EXHIBIT 7

CERA (Continuous Erythropoietin Receptor Activator): A New Erythropoiesis-Stimulating Agent for the Treatment of Anemia

Iain C. Macdougall, BSc, MD, FRCP

Address
Department of Renal Medicine, King's College Hospital, Denmark Hill, London SE5 9RS, UK
E-mail: Iain.macdougall@kingsch.nhs.uk

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Anemia is a common and debilitating condition in patients with chronic kidney disease and patients with cancer. Over the last 10 to 15 years, the introduction of erythropoietic therapy has transformed the management of anemia in both these conditions. The first therapeutic agent to be used for the stimulation of erythropoiesis was recombinant human erythropoietin (epoetin). At the turn of this century, darbepoetin alfa, a second-generation erythropoietic agent, became available. Darbepoetin alfa contains two additional N-linked carbohydrate chains, which confer greater metabolic stability in vivo. More recently, a third-generation molecule, Continuous Erythropoietin Receptor Activator (CERA), incorporating a large polymer chain, has been developed. CERA has an elimination half-life in humans that is considerably longer than the half-life of either epoetin or darbepoetin alfa. CERA may also have different receptor binding characteristics and pharmacology from other erythropoietic agents; these characteristics are the subject of ongoing investigation. CERA is currently in phase III clinical trials.

Introduction

Anemia occurs frequently in patients with chronic kidney disease (CKD) and also in patients with cancer, particularly those receiving chemotherapy or radiotherapy. Among other symptoms, anemia is typically associated with poor concentration, loss of cognitive function, and debilitating fatigue, which have a substantial negative impact on health-related quality of life. In addition, anemia is associated with an increased risk of cardiovascular disease and mortality in patients with CKD [1]. If not treated adequately, anemia can adversely affect clinical outcomes. A growing body of evidence suggests that patients with early CKD and anemia progress more rapidly to end-stage renal failure than patients without anemia or patients who receive treatment for the correction of anemia [2,3]. Similarly, patients with cancer and anemia have poorer local tumor control and worse survival rates than their nonanemic counterparts [4].

Erythropoiesis-stimulating agents (ESAs) have transformed the management of anemia over the past 10 to 15 years, producing benefits in terms of cognitive function, exercise capacity, and quality of life for patients with CKD or cancer. In patients with CKD, correction of anemia has been shown to have a positive impact on cardiovascular disease [3], specifically leading to regression of left ventricular hypertrophy [5,6]. Furthermore, correction of anemia with ESAs may also slow the progression of CKD [7]. There is also some evidence that treatment of cancer-related anemia with ESAs may improve the response to chemotherapy, local tumor control, and survival [8,9].

The first ESAs were recombinant human erythropoietin (epoetin alfa and beta), which could be administered either intravenously (IV) or subcutaneously (SC), and were generally given two or three times a week. The frequency of administration was dictated partly by the short biologic half-life of these products—about 6 to 8 hours following a single IV injection [10].

Around the turn of this century, darbepoetin alfa, a second-generation ESA, became available for the treatment of anemia. This new molecule was created by the addition of two extra N-linked carbohydrate chains, increasing the total number of sialic acid residues and conferring additional metabolic stability on the molecule [11]. Thus, the elimination half-life of IV darbepoetin alfa in humans was three times longer than that of standard epoetin [11].

Even more recently, a third-generation erythropoietic molecule, Continuous Erythropoietin Receptor Activator (CERA), was created by integrating a large polymer chain into the molecule, thus increasing the molecular weight to twice that of epoetin at approximately 60 kDa. This methoxy-polyethylene glycol polymer chain is integrated via amide bonds between the N-terminal amino group or the ε-amino group of lysine (predominantly lysine-52 or lysine-45), using a single succinimidyl butanoic acid linker.

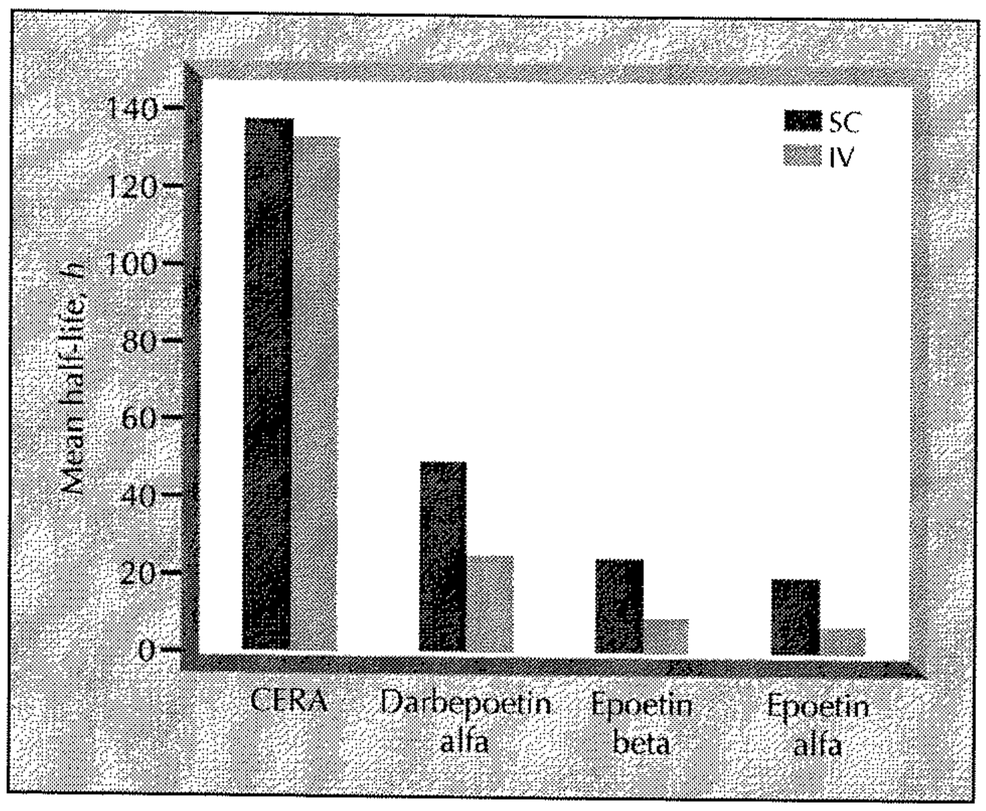

Figure 1. Mean half-lives of erythropoiesis-stimulating agents: Continuous Erythropoietin Receptor Activator (CERA) [15], darbepoetin alfa [11], epoetin beta, and epoetin alfa [10]. IV—intravenous; SC—subcutaneous.

Evidence is accumulating that CERA has very different receptor binding characteristics and pharmacokinetic properties from either epoetin or darbepoetin alfa [12]. It has a much lower affinity for the erythropoietin receptor compared with the natural ligand, leading to a reduced specific activity in vitro. Because the elimination half-life is so prolonged, however, CERA has increased erythropoietic activity in vivo.

As with all therapeutic products, investigations were conducted in cell lines and animals before being performed on humans. The aim of this article is to review the preclinical studies that were conducted in cell lines and animal models, and then to discuss the phase I, II, and III clinical studies that have been reported to date. Much of this work is very recent and has not yet been published in peer-reviewed journals; as a result, most of the references are abstracts published in relation to international meetings.

Effects of CERA In Vitro and in Animal Models

The erythropoietic activities of CERA and epoetin have been compared in vitro by measuring their effect on the proliferation of a human acute myeloid leukemia cell line (UT-7) that expresses the erythropoietin receptor. Across the dose range 0.003 to 3 U/mL, epoetin stimulated greater proliferation of UT-7 cells than did CERA [13••]. However, in vivo studies in normocythemic mice comparing identical amounts of protein across the dose range 60 to 1000 ng of protein per animal have shown that CERA was more effective than epoetin at stimulating bone marrow precursor cells and increasing reticulocyte count [13••]. At a dose of 1000 ng, CERA increased the mean reticulocyte count by 14%, compared with 9% with epoetin.

Preclinical studies in various animal models have investigated the pharmacodynamic and pharmacokinetic properties of CERA administered IV and SC in both single and multiple doses, across the dose range 0.75 to 20 µg/kg. In mice, a single SC injection of CERA 20 µg/kg increased the mean reticulocyte count by 13%, compared with 7.8% in response to a comparable dose of epoetin beta [14••]. The median duration of the response was approximately 3 days longer with CERA than with epoetin. In addition, a single IV or SC administration of CERA 2.5 µg/kg in mice elicited a greater reticulocyte response in terms of the magnitude and duration of response than multiple doses of epoetin 2.5 µg/kg. Further studies in mice showed that SC administration of CERA once weekly (1.25 µg/kg and 5 µg/kg) or once every 2 weeks (5 µg/kg) produced a greater reticulocyte response than epoetin 1.25 µg/kg administered three times per week [14••]. Moreover, approximately equal numbers of reticulocytes were produced with CERA 1.25 µg/kg administered once every 2 weeks as with epoetin 1.25 µg/kg administered three times weekly. Pharmacokinetic studies in animals showed that CERA has a longer half-life and lower systemic clearance than epoetin [12].

From the results of these preclinical studies, it appears that CERA has receptor binding and pharmacokinetic properties that give rise to more potent stimulation of erythropoiesis in vivo than epoetin, with regard to both the magnitude and duration of response. These findings suggested the potential for CERA to be administered at extended dosing intervals.

Effects of CERA in Healthy Subjects

Four phase I studies have been conducted in healthy subjects to investigate the pharmacokinetic and pharmacodynamic properties of CERA. In two single-ascending-dose studies, subjects were randomized to receive single IV doses (0.4–3.2 µg/kg) of CERA or placebo (n = 38) or single SC doses (0.1–3.2 µg/kg) of CERA or placebo (n = 70) [15]. In two multiple-ascending-dose (MAD) studies, subjects were randomized to receive three IV doses of CERA (0.4–3.2 µg/kg) or placebo once every 3 weeks (n = 61) or four SC doses of CERA (0.4–3.2 µg/kg) or placebo once every 2 weeks (n = 48) [16]. The half-life of CERA administered IV or SC was observed to be considerably longer than that previously reported for epoetin (alfa or beta) [10] or darbepoetin alfa [11] (Figure 1). The pharmacokinetics of CERA were apparently unaffected by repeated dosing.

In the MAD studies, the clearance of both IV and SC CERA was low (IV, 27.6–44.6 mL/h; SC, 97–347 mL/h) [16]. No accumulation was observed when steady-state was achieved with the different frequencies tested. The prolonged half-life and low clearance seen with both IV and SC CERA in healthy subjects support the data from animal studies, suggesting that it might be possible to administer CERA at extended dosing intervals.

Effects of CERA in Patients with Anemia

Patients with chronic kidney disease

Four phase II dose-finding studies have investigated the feasibility of CERA for the correction of anemia and the

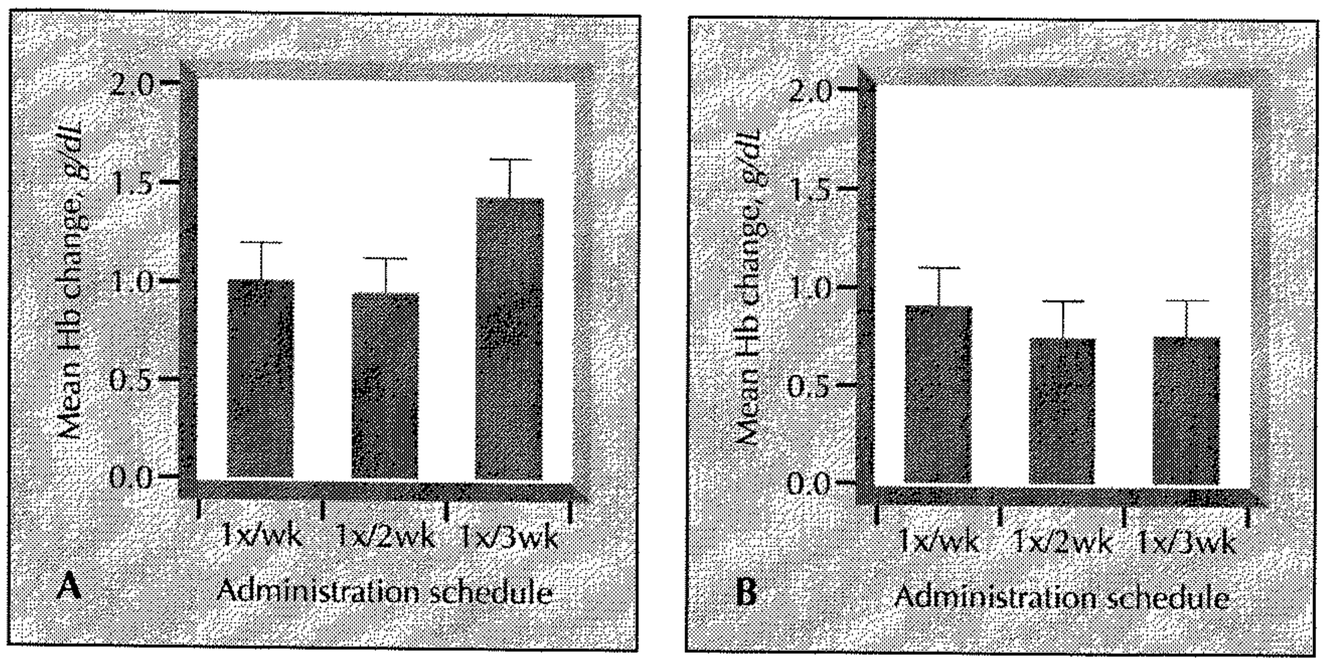

Figure 2. Mean (± SEM) hemoglobin (Hb) change from baseline after 6 weeks of treatment with Continuous Erythropoietin Receptor Activator (CERA) in (*A*) patients with chronic kidney disease receiving dialysis and (*B*) similar patients not receiving dialysis. Data were taken from the per-protocol populations of two separate multicenter studies, not yet published.

maintenance of hemoglobin (Hb) levels at extended administration intervals in more than 350 patients with CKD. In two studies, one in CKD patients receiving dialysis (n = 61) [17] and one in CKD patients not yet receiving dialysis (n = 65) [18••], SC CERA was administered for the correction of anemia. All patients were at least 18 years of age, with Hb 8 to 11 g/dL. None had been previously given an ESA.

The first study, conducted in patients receiving dialysis treatment, examined escalating doses of CERA in three patient groups [17]. After a 4-week run-in period, patients were randomized to receive one of three CERA doses (0.15, 0.30, or 0.45 µg/kg per week). Administration schedules of once per week, once every 2 weeks, and once every 3 weeks were assessed in each dose group. The second study, conducted in patients not receiving dialysis, also investigated escalating doses of CERA in three patient groups [18••]. After a 2-week run-in period, patients were randomized to receive one of three CERA doses (0.15, 0.30, or 0.60 µg/kg per week). Again, administration schedules of once per week, once every 2 weeks, and once every 3 weeks were assessed in each dose group. In both studies, individual dose adjustments were permitted according to defined Hb criteria after the initial 6-week period. Patients receiving dialysis were followed for 12 weeks and patients not receiving dialysis were followed for 18 weeks.

In these studies, the dose response to CERA treatment was statistically significant. Mean increases in Hb observed after 6 weeks of CERA treatment for both dialysis and non-dialysis patients are shown in Figure 2. In both studies, the Hb response was independent of the frequency of administration. These results suggest that CERA is capable of correcting anemia when administered to ESA-naive CKD patients at extended dosing intervals.

Two phase II, multicenter, dose-finding studies have been conducted to determine the efficacy of CERA for the maintenance of Hb levels in adult patients with CKD and anemia (Hb 10–13 g/dL) who are receiving dialysis treatment. In one study, 91 patients previously maintained on IV epoetin alfa given three times per week were switched to IV CERA [19]. After a 2-week run-in period, patients were randomized to one of three CERA doses based on their previous epoetin dose and data on exposure to CERA in healthy subjects. Administration schedules of once per week and once every 2 weeks were assessed in each dose group. Patients were followed for 19 weeks.

A statistically significant ($P < .0001$) dose-dependent Hb response was observed. At the highest dose studied, IV CERA maintained stable Hb levels within ± 1.5 g/dL from baseline in the highest percentage of patients when administered once every 2 weeks. These results suggest that IV CERA administered once every 2 weeks may maintain stable Hb levels in dialysis patients.

In the second maintenance study, 137 patients previously maintained on three-times-weekly SC epoetin treatment were switched to SC CERA [20••]. After a 2-week run-in period, patients were randomized to one of three CERA doses based on their previous epoetin dose and data on exposure to CERA from healthy subjects. Administration schedules of once per week, once every 3 weeks, and once every 4 weeks were assessed in each dose group. Patients were followed for at least 19 weeks; those given CERA every 4 weeks were followed for 21 weeks.

There was a statistically significant ($P < .001$) dose-dependent response to CERA in the three treatment groups, which was independent of the frequency of administration (up to once every 4 weeks). The results suggest that SC CERA administered once every 4 weeks may maintain stable Hb levels in dialysis patients.

Patients with cancer

A phase II dose-escalation study of CERA has been conducted in 64 adult patients with multiple myeloma and anemia (≤11 g/dL) [21••]. Groups of 8 to 10 patients received SC CERA once every 3 weeks for a core period of 6 weeks, with an optional 12-week extension period. Initially, patients were randomized to receive CERA at a dose of 2.0, 3.5, or 5.0 µg/kg. Following a review of the efficacy and safety data, additional patients were assigned sequentially to CERA 6.5 and 1.0 µg/kg, then 8.0 and 4.2 µg/kg. The results suggest that CERA produces a dose-dependent erythropoietic response at doses up to 4.2 µg/kg in patients with multiple myeloma.

Safety and Tolerability of CERA

In the studies reported to date for patients with CKD, CERA has generally been well tolerated, with no unexpected safety concerns. Available information indicates that the incidence of adverse events was in accordance with that expected for this study population [22]. Similarly, in the phase II study conducted in patients with multiple myeloma, adverse events were rare (four hypertension, one pyrexia) during the core study period [21••]. There has been no evidence of antibody development in any patient treated with CERA.

Conclusions

The advent of ESAs has revolutionized the treatment of anemia, leading to significant improvements in quality of life for patients with CKD or cancer. In addition, correction of anemia in CKD patients may slow disease progression [7]. Nevertheless, the development of anemia is frequently unrecognized, particularly in the early stages of CKD [23].

The existing products for the treatment of anemia, although highly effective, have a number of disadvantages. Among these is a need for fairly frequent injections (one to three times weekly) in the majority of patients. Recombinant human erythropoietin (epoetin), the original erythropoietic therapy, has a relatively short half-life and, although some studies have suggested that once-weekly administration is possible in certain selected patients [24–27], most patients with CKD receive this drug two or three times per week. Indeed, a recent study from Poland suggests that some patients who are stable on a regimen of weekly epoetin beta can be switched to epoetin beta once every other week [28].

Most of the studies conducted with darbepoetin alfa to date have focused on showing that this agent is effective as a once-weekly therapy in nearly all CKD patients. In patients stable on once-weekly administration, administration every other week is possible. Patients receiving once-weekly epoetin maintenance therapy can be switched to administration of darbepoetin alfa once every alternate week [29,30]. Two studies with darbepoetin alfa also explored the possibility of maintaining Hb levels in dialysis and predialysis patients with monthly administration [31,32], but the patient population in these studies was highly selected.

Many chemotherapeutic regimens for cancer are administered once every 3 or 4 weeks, so a longer-acting erythropoietic agent might allow better synchronization of erythropoietic therapy with chemotherapy in patients with cancer-related anemia. At the present time, epoetin beta and darbepoetin alfa are approved for once-weekly administration in patients with cancer-related anemia. Epoetin alfa has generally been administered three times weekly, although recent studies have shown that a weekly dose is effective in correcting and maintaining Hb levels in patients with cancer [33–35]. Studies with darbepoetin alfa have explored the possibility of extending the administration interval to once every other week [36] or once every 3 weeks [37] in patients with chemotherapy-induced anemia.

The pharmacokinetic data in both animals and humans confirm that CERA has a much longer half-life than epoetin or darbepoetin alfa. It thus has the potential to correct anemia and maintain Hb levels at extended administration intervals in patients with CKD or cancer. Studies in healthy subjects have shown that CERA elicits a dose-dependent erythropoietic response at extended administration intervals. Clinical studies have shown that CERA can be administrated at extended intervals (once every 3 weeks and once every 4 weeks) for the treatment of anemia in patients with CKD or cancer [17,18••,20••,21••]. CERA was generally well tolerated in these studies and there were no unexpected safety concerns. Like its predecessors, CERA contains a protein moiety, and thus there is a potential for immunogenicity. Integration of a polymer chain, however, may reduce these risks; to date there have been no reports of antibody formation in humans.

The potential for CERA to be administered at extended intervals may reduce the burden of anemia management for patients and health care providers. For example, CKD patients not yet on dialysis may prefer to self-administer their anemia therapy at monthly intervals (if possible), and oncologists may prefer to synchronize erythropoietic therapy with a patient's chemotherapy regimen. Further studies are of course required to determine the ability of CERA to offer these advantages of extended administration intervals, and these are ongoing.

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- •• Of major importance

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