypertensive nephrosclerosis (5 patients) and Adult polycystic kidney disease (3 patients).

Average baseline hemoglobin concentration was  $8.94 \pm 0.53$  g/dl. Baseline packed cell volume was  $26.57 \pm 1.44\%$  and average reticulocyte count at the beginning of the study was  $1.72 \pm 0.84\%$ . Baseline serum creatinine was  $3.69 \pm 1.90$  mg% and average GFR was  $46.53 \pm 10.78$  ml/min at the beginning of study.

CERA showed significant effect on hemoglobin concentration as there was significant rise of hemoglobin concentration at 2 months i.e.  $11.04 \pm 0.34$  g/dl from baseline value of  $8.94 \pm 0.53$  g/dl ( $p < 0.01$ ). Also when CERA was administered once monthly after initial fortnightly dosing, levels of Hb continued to be maintained at 4 months ( $10.90 \pm 0.37$  g/dl), & at 6 months ( $10.79 \pm 0.41$  g/dl) respectively which was statistically significant as compared to baseline ( $p < 0.05$ ) (Table-1, fig.1). Similarly there was a significant rise in the packed cell volume. Average PCV at the beginning of the study was  $26.57 \pm 1.44\%$  which increased to  $33.23 \pm 2.61\%$  ( $p < 0.05$ ) at 2 months,  $32.71 \pm 1.28\%$  at 4 months and  $32.30 \pm 1.21\%$  at 6 months respectively ( $p < 0.05$ ) (Table-2).

Hemoglobin cycling which is very important phenomenon seen in case of other erythropoiesis stimulating agents was not seen with CERA. When CERA was administered once a month after 2 months of therapy, there was a slight decline in Hb and PCV. But this decline was found to be statistically nonsignificant ( $p > 0.05$ ). Thereby concluding that Hb levels were maintained at extended dosing schedule of CERA (fig. 2). The various ferrokinetic parameters i.e. serum iron, serum ferritin, transferrin saturation and total iron binding capacity (TIBC) remained largely unaltered during the study. Serum ferritin level at the beginning of study were  $128.72 \pm 47.87$  mg/l which however decreased to  $116.69 \pm 34.58$  mg/l at 6 months. This clearly demonstrate the enhanced erythropoiesis induced by CER (Table-3). Renal parameters were largely comparable at the baseline and at the end of study. Serum creatinine at the baseline was  $3.69 \pm 1.90$  mg% and at 2 months it was  $3.70 \pm 1.75$  mg%, at 4 months it was  $3.71 \pm 1.56$  mg% and serum creatinine levels at the end of 6 months was  $3.85 \pm 1.68$  mg% ( $p > 0.05$ ). Similarly there was non significant fall in GFR at the end of 6 months (Table-4). Thus administration of CERA was not associated with deterioration of renal function. The most common adverse event was hypertension noted in 3 patients (10%). Diarrhoea and peripheral edema was seen in 2 patients, 1 patient developed constipation but these were of mild intensity and there was no need to discontinue the therapy. Therefore the observations of the present study reveal that there was significant improvement in various hematological parameters of predialysis patients of CKD. The hemoglobin cycling was not observed even after decreasing the frequency of administration of CERA. There was no effect on various ferrokinetic parameters.

**Table 1: Hemoglobin Concentration (g/dl)**

	At baseline (a)	At 2 months (b)	At 4 months (c)	At 6 months (d)
Hb (g/dl)	$8.94 \pm 0.53$	$11.04 \pm 0.34$	$10.90 \pm 0.37$	$10.79 \pm 0.41$

b vs. a <0.01 (Highly Significant); c vs. a <0.05 (Significant); d vs. a <0.05 (Significant)

**Table 2: Packed Cell Volume**

	At baseline (a)	At 2 months (b)	At 4 months (c)	At 6 months (d)
PCV(%)	$26.57 \pm 1.44$	$33.23 \pm 2.61$	$32.71 \pm 1.28$	$32.30 \pm 1.21$

b vs. a <0.05 (Significant); c vs. a <0.05 (Significant); d vs. a <0.05 (Significant)

**Table 3: Ferrokinetic Studies**

Parameters	Baseline	At 6 months	P Value
Serum iron (µg/dl)	$85.48 \pm 24.59$	$96.20 \pm 22.70$	>0.05
Sr. ferritin (µg/l)	$128.72 \pm 47.87$	$116.69 \pm 34.58$	>0.05
TIBC(µg/dl)	$236.93 \pm 48.24$	$240.17 \pm 25.26$	>0.05
TSAT(% transferrin Saturation)	$23.84 \pm 3.88$	$21.58 \pm 2.73$	>0.05

Table 4: Renal Parameters

	At baseline (a)	At 2 months (b)	At 4 months (c)	At 6 months (d)
Serum Creatinine (mg%)	3.69±1.90	3.70±1.75	3.71±1.56	3.85±1.68
GFR (ml/min)	46.53±10.78	43.66±6.32	43.43±5.89	42.63±4.54

b vs. a >0.05; c vs. a >0.05; d vs. a >0.05

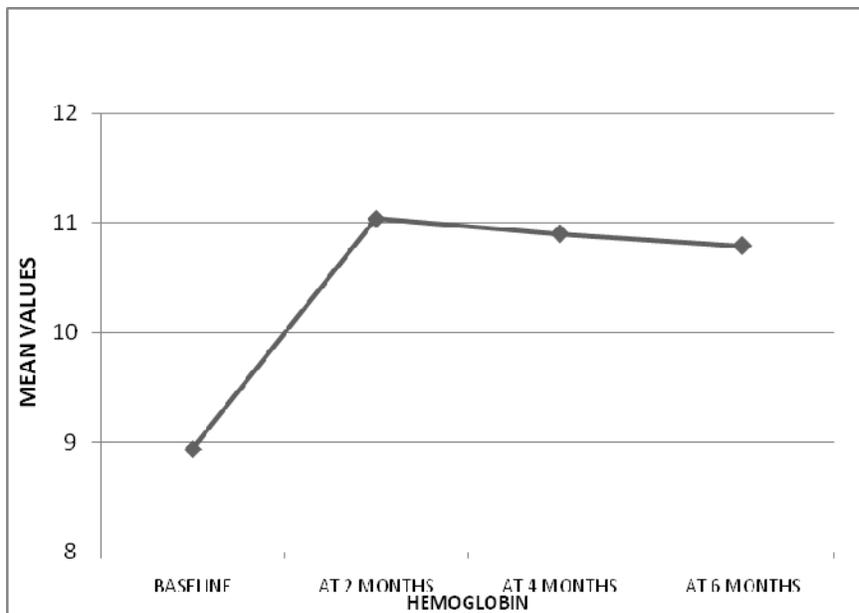


Fig. I: Showing Hemoglobin Concentration (g/dl)

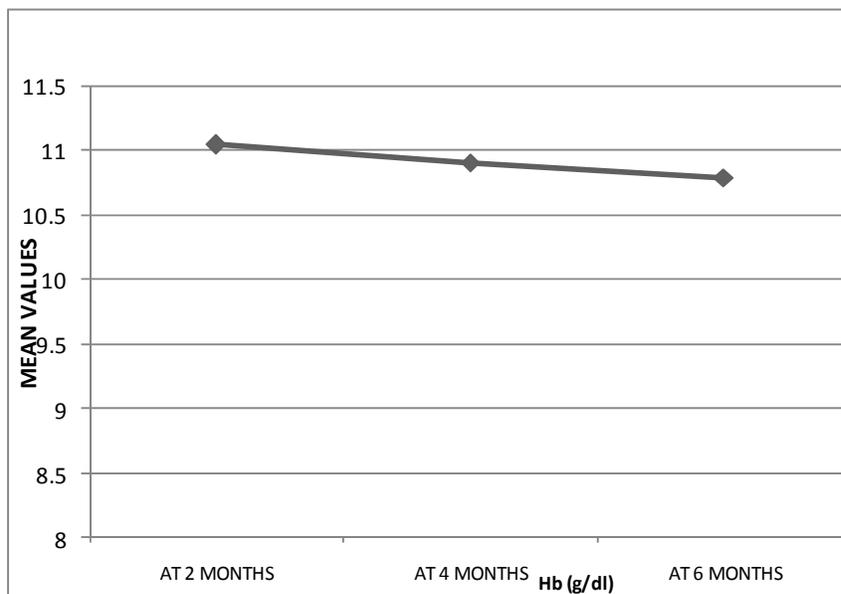


Fig. II: Showing Hemoglobin Cycling

**DISCUSSION**

Renal anemia drastically affects the patients at it results in symptoms such as fatigue, dyspnea and reduced mental acuity that degrades individual's overall performance and quality of life.<sup>1</sup> Anemia is associated more commonly with CKD stage 3 to 5 and is caused by relative deficiency of erythropoietin although reduced availability of iron and chronic inflammation are frequent contributing factors.<sup>12</sup> Other factors responsible for anemia in

chronic kidney disease are folic acid deficiency, aluminium toxicity; blood loss via repeated blood sampling, secondary hyperparathyroidism and uremic toxins.

Erythropoietin deficiency by far is the leading cause of anemia in patients with CKD. Erythropoietin is principal regulator of erythropoiesis and is mainly produced by renal tubular cells but also by liver in response to hypoxia<sup>13</sup>. Erythropoiesis stimulating agents (ESAs) have transformed the management of anemia over past 10 to

15 years producing benefits in terms of cognitive function, exercise capacity, quality of life for patients with CKD or cancer. Currently three different recombinant human erythropoietins (rHuEPOs) are in use. Epoetin alfa, epoetin beta and darbepoetin alfa. All these Epos are considered to have similar clinical efficacy.

In the present study baseline hemoglobin concentration was  $8.94 \pm 0.53$  g/dl. Our study showed that CERA had significant effect on hemoglobin concentration as evident by rise of hemoglobin at 2 months which was  $11.04 \pm 0.34$  g/dl ( $p < 0.01$ ). The average rise of Hb after 2 months of therapy was  $2.10$  g/dl ( $p < 0.01$ ). After 2 months when dosing interval of CERA was reduced to  $50 \mu\text{g}$  sc once monthly, the values of Hb measured at 4 months and 6 months were  $10.90 \pm 0.37$  g/dl and  $10.79 \pm 0.41$  g/dl respectively. At the end of study (6 months) average rise of Hb was  $1.85$  g/dl from baseline value which was statistically significant ( $p < 0.05$ ). Similar results were obtained for PCV. At the beginning, average packed cell volume (PCV) was  $26.57 \pm 1.44\%$  which showed significant increment after 2 months of therapy. At 2 month average PCV was  $33.23 \pm 2.61\%$  ( $p < 0.05$ ). When frequency of CERA was reduced to once monthly dosing, then mean PCV values at 4 months and 6 months were  $32.71 \pm 1.28\%$  and  $32.30 \pm 1.21\%$  respectively. At the end of study average rise of PCV was statistically significant compared to the baseline.

Klinger et al<sup>14</sup> showed that CERA once every 2 weeks was safe and effective for correction of anemia with greater than 90% of patients responding during 24 week treatment period i.e. 93% patients in CERA group, 91% patients receiving epoetin had at least 1g/dl rise in hemoglobin over baseline. Macdougall et al<sup>15</sup> demonstrated that anemia can be corrected in ESA naïve patients who have CKD and are not on dialysis with once every 2 weeks sc administration of CERA. Hemoglobin response rate in CERA group and darbapoetin alpha group were 97.5% and 96.35% respectively demonstrating that CERA once every two weeks was as effective as darbapoetin alpha once weekly for correction of anemia in predialysis patients with CKD. Canaud et al<sup>16</sup> demonstrated that patients receiving hemodialysis can be successfully converted to once fortnightly CERA from intravenous darbapoetin alfa maintenance therapy. In addition results confirm that simple dosing conversion scheme based on previous darbapoetin Alfa dose was effective in providing stable Hb maintenance. Patients successfully maintained mean Hb levels within 10.0-13.6 g/dl target range demonstrating noninferiority of CERA relative to darbapoetin alfa for Hb maintenance in patients receiving dialysis.

Both epoetin and darbapoetin require frequent dose adjustments to keep patients in the narrow therapeutic range. Despite frequent dose adjustments a sizeable percentage of patients are not able to get goal hemoglobin because patients regularly cycle from low hemoglobin to high hemoglobin. Longer dosing intervals may lead to less variability in hemoglobin levels over time by producing fewer peaks and troughs and thereby requiring fewer dosage adjustments. In the present study, we observed that when CERA was administered once monthly after 2 months of therapy, the Hb levels though declined slightly at 4 months to  $10.90 \pm 0.37$  g/dl and at 6 months to  $10.79 \pm 0.41$  g/dl respectively. But fall in Hb was not statistically significant in relation to values at 2 months and 4 months. Most of the time values remained in this target range. Similar results were obtained in case of PCV.

Sulowicz et al<sup>17</sup> showed that switching directly from administration of epoetin alpha or beta one to three times weekly to CERA at extended dosing intervals is effective for maintaining Hb levels within target range. Moreover mean Hb levels remained stable during evaluation and long term safety periods, demonstrating maintenance of Hb control over time. Fishbane et al<sup>18</sup> established that greater than 90% of patients experienced hemoglobin cycling with recombinant human erythropoietin therapy. The mean number of hemoglobin excursions were  $3.1 \pm 1.1$  per patient/year. The mean amplitude per hemoglobin excursions was  $2.51 \pm 0.089$  g/dl. It was most closely associated with frequent rHuEpo dose changes, hospitalisation and iron treatment practices.

In the present study most common adverse event with CERA was hypertension (3 patients) accounting for 10% of patients. However Hypertension was mild in nature and was well taken care. Hypertension has been associated with all ESAs. The mechanism of ESAs induced hypertension is thought to be related to stimulation of vascular endothelium by ESA resulting in increased circulating levels of endothelin. Furthermore the increase in hemoglobin associated with ESA therapy may increase blood viscosity resulting in vasospasm. Other adverse events like diarrhea (2 patients), constipation (1 patient) and peripheral edema (2 patients) were seen in this study but were of mild intensity. None of these side effects warranted withdrawal of treatment. Levin et al<sup>19</sup> concluded that adverse safety profile of intravenous methoxy polyethylene glycol epoetin beta was similar to that recorded for epoetin.

The growing number of patients with CKD and burden of managing this disease and its complications highlights the expected benefits of CERA. Moreover within the context of clinical practice there is a need to optimize the efficiency of anemia management. One approach to realizing such efficiency is to reduce the administration or frequency of ESAs. With CERA the time savings estimated to arise from reduction in administration frequency could represent an important benefit in clinical practice, facilitating greater efficacy of anemia management and enabling health care provider to devote more time to other aspects of patient care.

## REFERENCES

1. Macdougall IC, Eckardt KU. Anemia in chronic kidney disease. In: Fechalay J, Floege J, Johnson RJ, eds. Comprehensive clinical nephrology. 3<sup>rd</sup> ed. Philadelphia: Mosby Elsevier 2007. P. 853-60.
2. Beusterien KM, Nussenson AR, Port FK, Kelly M, Steinwald B, Ware JE Jr. The effect of recombinant human erythropoietin on functional health and well being in chronic dialysis patients. J Am Soc Nephrol 1996;7:763-73.
3. Revicki DA, Brown RE, Feeny DH, Henry D, Techan BP, Reidnick MR, et al. Health related quality of life associated with recombinant human erythropoietin therapy for predialysis chronic renal disease patients. Am J Kidney Dis 1995;25:548-54.
4. KDOQI clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease, 2007. Update of Hemoglobin target. Am J Kidney Dis 2007;50:471-530.
5. Brimble KS, Clase CM. Hemoglobin variability in dialysis patients. J Am Soc Nephrol 2007;18:2218-20.
6. Weiss G, Goodnoigh LT. Anemia of chronic disease. N Engl J Med 2005;352:1011-23.
7. Macdougall IC. CERA (continuous erythropoietin receptor activator): A new erythropoiesis - stimulating agent for treatment of anemia. Curr Hematol Rep 2005;4:436-40.
8. Brandt M, Lanzendorpr M, Frische J, Haselbeck A, Jarsch M. Different receptor binding activity of CERA (continuous erythropoietin receptor activator) compared with epoetin beta determined by surface Plasmon resonance and competition assay on UT-7 cells. Nephrol Dial Transplant 2006;21:1-9.
9. Macdougall IL, Robson R, Opatna S, Liogier X, Pannier A, Jordan P, et al. Pharmacokinetics and pharmacodynamics of intravenous and subcutaneous continuous erythropoietin receptor activator in patients with chronic kidney disease. Clin J Am Soc Nephrol 2006;1:1211-5.
10. Halstenon CE, Macres M, Katz SA, Schneiders JR, Watanabe M, Sobota JT, et al. Comparative pharmacokinetics and pharmacodynamics of epoetin alfa and epoetin beta. Clin Pharmacol Ther 1991;50:702-12.
11. Macdougall IC, Gray SJ, Elston O, Breen C, Jenkins B, Browne J, et al. Pharmacokinetics of novel erythropoietin stimulating protein compared with epoetin alfa in dialysis patients. J Am Soc Nephrol 1999;10:2392-5.
12. Oberador GT, Pereira BJ. Anemia of chronic kidney disease: an under recognised and undertreated problem. Nephrol Dial Transplant 2002;17:44-6.

13. Koury ST, Bondurant MC, Koury MJ. Localisation of erythropoietin synthesizing cells in murine kidneys by in situ hybridization. *Blood* 1988;71:524-7
14. Klinger M, Arias M, Vargemezis V. Efficacy of intravenous methoxy polyethylene glycol epoetin beta administered every two weeks compared with epoetin administered 3 times weekly in patients treated by hemodialysis or peritoneal dialysis. A randomized trial. *Am J Kidney Dis* 2007;50:989-1000.
15. Maccougall IC, Walker R, Provanzano R. CERA corrects anemia in patients with chronic kidney disease not on dialysis. Results of randomized clinical trial. *Clin J Am Soc Nephrol* 2008;3:337-47.
16. Canaud B, Mungardi G, Graun J, Aljama P, Locatelli F. Intravenous CERA maintains stable hemoglobin levels in patients on dialysis previously treated with darbapoetin alfa results from STRIATA randomized phase III study. *Nephrol Dial Transplant* 2008;23:3654-61.
17. Sulowicz W, Locatelli F, Rykelynck JP. Once monthly subcutaneous CERA maintains stable hemoglobin control in patients with chronic kidney disease on dialysis and converted directly from epoetin one to three times weekly. *Clin J Am Soc Nephrol* 2007;2:637-46.
18. Fishbane S, Berns JS. Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. *Kidney Int* 2005;68:1337-43.