Clinical Evaluation

Efficacy of Single Dose (Once Weekly Administration) of Recombinant Human Erythropoietin "*ReliPoietin™*" in Patients of CKD (Chronic Kidney Disease) with Anemia

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Abstract

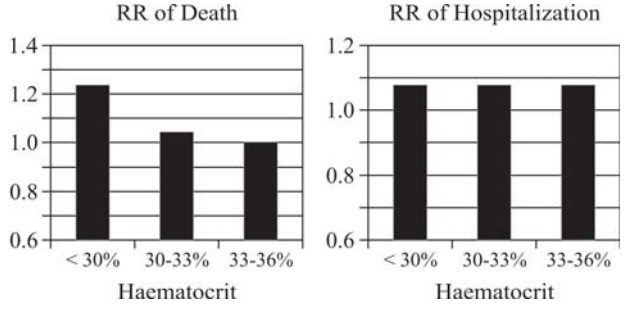
Erythropoeitin is indicated in anemia of end stage renal disease, pre-dialysis, on dialysis in various dosing regimens. Regimen of 10000 Ph. Eur IU / week of Erythropoetin was chosen (SC or IV) weekly to increase patient compliance instead of 50-100 IU / Kg thrice a week, without leading to direct toxic effects of Erythropoietin. In view of EPO going off patent worldwide, there was a need of effective substitute which could cater to the similar efficacy and safety, to also control the upsurging costs. The global market size of nearly $ 10 billion in 2008, with continuous growth mandates a clear perspective for the alternatives. In this pre-marketing study conducted at various centres in 68 evaluable patients, the responder rate was 88.2% at 9th week following the 9th dose where both Hb and Hct improved indicating the potential advantages to the patients in terms of: fewer blood transfusions and improved exercise capacity. *Relipoeitin*™ has equivalent efficacy compared to the innovator as assessed in the following pre-marketing study and has no significant change in the safety profile as compared to innovators.

Introduction

Anemia is a severe complication of CKD (Chronic Kidney Disease) seen in more than 80% of patients with impaired renal function[1]. Anemia, as defined by the NKF (National Kidney Foundation) is haemoglobin concentration <12g/dl for women and <13.5g/dl in men of <70 years of age and <12g/dl in men of >70 years of age. This is evident in both pre-dialysis and those who are maintained on dialysis. Anemia generally appears in patients with chronic renal failure once the GFR (Glomerular Filteration Rate) declines to < 60 ml/min and in 90% of patients it is evident once GFR is < 15ml/min. The ability of intestinal tract to absorb iron may be decreased due to uremic enteritis or increased pH due to use of antacids. Anemia has also been implicated in the development of congestive heart failure and left ventricular hypertrophy[3], if left untreated, anemia can cause death[1].

Fig. 1 Depicts the outcomes of anemia in terms of mortality and hospitalization, basically co-related to low haematocrit levels.

Fig. 1
Anemia and Patient Outcomes



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Prior to the mid-1980s, there were no effective therapies for the treatment of anemia in patients with CKD. Anemic patients were managed primarily by regular blood transfusions performed at every 2 to 3 weeks, and to a lesser extent with anabolic steroids. Both methods of treatment had major limitations.

In 1983, the gene for human Erythropoietin was identified by Fu-Kuen Lin and in 1985; clinical trials were initiated to evaluate the efficacy and safety of recombinant human Erythropoietin. By 1990, recombinant human Erythropoietin (epoetin) was licensed in the United States and Europe for the treatment of anemia associated with chronic renal failure, including patients on dialysis (end-stage renal disease) and patients not on dialysis[2,4].

Erythropoietin is produced in the peritubular cells of the kidney and is the major hormone involved in the production of red blood cells (Erythropoietin). When Erythropoietin levels are low, an inadequate number of oxygen-carrying red blood cells are produced. Anemia starves the body of oxygen and causes decreased exercise capacity, cognitive impairment, and diminished quality of life[1]. Erythropoietin functions by binding to the Erythropoietin receptor: a 72–78 kDa glycosylated and phosphorylated transmembrane polypeptide. The Erythropoietin receptor is a member of the super family of cytokine receptors. The number of Erythropoietin receptors varies during RBC differentiation. The binding of Erythropoietin to its receptor results in homodimerisation of the receptor, followed by activation of several signal transduction pathways: JAK2/STAT5 system, G-protein (RAS), calcium channel, and kinases.

The EU patent / market exclusivity for Erythropoietin has expired for all the leading brands: Epogen (Amgen) & Eprex (J & J). The market of EPO in 2000 expected total sales of $ 4.7 billion worldwide excluding Japan and increased 24 % year over year, predominantly for anemia in cancer patients on chemotherapy, subsequent to CKD patients[7].

ReliPoietin™ is recombinant Erythropoietin alpha developed by Reliance Life Sciences. It has a molecular weight of 29kDa. The protein component of *ReliPoietin*™ contributes approximately 60% of the molecule and is composed of 165 amino acids with the remainder of the molecule being due to glycosylation, was evaluated in the following an open study.

Although rHuEPO, as Erythropoietin alpha, has been available worldwide for decades its biogeneric development is recent following the development of specialized manufacturing facilities in non-patented territories that made possibility of generic production practicable. With the advent of refined and modernized production methods and access to new cell lines it is now feasible to produce rHuEPO (*ReliPoietin*™) at a reasonable cost corridor of identical products currently marketed.

The purpose of this study was to demonstrate safety and efficacy of *ReliPoietin*™ in the treatment on anemia in CKD patients.

Materials & Methods

The study was prospective, multicentric and open label, single arm with an objective to evaluate safety and efficacy of *Relipoitin*™ when administered a dose of 10,000 IU once a week for 8 weeks subcutaneous or intravenous in patients with chronic kidney disease. The study was conducted in 5 centres across India from June 2007 to October 2007. Patients were included in the study with following inclusion/exclusion criteria:

Major inclusion criteria for the above study were: 1) Patients with either sex with Hb levels between 7g/dL to 10g/dL. 2) Patients with chronic kidney disease. 3) Patients with a therapeutic indication for treatment of anemia, after correction of anemia secondary to iron, folate or B12 deficiency (Transferrin saturation > 20%, Serum ferritin > 100 mg/ml). 4) Patients who were rHuEPO naïve or had been off rHuEPO or similar Erythropoietin drugs for more than 1week.

Major exclusion criteria for the above study were: 1) Patients with uncontrolled hypertension. 2) Patients with blood clotting abnormalities. 3) Patients who were known hypersensitive to rHuEPO. 4) Patients with history of anemia due to causes other than anemia of CKD.

Patients satisfying the eligibility criteria were enrolled in the study. Patients at each site were enrolled only after receiving approval from the respective institutional ethics committees. All patients provided written informed consent prior to enrollment in the study.

The primary efficacy variable of the study was the proportion of subjects who responded to treatment. A responder is defined as: increase in haemoglobin (Hb) to 12 g/dL and/or increase in Hct in the range of 30%-36%

and/or increase in Hb by 1 g/dL over a two week period of treatment. Safety assessments included recording of adverse events and treatment emergent adverse events until resolution.

Each of the patients enrolled on the study received *ReliPoietin*™ at a dosage of 10,000 IU once a week. Total of 9 doses, through subcutaneous or intravenous injections were administered. The patients presented to the clinic twice weekly for haemoglobin assessments.

Statistical Methods

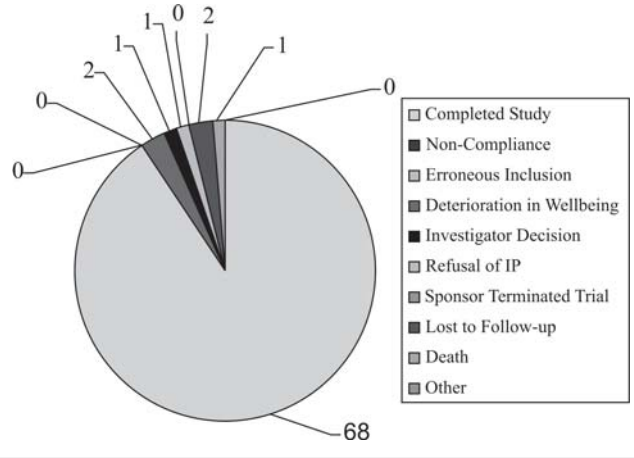
Statistical testing for the primary efficacy variable was a one-tailed confidence limit performed at the 0.05 level. All other statistical testing was performed at the 0.05 level using two-tailed tests. A p value of ≤ 0.10 but > 0.05 was considered evidence of a trend.

Subject Disposition

A total of 112 patients from CKD were screened from the 5 sites across India. The study enrolled 75 patients out of which 68 were eligible for the evaluable population. All 75 subjects were analyzed in the intent-to-treat & safety populations. All patients from the evaluable population completed the study. 7 patients had to be prematurely discontinued and were not considered for the efficacy analysis. Out of the seven patients, two discontinued because of deterioration in well being, one patient was discontinued based of investigator decision, one patient refused administration of IP after the first dose, two patients lost to follow-up and one died of cardio-respiratory arrest, as depicted in the **Fig. 2**.

Fig. 2

Subject Disposition



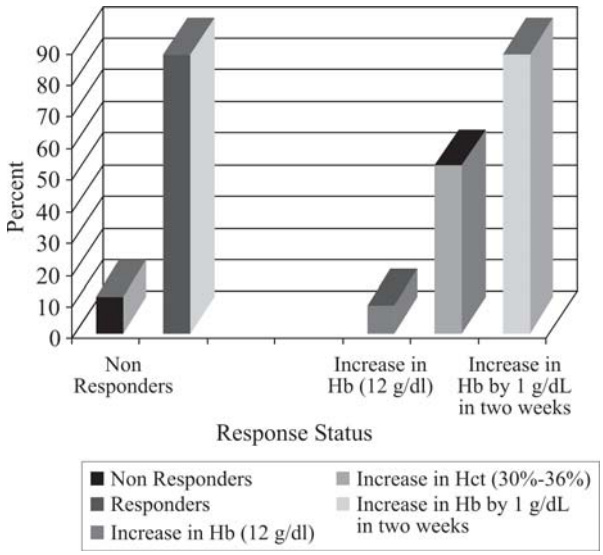
Results

As per definition of responders, total 60 (88.2%) patients in the evaluable population responded to *ReliPoietin*™ treatment. 8 (11.8%) patients did not respond to *ReliPoietin*™ in spite of taking all 9 doses. The multi-factorial possible reasons are: Phosphate binders during dialysis reduce absorption of iron. Stress ulceration from chronic disease may result in GI blood loss, underproduction of EPO in end stage renal disease (ESRD).

6 patients achieved Hb levels above 12 g/dl and 36 patients showed an increase in haematocrit levels to between 30% - 36% during the study. Of the six patients, in four patients the *ReliPoietin*™ dosing was withheld as they had attained the protocol defined target of 12 g/dl of haemoglobin (**Fig. 3**).

Fig. 3

Response Status in Evaluable Population



The mean Hb values improved from 8.13 g/dl (Range 5.9, 9.9) at baseline to 9.37 g/dl (Range 6.5, 13.3) at the end of 9 weeks of treatment in the evaluable population. A statistically significant ($p<0.0001$) mean rise in Hb levels of 1.24 g/dl was observed for the change from baseline to the end of 9 weeks of *ReliPoietin*™ therapy (**Fig. 4**). There were statistically significant increases in the change from baseline Hb levels from the interim visit between weeks 2 and 3 onwards until the end of treatment visit ($p<0.0030$).

The haematocrit values at baseline ranged from 23.82% (Range 17, 29) and rose to 28.52% (Range 20, 41) at end

Fig. 4
Increase in Hb levels from baseline until end of treatment

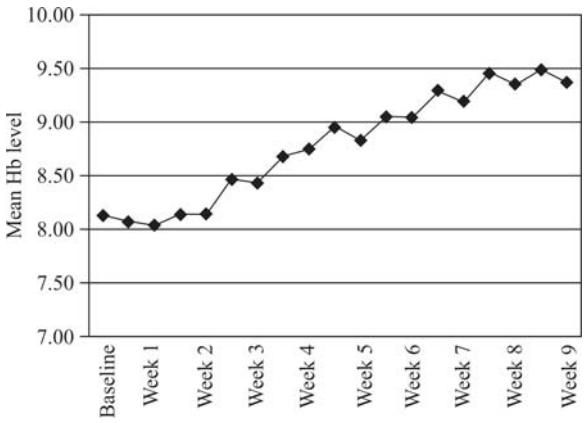
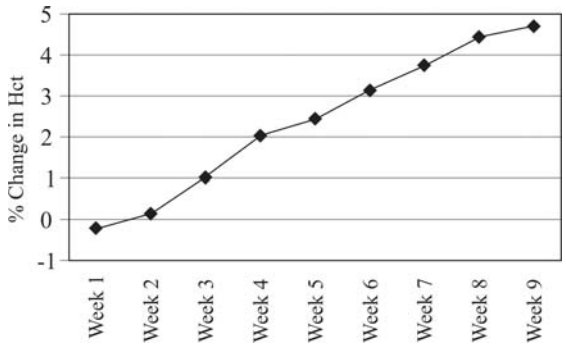


Fig. 5
Haematocrit - Percent change from Baseline



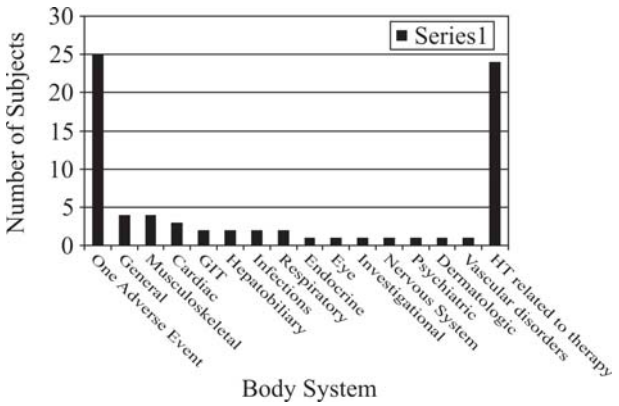
of *ReliPoietin*™ treatment (**Fig. 5**). There was a statistically significant rise in change from baseline Hct levels from week 3 until end of treatment ($p<0.0001$) in both the populations.

There was a mean percent change of 21.2% from baseline in the haematocrit values at end of treatment. Similar results were observed in the ITT population. The results were statistically significant ($p<0.0001$).

Safety Evaluation

Out of the 75 subjects enrolled on the study, all patients were administered 10,000 IU of *ReliPoietin*™ once a week; a total of 9 doses over 9 weeks either subcutaneously or intravenously.

Fig. 6
Reported Adverse Events



20 (26.7%) patients on *ReliPoietin*™ treatment suffered at least one adverse event. Six SAEs were reported during the study. The SAEs includes cardio-respiratory arrest, left ventricular failure, dyspnoea, pulmonary oedema, lower respiratory tract infection and convulsions. The other non serious adverse events observed were bilateral crepitations, joint effusions, peripheral odema, liver disorder (raised ALT), congestive cardiac failure, osteoporosis, malaria, hypertension, hyperparathyroidism, ascites, cataract, anxiety, raised eosinophil counts, dry skin and mouth ulceration (**Fig. 6**).

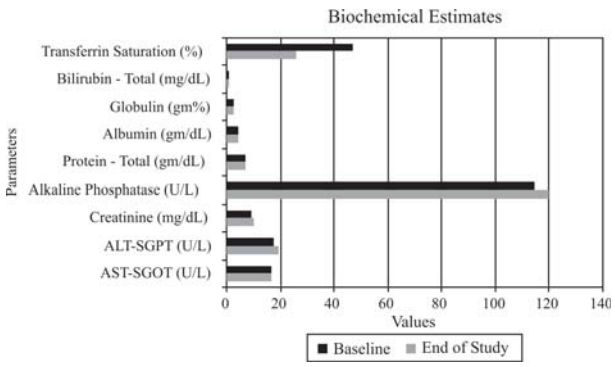
Fig. 3 shows there were no significant changes in mean AST and ALT levels from baseline to end of treatment. There was mild rise in ALT in 4 subjects. The mean creatinine levels did not change much from baseline (9.41mg/dl) to end of treatment (9.95 mg/dl).

The mean alkaline phosphatase levels did not show any significant change from baseline to end of treatment. However, there were 18 patients with abnormal alkaline phosphatase levels present from baseline. The raised alkaline phosphatase levels in 16 patients were due to the Underlying Chronic Renal disease and hence, not considered clinically significant.

The mean RBC count increased from baseline to end of study by 0.55 million/cmm. The reticulocyte count had an increase of 0.04% from baseline to end of study. However, this increase was not clinically significant.

The mean pulse, SBP and DBP remained almost constant

Fig. 7
Summary of Blood chemical estimates



from baseline to week 9/End of study. The systolic blood pressure ranged from 100 mmHg to 200 mmHg at baseline to 110 mmHg to 160 mmHg at end of treatment. The diastolic blood pressure ranged from 70 mmHg to 100 mmHg. Thus following *ReliPoietin*™ therapy, the patients were stable, no significant postural hypotension; neither sudden upsurge of blood pressure was noticed (**Fig. 7**).

Discussion

Anemia is a severe and persistent complication of chronic kidney disease (CKD) that is seen in more than 80% of patients with impaired renal function[1]. Multiple mechanisms are involved in the pathogenesis of renal anemia, the primary cause is the inadequate production of Erythropoietin by the damaged kidneys. The result is decrease in RBC production and anemia. Untreated anemia in end stage renal disease (Stage V CKD) leads to associated complications such as congestive heart failure, left ventricular hypertrophy and death. Treatment of anemia improves exercise capacity and quality of life[3].

Recombinant Erythropoietin is the mainstay of treatment of anemia of chronic kidney disease. This study was designed to study the efficacy and safety of *ReliPoietin*™ in chronic kidney disease patients with anemia. A total of 75 patients were studied in this clinical trial of which 68 were considered as the evaluable population. Treatment responders were defined as patients meeting one of the following criteria: 'Hb at least 12 g/dL' OR 'Hct increased by 30%-36%' OR 'Hb increased by at least 1 g/dL over a period of two weeks on treatment.

60 patients out of 68 in the evaluable population responded to *ReliPoietin*™ treatment. 8 patients did not respond to *ReliPoietin*™ despite taking all 9 doses. This may have been due to the end stage renal disease wherein the major causes are relative deficiency of Erythropoietin, decreased Erythropoietin production, reduced red cell survival, and the increased blood loss.

Statistically and clinically significant improvement in mean haemoglobin and mean haematocrit levels were observed following 9 doses of *ReliPoietin*™. The mean Hb levels improved from 8.13 g/dl at baseline to 9.37 g/dl at the end of 9 weeks of treatment in the evaluable population with a mean change from baseline value of 1.24 g/dl ($p<0.001$). A statistically significant difference was noted from the interim visit between weeks 2 and 3 onwards until the end of treatment. 6 patients achieved Hb levels equal to or above 12 g/dl.

Similarly, statistical significance was observed in the haematocrit levels where it improved from 23.83% at baseline to 28.52 % with a mean change from baseline value of 4.69% ($p<0.0001$) at end of study. The improvement was observed from week 3 onwards until end of treatment. 36 patients achieved an improvement in haematocrit levels in 30% to 36% range.

Table 1

Features	**International Comparator**	***ReliPoietin*™**
Sample size	135	75
Dosage and regimen	59 + 29 U/kg/wk – thrice weekly dose	10000 U/wk
Route of administration	Sc or iv	Sc or iv
Mean Hct – study completion (%)	32.3+/- 0.71%	28.52 +/- 4.26 %
Responders (%)	89.8	88.2

The most common side effect of Erythropoietin therapy is aggravation of hypertension. 70 patients out of the 75 enrolled in this study were controlled on antihypertensive therapy at onset of study. They received either angiotensin II blockers or the calcium channel antagonists with or without diuretic. One patient was discontinued because of persistent increase in blood pressure to 170/90 mm of Hg.

ReliPoietin™ has shown similar efficacy as the originators wherein in a non randomized, open label, multicentric study 1557, adult population was administered Epoetin alpha 10,000 IU and overall 89.8 % of the patients responded to once weekly dose , exhibiting an increase in Hb level of > or =1 g/dl from baseline[6].

Table 1 compares the mean Hct and responders at end of study completion in patients with anemia secondary to chronic renal disease, international trials v/s *ReliPoeitin* ™ trial

ReliPoietin™ was reasonably well-tolerated in patients with chronic kidney disease. Therapy results were beneficial to anemic patients of chronic kidney disease and were comparable to the innovators.

Summary

ReliPoietin™ is a biosimilar of recombinant erythropoietin, available in the Indian market for over last 2 years. In pre-marketing study conducted in 68 evaluable patients, the responder rate was 88.2% at 9th week following the 9th dose where both Hb and Hct improved indicating the potential advantages to the patients in terms of: fewer blood transfusions, improved exercise capacity, improved cognitive function and improved quality of life, which is often desired in terminal conditions. Further this biosimilar provided pharmacoeconomic advantage to the patients as compared to innovator products.

References

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