Original Article

Comparative Efficacy and Safety of Biosimilar Darbepoetin Alfa in Adults with Anemia of Chronic Kidney Disease

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Abstract

Introduction: The present study compared the efficacy, safety, and immunogenicity of the biosimilar darbepoetin alfa to the reference innovator darbepoetin alfa in the treatment of anemia in chronic kidney disease (CKD) patients. **Materials and Methods:** Out of 140 randomized individuals, 107 individuals were administered biosimilar darbepoetin alfa (study arm) and 33 individuals received reference innovator darbepoetin alfa (reference arm). Primary objective evaluated was hemoglobin responder rate for individuals achieving >1 g/dL rise in Hb from baseline to week 8. The secondary objectives were proportion of individuals achieving rise in hemoglobin (>1 g/dL rise from baseline) at week 24 to assess the proportion of individuals maintaining mean Hb within target range and evaluation of safety. **Results:** The hemoglobin responder rate for individuals achieving >1 g/dL rise in Hb from baseline to week 8 was similar in both the study and reference arms (56 [62.92%] and 22 [70.97%]). Overall, 86.27% individuals treated with biosimilar darbepoetin alfa achieved hemoglobin rise >1 g/dl as compared to 86.67% individuals in the reference darbepoetin arm at 24 weeks. Individuals maintaining Hb value within the target range at the end of week 24 were also similar in both the arms (60.80% and 60.00% in study and reference arms, respectively). There were 147 treatment emergent adverse events (34.58% in the study arm and 42.42% in the reference arm). **Conclusion:** The biosimilar darbepoetin alfa (DarbeRel™) showed clinical biosimilarity to reference innovator darbepoetin alfa in anemia of CKD.

Keywords: Anemia, chronic kidney disease, darbepoetin alfa, hemoglobin

Introduction

The prevalence of CKD is high both in rural and urban parts of India. The incidence of CKD has doubled in the last 15 years. India has more than 1 billion population; there are ~7.85 million chronic renal failure patients in India.[1,2] One of the major challenges for management of CKD in India is presentation of patients to the nephrologist at later stages. Indian CKD registry reported close to 48% patients presenting in Stage V.[3] Nearly, 78.9–96.5% patients suffer from anemia in later stages. With respect to the etiologic disease subgroups, subgroups with diabetic nephropathy had the highest overall prevalence of anemia (75.9%) than other etiologic subgroups.[4] Anemia associated with CKD is a risk factor for impaired physical capacity and reduced quality of life and may contribute to the increased morbidity and mortality seen in CKD. Anemia may underlie the high cardiovascular mortality observed in the CKD population as a low hematocrit (Hct) is an independent risk factor for death in this population. In one study, for example, a 3% decrease in Hct was associated with a 7% increased risk of death.[5]

Erythropoiesis-stimulating agents (ESAs) such as rHuEPO and darbepoetin alfa have been used for the treatment of renal anemia. Erythropoietin (EPO) is an indispensable erythropoietic hormone primarily produced from renal EPO-producing cells (REPs). EPO production in REPs is tightly regulated in a hypoxia-inducible manner to maintain tissue oxygen homeostasis. Insufficient EPO production by REPs causes renal anemia and anemia associated with chronic disorders.[6] Darbepoetin alfa stimulates erythropoiesis by the same mechanism as the endogenous EPO. The chemical composition of darbepoetin alfa includes five N-linked carbohydrate chains whereas the endogenous hormone and r-HuEPOs have three [Figure 1]. Due to its increased

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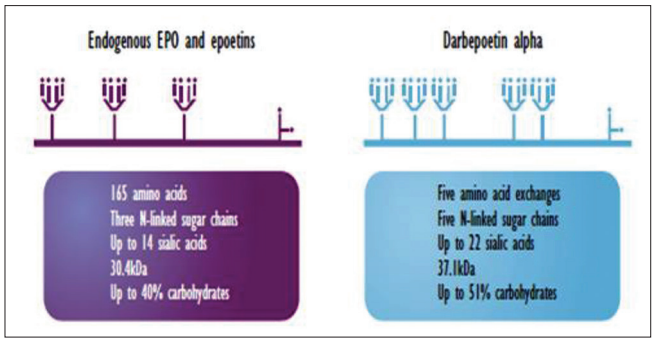

Figure 1: Darbepoetin alfa structure comparison

carbohydrate content, darbepoetin alfa has a longer terminal half-life than r-HuEPO and consequently a greater *in vivo* activity. Darbepoetin alfa, the first ESA to offer extended dosing intervals over the erythropoietin molecules, has played an important role in enhancing anemia management.[7] The equivalence of subcutaneous and intravenous dose requirements for darbepoetin alfa offers greater simplicity of anemia management for physicians, relative to rHuEPO. One of the principal benefits which can be derived from the switch from older ESAs to darbepoetin alfa is the reduction in dose and convenience. Dose savings have been demonstrated in a number of studies on switching to darbepoetin alfa.[5] In a recent meta-analysis, the dose efficiency of darbepoetin alfa relative to rHuEPO was calculated to be 32%.[8]

Reliance Life Sciences has developed recombinant darbepoetin alfa, as biosimilar to the innovator's product. Biosimilar darbepoetin alfa gives substantial opportunities for availability or access and cost savings. Apart from the physicochemical and biological biosimilarity, clinical comparative study contributes to the clinical biosimilarity. This was a phase III regulatory clinical trial to evaluate the efficacy and safety of RLS developed darbepoetin alfa versus innovator biosimilar in patients with anemia due to chronic kidney disease (CKD).[9]

Materials and Methods

The study was a prospective, multicentric, randomized, open-label, two-arm, parallel group, active control, comparative clinical study (CTRI/2013/09/004005) to evaluate efficacy and safety of biosimilar darbepoetin alfa (DarbeRel™) (study arm)/reference innovator darbepoetin alfa, in individuals for correction of anemia due to CKD. The study was performed in accordance with principles stated in the Declaration of Helsinki, International Conference on Harmonization, ICMR Ethical guidelines for Biomedical Research on Human participants and applicable regulatory requirements.

All individuals ≥18 years of age, male or female with anemia due to CKD who were on hemodialysis or peritoneal dialysis, who were ESA therapy-free for at least 3 months, whose Hb is <9 g/dL based on two screening visits at least 7 days apart, and with transferrin saturation more than 20% were enrolled in the study. Individuals with severe, uncontrolled systemic disease, who had RBC transfusion to treat anemia within 8 weeks before enrollment, individuals with New York Heart Association class III or IV Congestive Heart Failure or had uncontrolled hypertension, individuals with hyperparathyroidism (>1500 pg/ml), individuals who had undergone major surgical procedure or androgen therapy who were scheduled to receive a renal transplant, individuals who had history of intolerance or hypersensitivity to ddarbepoetin alfa and those who were pregnant or breastfeeding were excluded from the study.

A total of 141 individuals were randomized in the study, out of which 140 individuals were dosed. All individuals who had given written informed consent to participate in the study were assigned a sequential subject number at the screening visit. The randomization schedule was generated by statistician at Reliance Life Sciences. Randomization was managed centrally. Subject identification number was a unique number having site number and subject number. All individuals who were randomized and dosed in the study were considered as intention to treat (ITT) population; hence, a total of 140 individuals were considered as ITT population and considered for safety analysis. After randomization, 107 individuals received the biosimilar darbepoetin alfa and 33 individuals received reference product. A total of 88 individuals in study arm and 31 individuals in reference product arm completed 8 weeks of treatment. A total of 62 individuals in study arm and 24 individuals in reference product arm completed week 8 of the treatment without any major protocol deviation.

Primary efficacy parameters evaluated hemoglobin responder rate for individuals achieving >1 g/dL rise in Hb from baseline to week 8 for biosimilar darbepoetin (study arm)/innovator darbepoetin alfa (reference arm) in individuals with anemia due to CKD. The secondary objectives evaluated proportion of individuals achieving rise in hemoglobin (>1 g/dL rise from baseline) at week 24, average dose of study darbepoetin alfa/reference darbepoetin alfa for correction of anemia, and the proportion of individuals maintaining mean Hb within target range (9–11.5 g/dl).

The study dose of either darbepoetin alfa was 0.75 µg/kg once every 2 weeks subcutaneously. The dose modification was carried out when the two consecutive out of range Hb values, taken at least 7 days apart, exceeded 11.5 g/dL. Furthermore, when the hemoglobin levels increased rapidly (e.g., more than 1 g/dL in any 2-week period, i.e., exceeds 11.5 g/dL), the dose was reduced by 25% or more. In case the individuals had not responded adequately, hemoglobin had not increased by 1 g/dL after 4 weeks of therapy; the dose was increased by 25%. The dose was not increased more frequently than once every 4 weeks.

Statistical methods

Sample size was based on the 70% of responders at week 8, with an absolute equivalence margin of ±25%, for a power of 80% and a two-sided significance level of 0.05, with an adjustment for randomization ratio. Statistical testing was performed at the 0.05 level using two-tailed tests. All the

individuals who were randomized and dosed in the study were treated as ITT population. For data presentation, all efficacy analysis was presented using ITT population who completed 8 week of therapy. The details of study disposition are presented in Figure 2.

Results

The primary efficacy was assessed by hemoglobin responder rate, i.e., proportion of individuals achieving >1 g/dL rise in Hb from baseline to week 8. Out of 88 individuals in study arm, 56 (62.92%) individuals achieved hemoglobin rise >1 g/dl, and out of 31 individuals in reference arm, 22 (70.97%) individuals achieved hemoglobin rise >1 g/dl at the end of week 8 [Table 1]. The difference between biosimilar darbepoetin and reference product arm in rise in Hb level was nonsignificant ($P = 0.238$).

In the secondary efficacy analysis, out of 51 individuals in study arm who completed week 24 assessment at this stage of the study, 44 (86.27%) individuals achieved hemoglobin rise >1 g/dl. Out of 15 individuals in reference arm who completed week 24 assessment at this stage of the study, 13 (86.67%) individuals achieved hemoglobin rise >1 g/dl at the end of week 24. The difference between biosimilar darbepoetin and reference darbepoetin arms in rise in Hb level at week 24 was nonsignificant ($P = 0.909$).

Out of 51 individuals in study arm, 31 (60.80%) individuals maintained the Hb value in 9–11.5 g/dl, and out of 15 individuals in reference arm, 9 (60.00%) individuals maintained the Hb value in 9–11.5 g/dl at end of week 24. The difference between biosimilar darbepoetin arm and reference arm in maintaining Hb level in predefined 9–11.5 g/dl range was nonsignificant ($P = 0.956$). The average dose required to achieve the target range of 9–11.5 g/dl was 38.57 µg for study arm and 38.43 µg for reference arm at week 24.

The mean baseline hemoglobin level was 8.1 g/dL in study arm and 7.4 g/dL in reference arm which were raised to 9.3 g/dL and 8.1 g/dL in both arms, respectively, at the end of week 8. There was 14.81% and 9.46% rise of hemoglobin level observed in study arm and reference arm, respectively, at week 8. There was no significant difference observed for rise in Hb count between both the treatment arms ($P = 0.280$) at week 8. The mean baseline reticulocyte count was 1.7 in study arm and 1.9 in reference arm. Initially, there was an increase in reticulocytes counts; however, it was followed by decline in reticulocyte count at week 8 in both arms. The increase in reticulocytes count during initial phase of dosing may be attributed to low hemoglobin level.

A total of 140 individuals who were dosed were considered for safety analysis. A total of 107 evaluable individuals were included from study biosimilar darbepoetin arm and 33 from the reference innovator darbepoetin arm. In this study, 156 adverse events were reported, out of which, 105 were reported in 41 (38.32%) individuals in the study arm,

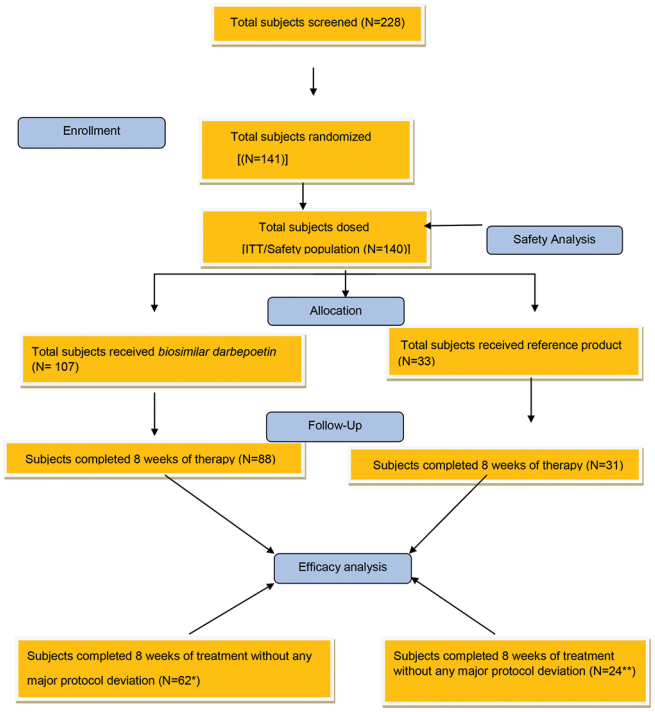

Figure 2: Subject disposition

Table 1: Summary of subjects achieving >1 g rise in Hb (week 8)

Parameter	Treatment Arm (*n*)		Total (120)	*P*
	Study arm (89)	Reference arm (31)		
No. of subjects with >1 g Rise in Hb	56 (62.92%)	22 (70.97%)	78	0.238

and 51 were reported in 15 (45.45%) individuals in the reference arm [Table 2]. A total of 147 treatment-emergent adverse events (TEAEs) were reported, out of which, 98 were reported in 37 (34.58%) individuals in the study arm and 49 were reported in 14 (42.42%) individuals in the reference arm. There was one subject in both the arms with at least one treatment-emergent severe adverse event.

Nine serious adverse events (SAEs) were reported which were coded into a total of 11 SAE terms, of which, 7 were reported in the study arm and 4 was reported in the reference arm. There were 7 (6.54%) individuals including 5 (4.67%) fatal cases in the study darbepoetin arm and 2 (6.06%) individuals in the reference arm with at least one SAE. The percentage of individuals with adverse events in each arm was compared for statistical significance and the difference was found to be nonsignificant ($P > 0.05$).

In the study of darbepoetin alfa arm, the most commonly reported (incidence ≥5%) TEAEs were related to general disorders and administration site conditions 20 (17.95%) followed by gastrointestinal disorders 10 (9.35%), nervous system disorders 9 (8.41%), and infections and infestations

Table 2: Summary of all adverse events (safety population [*n*=140])

Variable	Biosimilar darbepoetin (*n*=107) *n*% E	Reference darbepoetin (*n*=33) *n*% E	*P*
At least one Adverse Event	41 (38.32%) 105	15 (45.45%) 51	0.469
At least one Treatment emergent (TE) Adverse Event	37 (34.58%) 98	14 (42.42%) 49	0.421
At least one TE Adverse Event Related to Study Drug	2 (1.87%) 2	0 (0.00%) 0	NA
At least one TE Severe Adverse Event	1 (0.93%) 1	1 (3.03%) 3	0.417
At least one TE Serious Adverse Event	7 (6.54%) 7	2 (6.06%) 4	1.00 (NS)
At least one Infusion reaction	0 (0.00%) 0	0 (0.00%) 0	NA
Death	5 (4.67%) 5	0 (0.00%) 0	NA
Subjects discontinued due to TE Adverse Event	1 (0.93%) 2	0 (0.00%) 0	NA

8 (7.48%) system organ class [SOC]. General disorders and administration site conditions included asthenia 2 (1.87%), chills 4 (3.74%), disease progression 2 (1.87%), and edema peripheral 5 (4.67%), and pyrexia 8 (7.48%). Nervous system disorders included mainly dizziness 2 (1.87%), headache 5 (4.67%), and uremic encephalopathy 2 (1.87%). Gastrointestinal disorders included vomiting 5 (4.67%), abdominal pain upper 3 (2.80%), and nausea 1 (0.93%). Infections and infestations included urinary tract infection 4 (3.74%) and rhinitis 2 (1.87%).

The incidence of SAEs was comparable in both arms (6.54% in study arm versus 6.06% in the reference arm). In the study arm, the most commonly reported SAEs were in the general disorders and administration site conditions, observed in 2 (1.87%) individuals followed by nervous system disorders in 2 (1.87%). In the reference arm, 3 SAEs was observed in 1 subject (3.03%) in the SOCs of infections and infestations, respiratory, thoracic and mediastinal disorders and vascular disorders. In both treatment arms, there was no major significant change from baseline in hematological parameters.

Immunogenicity testing was done for individuals at baseline and who did not respond to study treatment until week 24 or up to withdrawal. Confirmatory ELISA was done for 51 samples covering study and reference arm. Samples were interpreted as positive only if there is more than 50% drop in optical density values after spiking with the drug. It was concluded that the above serum samples were negative for antidrug antibodies.

Discussion

Darbepoetin alfa, the first ESA to offer extended dosing intervals over the erythropoietin molecules, has played an important role in enhancing anemia management in CKD patients. The equivalence of subcutaneous and intravenous dose requirements for darbepoetin alfa offers greater simplicity of anemia management for physicians relative to the erythropoietins since a change in administration route is less likely to necessitate dose adjustment. One of the principal benefits to be derived from the switch from older ESAs (epoetin alfa or epoetin beta) to darbepoetin alfa is the reduction in dose. Dose savings have been demonstrated in a number of studies on switching to darbepoetin alfa QW or Q2W. Five-step chromatography for purification and orthogonal testing according to guidelines has ensured the physicochemical and biological similarity of the biosimilar darbepoetin alfa.

The present study established the clinical biosimilarity of biosimilar darbepoetin alfa (DarbeRel™) to the reference innovator darbepoetin alfa. The primary efficacy in achieving a hemoglobin response (i.e., >1 g/dl increment in hemoglobin over baseline) over the first 8 weeks was comparable in both the arms. The response was also comparable in both groups after excluding the individuals with major protocol deviation which thus showed no impact of these on efficacy assessment. In the secondary end point analysis, proportion of individuals achieving >1 g/dL rise in Hb from baseline to week 24 showed no difference between biosimilar darbepoetin alfa and the reference product. The proportion of patient maintaining the target hemoglobin range (9–11.5 g/dl) was comparable in both arms at week 24. This individual fluctuation of hemoglobin observed in this study was consistent with the observation made in earlier studies. Mean rise in hemoglobin level at week 8 also showed no significant difference in both the treatment arms. Initially, there was an increase in reticulocyte counts; however, it was followed by decline in reticulocyte count at week 8. This trend was seen in both biosimilar and reference darbepoetin alfa arms. This fluctuation in reticulocyte count was consistent and may be attributed to maturation of reticulocyte and increase in hemoglobin level responsible for feedback inhibition of bone marrow. Pharmacodynamic assessment showed comparable pattern in both treatment arms.

There were no concerns regarding the safety profile of the study drug, biosimilar darbepoetin alfa. Most adverse events were not related to study drug and were consistent with common intercurrent events typically found in dialysis populations, and they were comparable in both treatment arms. The adverse event profile was comparable in both arms and similar to that associated with disease condition and stage of the disease, ESA therapy. Barring one case of accelerated hypertension (which was not causally associated with the study medications), there was no other event that could be attributed to hypertension or its sequelae. The incidence of SAEs in both treatment arms was comparable. There were no antibodies to darbepoetin alfa detected right until 24 weeks for all samples tested. Clinically also, no case of pure red cell aplasia was observed with either arm medications.

Conclusion

Anemia in patients with CKD is associated with decreases in cardiac and renal functions and quality of life and poses a significant clinical and economic burden on healthcare systems. The frequent dosing regimen of EPO, up to three times per week pushed the development of ESA agents with longer half-life, hence lowering dosing frequency. Darbepoetin alfa is the first long-acting ESA with established dosing efficiency.

The biosimilar darbepoetin alfa (DarbeRel™) showed clinical biosimilarity to reference innovator darbepoetin alfa in the treatment of anemia in CKD patients and established the therapeutic equivalence to the reference innovator darbepoetin alfa. The use of an economical biosimilar darbepoetin alfa with reduced dosing frequency and dose efficiency advantage will provide an added thrust for patient convenience and compliance.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Adejumo OA, Akinbodewa AA, Okaka EI, Alli OE, Ibukun IF. Chronic kidney disease in Nigeria: Late presentation is still the norm. Niger Med J 2016;57:185-9.
2. Dash SC, Agarwal SK. Incidence of chronic kidney disease in India. Nephrol Dial Transplant 2006;21:232-3.
3. Udayaraj UP, Haynes R, Winearls CG. Late presentation of patients with end-stage renal disease for renal replacement therapy – Is it always avoidable? Nephrol Dial Transplant 2011;26:3646-51.
4. Ryu SR, Park SK, Jung JY, Kim YH, Oh YK, Yoo TH, *et al.* The prevalence and management of anemia in chronic kidney disease patients: Result from the KoreaN Cohort Study for Outcomes in Patients with Chronic Kidney Disease (KNOW-CKD). J Korean Med Sci 2017;32:249-56.
5. Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, *et al.* Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol 2001;38:955-62.
6. Rajapurkar MM, John GT, Kirpalani AL, Abraham G, Agarwal SK, Almeida AF, *et al.* What do we know about chronic kidney disease in India: First report of the Indian CKD registry. BMC Nephrol 2012;13:10.
7. Gaydarova M, Boueva A, Svetlana Marinova S, Zlatanova G. Use of darbepoetin alfa (aranesp®) for anemia treatment in children with chronic kidney disease – clinical experience of bulgarian pediatric group. J IMAB Ann Proc (Sci Pap) 2017;23:1421-6.
8. Carrera F, Burnier M. Use of darbepoetin alfa in the treatment of anaemia of chronic kidney disease: Clinical and pharmacoeconomic considerations. NDT Plus 2009;2:i9-17.
9. Prospective, multi-centre, randomized, open-label, two-arm, parallel group, active control, comparative clinical study to evaluate efficacy and safety of DarbeRelTM/ Aranesp® when given subcutaneously in subjects for correction of anemia due to Chronic Kidney Disease. Clinical study report. 2015;1:1-242.