

ORIGINAL ARTICLE

A Single Arm, Prospective, Open Label, Multicentre Study for Evaluation of Efficacy and Safety of IV CERA for Treatment of Chronic Renal Anaemia in Dialysis Patients not Currently Treated with ESA

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Abstract

Introduction: CERA, a continuous erythropoietin receptor activator, has reported effective correction of anaemia in international clinical trials.

Objective: Objective of this study was to evaluate efficacy and safety of CERA in Indian patients who were on dialysis and has not received erythropoiesis stimulating agent (ESA) therapy in last 8 weeks. .

Methods: In this open label, single arm, prospective, multi-centre study, 189 patients on dialysis, having Haemoglobin (Hb) between 8 – 10 g/dL and not receiving any ESA for last 8 weeks were included at 14 centers across India. CERA was given intravenous (IV) at the dose of 0.6 µg/kg every two weeks. Primary end point of the study was mean change in Hb concentration from baseline to end of the treatment period (TP) of 16 weeks.

Results: Mean change of Hb from baseline to end of TP was 2.11 ± 1.37 g/dL and 2.08 ± 1.29 g/dL in intent to treat (ITT) and per protocol (PP) population respectively. Mean time to achieve Hb response was 6.10 ± 3.87 weeks and 6.16 ± 3.92 weeks in ITT and PP populations respectively. Out of 68 adverse events (AEs) seen during study period, 33 were serious adverse events (SAEs). As per investigators all SAEs were related to underlying disease and not to the study medication.

Conclusion: It is concluded that CERA administered once in two weeks in dialysis patients effectively corrected chronic kidney disease (CKD) related anaemia and was well tolerated with no significant untoward effect directly related to drug therapy in Indian population.

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Received: 12.12.2012; Revised: 25.01.2013; Re-revised: 12.04.2013; Accepted: 02.07.2013

Introduction

Anaemia is a common complication of CKD that results primarily from inadequate erythropoietin production by damaged kidney.¹ Anaemia is associated with an increased risk of morbidity, mortality, hospitalisation and diminished physical well-being,

quality of life.²⁻⁴ The use of erythropoiesis-stimulating agents (ESAs) for management of renal anaemia relieves the symptoms of anaemia and is associated with improvements in quality of life.^{4,5} However, because of short half-lives of ESAs (Epoetin alpha and beta ~ seven-nine hours, darbepoetin alpha ~ 25 hours) frequent administration is required (three times to once weekly). One of the reasons for fluctuations of haemoglobin (Hb) levels is short half-life of ESAs.^{6,7} Dosing interval of ESAs with short half-life may contribute to the problem of Hb cycling.⁸

Thus, Maintaining Hb levels within target ranges requires close monitoring of Hb and often requires frequent dosage adjustment of ESAs. Hence, maintaining Hb levels may be time consuming and may burden renal units, which already have to cope up with growing incidence and prevalence of CKD.⁹ Consequently, there is need of agents with extended dosing interval to provide predictable and stable Hb responses with minimal intervention from health care professionals.

CERA, a continuous erythropoietin receptor activator, differs from other epoetins through integration of an amide bond between N-terminal amino group and methoxy polyethylene glycol butanoic acid. Molecular weight of CERA is approximately twice that of erythropoietin.¹⁰ CERA shows an interaction with erythropoietin receptor that is different from that of epoetin. Its reduced affinity for the receptor and longer interaction in the receptor environment allows continuous stimulation of erythropoiesis.¹¹ CERA has longest half-life amongst currently available ESAs in India, making it possible to achieve smooth and steady Hb correction and stable maintenance at extended intervals.¹²⁻¹⁷

International clinical trials have proven efficacy and safety of CERA.¹²⁻¹⁷ This study was done to generate the data of efficacy and safety of CERA in Indian patients.

Subjects and Methods

Subjects

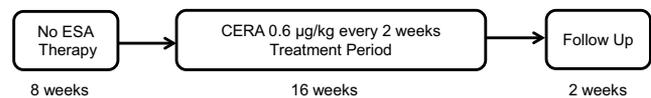
Patients greater than 18 years of age with chronic renal anaemia and who were on haemodialysis or peritoneal dialysis therapy with the same mode of dialysis for at least previous 4 weeks were recruited in the study. Patients on dialysis were required to have Hb level between 8 - 10 g/dL and should not have received any ESA therapy in previous 8 weeks. One of the pre-requisite was to have adequate iron status (serum ferritin >100 ng/mL and TSAT > 20% or hypochromic red cells < 10%). Patients who had blood transfusion in last 4 weeks, uncorrected folic acid or vit B₁₂ deficiency in last 8 weeks, cardiovascular event in last 12 weeks and epileptic seizure in last 24 weeks

were excluded from the study. Other exclusion criteria were poorly controlled hypertension, significant acute or chronic bleeding, active malignant disease (except non-melanoma skin cancer), history of haemolysis, history of haemoglobinopathies, platelet count > 500 × 10⁹/L or < 100 × 10⁹/L, history of pure red cell aplasia and pregnancy or lactation period

The study was conducted in accordance with Good Clinical Practice guidelines, schedule Y and was approved by institutional/independent ethics committees. All patients provided written, informed consent prior to screening.

Study design and Drug

This was a single arm, open label, multi-centre, prospective study to evaluate efficacy and safety of CERA (MIRCERA; F-Hoffman-La-Roche) for correction of Hb level in dialysis patients with chronic renal anaemia. Patients who did not receive any ESA therapy in last eight weeks were screened and entered the 16 week treatment period. CERA was administered at the dose of 0.6 µg/kg every two weeks during the treatment period. After completion of treatment period, follow up was done for two weeks.



Assessments

Patients were assessed at baseline/screening (week 0) and then every two weeks during the treatment period. Hb, BP, and heart rate were measured at each visit. Iron and other laboratory parameters were measured at screening/baseline, 4 weeks, 10 weeks and 16 weeks. Electrocardiograms (ECG) were performed at screening/baseline and at week 16. It was decided to perform anti-EPO antibody testing only if clinically indicated.

Efficacy and safety evaluation

Primary efficacy parameter was to measure mean change in Hb concentration (g/dL) from baseline (week 0) to last visit (week 16) of the treatment period (TP). Secondary efficacy parameters were time to achievement of response (achievement of Hb levels within target range i.e. 10.0- 12.0 g/dL), percentage of patients whose average Hb concentration was within the range of 10.0- 12.0 g/dL in the last four weeks of TP. Safety was assessed by evaluating adverse events (AEs), serious adverse events (SAEs) at every visit from week 0 to week 18.

Statistical Analysis

Mean change in Hb concentration (g/dL) was analysed using paired t-test to determine a significant difference from baseline to the subsequent visits at 5% level of significance. Time to achievement of response was analysed using descriptive statistics.

Table 1 : Total adverse events

Adverse Events as per SOC	n (%)
General disorders and administration site conditions	18 (9.52)
Infections and infestations	10 (5.29)
Cardiac disorders	7 (3.70)
Gastrointestinal disorders	7 (3.70)
Vascular disorders	5 (2.65)
Metabolism and nutrition disorders	5 (2.65)
Musculoskeletal and connective tissue disorders	3 (1.59)
Investigations	3 (1.59)
Injury, poisoning and procedural complications	2 (1.06)
Respiratory, thoracic and mediastinal disorders	2 (1.06)
Surgical and medical procedures	2 (1.06)
Psychiatric disorders	1 (0.53)
Renal and urinary disorders	1 (0.53)
Blood and lymphatic system disorders	1 (0.53)
Ear and labyrinth disorders	1 (0.53)
Total	68

SOC: system organ class

The percentage of patients whose average Hb concentration was within the range 10.0- 12.0 g/dL in the last four weeks of TP was summarised using frequencies, relative frequencies and 95% confidence interval. Safety information was summarised using frequencies and relative frequencies by preferred term and system organ class and was tabulated according to severity and relationship to study drug. Descriptive statistics was presented as "n", mean, standard deviation, median, maximum, minimum, 95 percent confidence interval of the mean. All variables were analysed for intent to treat (ITT: patients receiving at least one dose of CERA) and per protocol (PP: patients completing study as per protocol) populations.

Results

Patient characteristics

The study was carried out at 14 centers in India. Study began in July 2008 and completed in October 2009. Across 14 centres, 189 patients were enrolled in the study out of which 31 patients were withdrawn. Two patients were withdrawn due to adverse event; eight patients died during the study; six patients were withdrawn due to blood transfusion; five patients were withdrawn due to refused treatment/ did not cooperate/ withdrew consent and other reasons; four patients were withdrawn due to failure to return and one patient violated the protocol. ITT population comprised of 189 patients and PP population 157 patients.

Out of 189 enrolled patients, 139 (73.54%) were male and 50 (26.46%) were female. Mean age and weight of study population was 49.74 ± 14.01 years and 58.8 ± 11.6 kgs respectively. Mean haemoglobin, serum iron and TSAT at baseline was 8.8 ± 0.7 g/dL, 91.7 ± 53.4 ($\mu\text{g/dL}$) and 40.4 ± 27.9 % respectively.

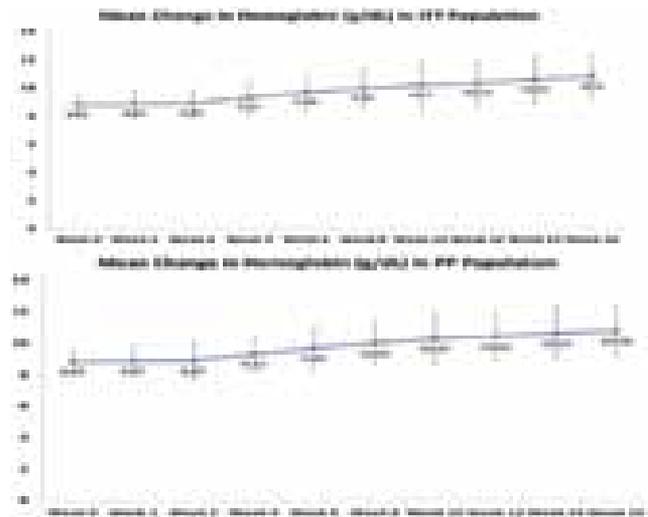


Fig. 1: Mean Change of Haemoglobin in ITT and PP Population

Systolic and diastolic blood pressure at base line was 114 ± 17.6 and 85.8 ± 8.6 mm Hg respectively. Serum creatinine at baseline was 8.2 ± 3 mg/dL.

Hypertension/large vessel disease (68.78%) was found to be commonest cause of CKD followed by diabetes (36.51%). Other causes were glomerulonephritis (19.58%), interstitial nephritis/pyelonephritis (11.11%), polycystic kidney disease (5.82%).

Efficacy Evaluation

Primary Efficacy Assessment (Mean Change in Haemoglobin)

Mean Hb at baseline to end of 16 weeks increased from 8.81 ± 0.7 g/dL to 10.80 ± 1.57 g/dL in ITT population ($P < 0.0001$) and from 8.83 ± 0.7 g/dL to 10.78 ± 1.57 g/dL in PP population ($P < 0.0001$) (Figure. 1). Compared to baseline at the end of 16 weeks treatment, mean Hb increased by 2.11 ± 1.30 and 2.08 ± 1.29 in ITT and PP population respectively ($P < 0.0001$).

Secondary Efficacy Assessments

Time (in weeks) to achievement of Hb response (Hb Levels within the range 10.0 to 12.0 g/dL) was 6.10 ± 3.87 weeks and 6.16 ± 3.92 weeks in ITT and PP population respectively (Figure. 2). Hb response was achieved in 144 and 126 patients in ITT and PP population respectively.

In post hoc analysis it was found that during initial eight weeks of treatment period only one patient (0.56% and 0.64% in ITT and PP population respectively) had overshoot of Hb > 13 g/dL. During 16 weeks treatment period 6.71% and 6.37% in ITT and PP population respectively had overshoot of Hb > 13 g/dL.

During last four weeks of TP, 46.20% (95% CI; 38.6-54, n=79) and 49.68% (95% CI; 41.6-57.8, n=78)

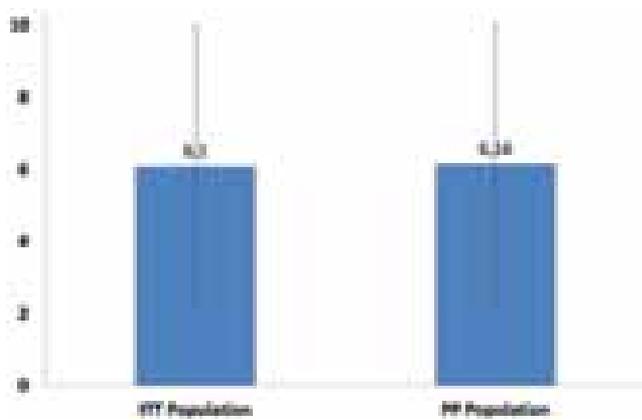


Fig. 2 : Time (in weeks) to Achievement of Response – Hb Levels within the Range 10.0 to 12.0 g/dL

patients in ITT and PP population respectively maintained Hb in target range of 10-12 g/dL.

Safety

AE data of all the 189 patients were recorded in terms of intensity, causality and relation to the study drug. Subject's tolerance for CERA was assessed in the safety population.

A total of 68 AEs were reported in 53 patients (Table 1). Pyrexia was most common AE (n=15) followed by infections (n=10). Thirty three SAEs were reported in 24 patients and none of the SAE was causally considered to be related to study medication. All SAEs were considered related to underlying disease (CKD, dialysis) by investigator. Eight patients reported cardiovascular SAEs which were cardio-respiratory arrest (four), pericardial effusion (one), accelerated hypertension (one) and post-dialysis hypotension (two).

Blood transfusion was needed in six patients and none of the patients had a clinical indication for testing anti-EPO antibodies.

Discussion

This study was carried out to evaluate efficacy and safety of CERA for correction of renal anaemia in the Indian population.

Our results show that CERA once every two weeks was effective and well tolerated for the correction of Anaemia in Indian CKD patients on dialysis. There was a significant increase in mean Hb from baseline to the end of treatment period (16 weeks) by 2.11 g/dL \pm 1.37 g/dL and 2.08 \pm 1.29 g/dL in the ITT and PP populations respectively. These findings are in line with the phase III Hb correction study of CERA in the dialysis population (AMICUS¹³) where mean changes in Hb levels from baseline to end of correction period of 24 weeks were 2.70 \pm 1.45 g/dL. In our study mean Hb attained statistical significance ($p < 0.05$) as early as four weeks from baseline and remained significant

throughout the treatment period. The mean time to achieve response i.e Hb levels within the range of 10-12 g/dL was 6.10 \pm 3.87 weeks and 6.16 \pm 3.92 weeks in the ITT and PP populations respectively. The median time to achieve response was six weeks both in the ITT and PP population. The median time to response in the phase III correction study of CERA in the haemodialysis population (AMICUS¹³) was ~ eight weeks. This could possibly be explained by the higher target Hb in AMICUS trial (≥ 11 g/dL and ≤ 13 g/dL) whereas in our study the target Hb was ≥ 10 g/dL and ≤ 12 g/dL in line with FDA guidance on target Hb for patients with chronic renal anaemia.

During last four weeks of TP, 46.20% (95% CI; 38.6-54, n=79) and 49.68% (95% CI; 41.6-57.8, n=78) patients in ITT and PP population respectively maintained Hb in target range of 10-12 g/dL in spite of short duration of the study of 16 weeks. In international clinical trials,¹²⁻¹⁷ such duration was considered for titration of the dose of CERA followed by efficacy evaluation. Our trial was post marketing trial designed to collect the efficacy and safety data in Indian population in conditions more mimicking the real life clinical settings for such patient population. These findings are justified taking into consideration the small duration of the trial, less stringent inclusion/exclusion criterion, so the conditions mimicked real life clinical settings.

In post hoc analysis it was found that during 8 weeks of treatment period only one patient (0.56% and 0.64% in ITT and PP population respectively) had overshoot of Hb > 13 g/dL. During 16 weeks treatment period 6.71% (n=11) and 6.37% (n=10) in ITT and PP population respectively had overshoot of Hb > 13 g/dL. In phase III AMICUS trial¹³ in dialysis population 8.2% and 60% patients had overshoot of Hb > 13 g/dL during first eight weeks and entire study duration of 24 weeks respectively. Higher incidence in AMICUS trial may be because of higher target Hb of > 11 g/dL whereas in our study it was > 10 g/dL and < 12 g/dL

Overall CERA was well tolerated. None of the investigator related any SAE and AE to the study medication except in one patient in whom increase in haemoglobin was considered related to the study medication, which may be due to pharmacodynamic action of the drug. Mortality of 4.23% is higher than deaths reported in the AMICUS study¹³ (1.5%). None of the deaths or SAE reported in the study was considered to be related to study medication as per Investigator's judgment and all deaths were attributed by investigators to underlying or co-morbid disorders. This may be because of slightly higher mean age of the study population which was 49.11 years in our study compared to the various reports on mean age of dialysis patients in India reported in literature of similar population. Many studies have reported mean

age of patients of ESRD in India. *Michael P. Hezel*¹⁸ has reported that mean age of patients with ESRD in India is in between 32-42 years. *Sakhuja and Sud et al*¹⁹ have reported mean age of 42 years at the time of detection of ESRD in India. *Gidithi s et al*²⁰ studied demographics and clinical data of Indian patients on haemodialysis at a tertiary care centre. They reported 15.1% deaths during first 90 days of initiation of haemodialysis and 17.1% during three year period. They have attributed causes of death to ischaemic heart disease, stroke, pneumonia, sepsis and catheter related infection. Comorbidities play important role in mortality in haemodialysis patients.

We acknowledge certain limitations of this study; open-label, single arm design, small duration of study, inadequate titration period, less stringent inclusion, exclusion criterion and mimicking real life clinical setting simulation as compared to the international phase III AMICUS design.

Conclusion

Results of this first clinical trial of CERA in India showed that CERA once every two weeks corrected anaemia in CKD patients on dialysis and produced a smooth and steady rise in Hb levels. Our results show that CERA once every two weeks was safe and well tolerated. This less frequent dosing schedule of CERA may offer clinicians and patients a simplified anaemia management as compared to traditional erythropoiesis stimulating agents.

Source of funding: Study was sponsored by Roche Products (India) Pvt Ltd. (RPIPL)

Conflict of interest: Dr. G.K. Nainan, Dr. Vivek R. Pathak, Dr. Sanjiv Saxena, Dr. Dinesh Mittal, Dr. Gokulnath, Dr. Rajan Isaac, Dr. D.S. Rana, Dr. Bharat V. Shah, Dr. D.S. Ray, Dr. C.M. Thiagarajan are advisory board members of (RPIPL). Dr. Anil A. Kukreja and Dr. Rupesh R. Pophale are full time employees of RPIPL.

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