
C.E.R.A. (Continuous Erythropoietin Receptor Activator): A new perspective in anaemia management

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Abstract

Continuous Erythropoietin Receptor Activator (C.E.R.A.), an innovative agent with unique receptor activity and a prolonged half-life, is currently in development to provide correction of anaemia and stable control of haemoglobin (Hb) levels at extended administration intervals in patients with chronic kidney disease (CKD) on dialysis and not on dialysis. Phase II studies suggest that C.E.R.A. can correct anaemia and maintain Hb levels when administered intravenously or subcutaneously at extended intervals of up to once monthly. C.E.R.A. is currently undergoing evaluation for the control of anaemia in patients with CKD in a large-scale Phase III programme.

Keywords: anaemia, chronic kidney disease, haemoglobin

Introduction

Chronic kidney disease (CKD) is highly prevalent, with increasing numbers of patients affected by the disease worldwide (1). The progressive nature of CKD and ensuing end-stage renal disease is associated with high and increasing treatment costs that are creating a significant burden on global healthcare resources (2). Forecasts indicate that the incidence of CKD is expected to continue rising (3,4), reflecting the growing incidence of diabetes and the ageing population (1).

Anaemia is already highly prevalent in the early stages of CKD (5–7) and is associated with increased mortality and morbidity (8–10). Evidence suggests that patients with CKD and anaemia progress more rapidly to dialysis than patients without anaemia (11,12). In addition, anaemia negatively impacts on cardiovascular disease (13,14), cognitive function (15) and quality of life (16,17).

National and international clinical guidelines exist to facilitate the management of anaemia in patients with CKD (18–21). A number of studies demonstrate that maintaining haemoglobin (Hb) levels within recommended targets is associated with positive clinical outcomes (10,22–25). Extrapolation of data from the Dialysis Outcomes and Practice Patterns Study estimated a potential gain of 23 910 patient-years in the US haemodialysis population over a 5-year period if patients were brought within Hb targets (≥ 11 g/dL) (24).

Challenges in anaemia management

Despite the proven benefits, management of renal anaemia remains suboptimal; anaemia is often under-recognised and under-treated (5,26). The use of erythropoiesis-stimulating agents (ESAs) before the initiation of dialysis is still uncommon in most countries (27,28) with many CKD patients only receiving treatment once anaemia is advanced. Furthermore, with current treatment, approximately two-thirds of patients with CKD have Hb levels outside guideline targets (29,30). In addition, substantial variability in Hb values over short periods of time has been demonstrated in many patients with CKD treated with ESAs (29,31–34). This variability in ESA response may be due to a range of factors, such as dialysis effects, intercurrent illness and iron therapy.

Effective management of anaemia is already time consuming, and the burden on healthcare providers can only increase as the prevalence of CKD continues to rise. Currently most available ESAs require frequent administration (up to three times per week) (19,20). Furthermore, frequent monitoring and dose adjustment is required to maintain Hb levels within guideline targets with current treatment. New agents that offer more effective anaemia management by providing stable Hb levels at extended administration intervals may reduce the burden on healthcare professionals.

C.E.R.A.

Continuous Erythropoietin Receptor Activator (C.E.R.A.), an innovative agent with unique receptor activity and a prolonged half-life, is currently in development to provide correction of anaemia and stable control of Hb levels at extended administration intervals in patients with CKD on dialysis and not on dialysis. C.E.R.A. is chemically synthesised, and differs from erythropoietin through the integration of amide bonds between amino groups and methoxy polyethylene glycol-succinimidyl butanoic acid (35).

Evidence is accumulating that C.E.R.A. has unique receptor properties, acting differently to epoetin at the receptor level (36). Data suggest that C.E.R.A. has a much lower affinity for the erythropoietin receptor compared with epoetin beta, leading to a reduced specific activity *in vitro*. However, since the elimination half-life is so prolonged, C.E.R.A. has increased erythropoietic activity *in vivo* (37).

Phase I studies in healthy subjects

Four Phase I studies have been conducted in healthy subjects to investigate the pharmacokinetic and pharmacodynamic properties of C.E.R.A. In two single ascending dose studies, subjects were randomised to receive single intravenous (IV) doses of C.E.R.A. (0.4–3.2 μ g/kg) or placebo (n=38) or

single subcutaneous (SC) doses of C.E.R.A. (0.1–3.2 µg/kg) or placebo (n=70) (38). In two multiple ascending dose studies, subjects were randomised to receive three IV doses of C.E.R.A. (0.4–3.2 µg/kg) or placebo (n=61) once every 3 weeks or four SC doses of C.E.R.A. (0.4–3.2 µg/kg) or placebo (n=48) once every 2 weeks (38). In the single ascending dose studies, a dose-dependent erythropoietic response was seen with both IV and SC C.E.R.A. administration. C.E.R.A. induced an increase in reticulocyte counts that peaked within 10 days and returned to baseline after 20 days. Consistent results were obtained in the multiple ascending dose studies: a dose-dependent erythropoietic response was observed with both routes of administration. The half-life for C.E.R.A. was observed to be considerably longer than those reported for currently available ESAs (Table 1) (39–42). In the multiple ascending dose studies, the clearance of both IV and SC C.E.R.A. was low (IV 27.6–44.6 ml/h; SC 97–347 ml/h) (41). The prolonged half-life and low clearance observed with C.E.R.A., together with its unique receptor activity, give rise to a different pharmacological profile compared with currently available ESAs and suggest that extended administration intervals are possible.

Table 1. Half-lives of C.E.R.A. and currently available erythropoietic stimulating agents in healthy volunteers (39–42)

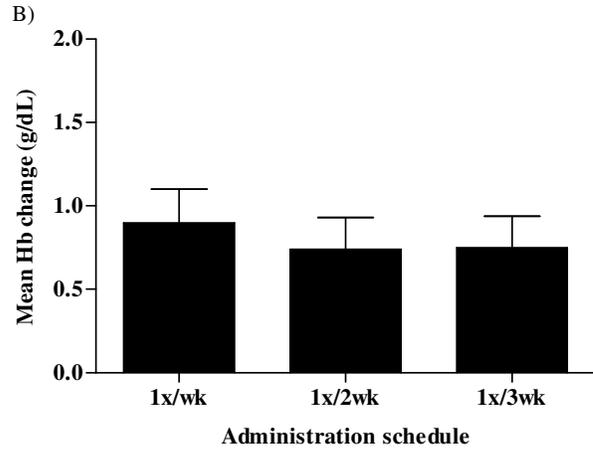
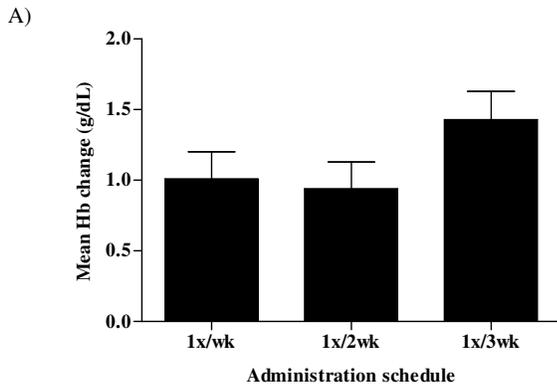
	Mean half-life (h)	
	IV	SC
C.E.R.A.	133	137
Epoetin alfa	6.8	19.4
Epoetin beta	8.8	24.2
Darbepoetin alfa	25.3	48.8

IV, intravenous; SC, subcutaneous.

Phase II studies in patients with CKD and anaemia

Four Phase II dose-finding studies have investigated the feasibility of C.E.R.A. for the correction of anaemia and maintenance of Hb levels at extended administration intervals in more than 350 patients with CKD.

Fig 1. Mean (±SEM) haemoglobin (Hb) change from baseline after 6 weeks’ treatment with C.E.R.A. in A) patients with chronic kidney disease receiving dialysis and B) patients with chronic kidney disease not receiving dialysis (35).



In two studies, one in CKD patients receiving dialysis (n=61) (43) and one in CKD patients not yet receiving dialysis (n=65) (44), SC C.E.R.A. was administered for the correction of anaemia. All patients were aged ≥18 years, with Hb 8–11 g/dL and were ESA-naïve. These studies examined escalating doses of C.E.R.A., with once-weekly, once every 2 weeks, and once every 3 weeks schedules being assessed in each dose group. Mean increases in Hb are shown in Figure 1. There was a significant dose response to C.E.R.A. and the Hb response was independent of the frequency of administration (43,44). These results suggest that C.E.R.A. is capable of correcting anaemia to guideline targets within the recommended timeframe when administered to ESA-naïve CKD patients at extended administration intervals.

Two Phase II, multicentre, dose-finding studies have been conducted to determine the efficacy of C.E.R.A. for the maintenance of Hb levels in adult patients with renal anaemia (Hb 10–13 g/dL) on dialysis. In one study, 91 haemodialysis patients previously maintained on three-times weekly IV epoetin alfa were switched to IV C.E.R.A. (45). After a 2-week run-in period, patients were randomised to one of three C.E.R.A. doses based on their previous epoetin dose and data on exposure to C.E.R.A. from healthy subjects; once-weekly and once every 2 weeks administration schedules were assessed in each dose group for 19 weeks. A significant ($P<0.0001$) dose-dependent Hb response was observed.

In the second maintenance study, 137 dialysis patients previously maintained on once to three-times weekly SC epoetin treatment were switched to SC C.E.R.A. (46). After a 2-week run-in period, patients were randomised to one of three C.E.R.A. doses based on their previous epoetin dose and data on exposure to C.E.R.A. from healthy subjects; once-weekly, once every 3 weeks and once monthly administration schedules were assessed in each dose group. Patients were followed for a total of 19 weeks; those in the once monthly group were followed for 21 weeks. There was a significant ($P<0.001$) dose-dependent response to C.E.R.A. in the three treatment groups that was independent of the frequency of administration. The results suggest that SC C.E.R.A. administered up to once monthly may maintain stable Hb levels in dialysis patients.

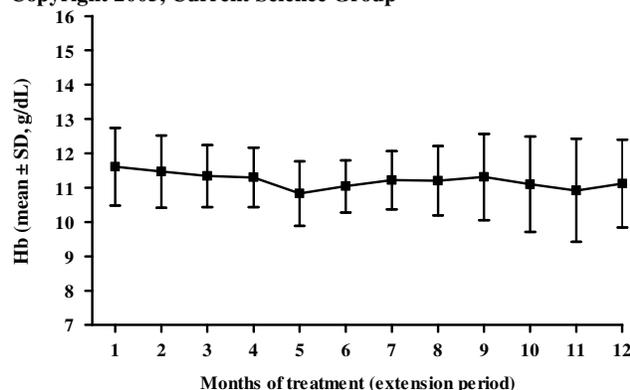
A 12-month extension period followed the core period of both maintenance studies, which aimed to maintain Hb levels in the range 11–12 g/dL (47,48). C.E.R.A. maintained stable Hb levels at extended administration intervals over the 12-

month period (Figure 2); mean Hb levels over time were 11.51 g/dL (95% confidence interval (CI): 11.31, 11.71), 11.18 g/dL (95% CI: 10.91, 11.46) and 11.15 g/dL (95% CI: 10.91, 11.39) for once every 2 weeks, once every 3 weeks and once monthly administration schedules, respectively (47,48). Data from these long-term extension studies indicate that C.E.R.A. can control anaemia when administered at extended intervals, maintaining sustained and stable Hb levels in dialysis patients.

A large-scale Phase III programme is underway evaluating the efficacy and safety of C.E.R.A. in approximately 2400 patients with CKD on dialysis and not on dialysis from 29 countries.

Fig 2. Mean (\pm SD) haemoglobin (Hb) over time following once monthly subcutaneous administration of C.E.R.A.

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Tolerability

C.E.R.A. was generally well tolerated in healthy volunteers (38,49). Similarly, in patients with CKD, C.E.R.A. was generally well tolerated with no unexpected safety concerns. Available information indicates that the incidence of adverse events (AEs) was in accordance with that expected for this study population (50). The most frequent AEs in the two 12-month maintenance study extension periods (n=109) were hypotension and muscle cramp (8.05% and 4.39% of all AE episodes, respectively) (50). The most common serious AEs were hypotension (five events), myocardial infarction (five events), cellulitis (four events) and pancreatitis (four events). In all studies conducted to date (healthy volunteers and patients with CKD), there has been no evidence of antibody development in any patient treated with C.E.R.A.

Conclusions

C.E.R.A.'s pharmacokinetic properties, including a prolonged half-life and low clearance, together with its unique receptor binding properties, result in a different pharmacological profile compared with currently available ESAs and suggest that extended administration intervals are feasible. Phase II studies in patients with CKD suggest that C.E.R.A. can correct anaemia and maintain Hb levels at extended intervals of up to once monthly. C.E.R.A. is currently undergoing evaluation for the management of anaemia in patients with CKD in a large-scale Phase III programme, with preliminary results expected soon. The potential for C.E.R.A. to be

administered at extended administration intervals may simplify anaemia management, reducing the burden for patients and healthcare professionals.

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