ORIGINAL ARTICLE

Darbepoetin Alfa Versus Erythropoietin Alfa for Treatment of Renal Anemia in Patients with Chronic Kidney Disease at the Pre-Dialysis Stage: A Randomized Non-inferiority Trial

Mehta KS[1], Sinha SD[2*], Bandi Vamsi[3], Bala Reddy[4], Naidu NR[2], Thakur PA[2*], Chary Sreenivasa[2], Reddy VPR[5], Pandey R[6], Durugkar S[7]

Abstract

Background: Darbepoetin alfa (DA-α) is a long-acting erythropoiesis-stimulating glycoprotein with a three-fold longer half-life than Erythropoietin alfa (EPO). The objective of this study to determine whether DA-α is as effective and well tolerated as EPO for treating renal anemia among Indian pre-dialysis patients with chronic kidney disease (CKD).

Patients and Methods: In this phase III, randomized, active-controlled, non-inferiority study, the pre-dialysis patients with CKD who had hemoglobin (Hb) levels <10 gm/dL received either EPO (50 IU/kg, thrice weekly) or DA-α (0.45µg/kg, once weekly) subcutaneously (1:1) for 12-24 weeks (correction phase). The patients with Hb levels ≥10 gm/dL were switched directly to DA-α or EPO for 12 weeks maintenance phase. The primary efficacy endpoint was to compare the mean change in Hb level from baseline to end of correction phase (EOC) between DA-α and EPO. Safety was also evaluated.

Results: In ITT population (n=63), the mean change in Hb from baseline to EOC was similar in the DA-α (11.28 g/dL) and EPO (11.02 g/dL) groups. The difference in the mean change in Hb between these two groups was 0.23g/dL (95% CI -0.62, 1.09, p=0.5837). After adjusting for covariates (using analysis of covariance model), the difference in the mean change in Hb between these two groups was 0.20g/dL (95% CI -0.461, 0.866). In ITT population, the lower limit of the two-sided 95% CI of primary endpoint was above the pre-specified non-inferiority margin of -0.5 g/dL. Similar trend of non-inferiority was observed for PP population (n=46). Safety profile of DA-α and EPO was similar.

Conclusion: Our study results demonstrate that DA-α given at a reduced dose frequency is as effective and well tolerated as EPO for treating renal anemia in pre-dialysis patients with CKD.

Introduction

Anaemia is considered to be a common complication associated with chronic kidney disease (CKD), occurs due to decreased production of endogenous glycoprotein hormone erythropoietin by the damaged kidneys.[1] Several lines of clinical evidences have confirmed the direct relationship between the severity of the anaemia and the deterioration in kidney function.[2,3] Anaemia manifestation occurs early in pre-dialysis due course of CKD[4] and is associated with development of cardiovascular disease[5] and increased mortality[6] in patients with pre-dialysis CKD. Improvements of quality of life[7] and cardiovascular complications[8] have been seen by correcting the anaemia with the help of ESAs.

Recombinant human Erythropoietin (r-HuEPO) is a glycoprotein that is similar to endogenous human erythropoietin (HuEPO) in terms of biological activity and physical characteristics. Recombinant human Erythropoietin is a short acting erythropoiesis-stimulating agent (ESA) has been available for almost two decades as gold standard therapy for the treatment of anaemia in patients with CKD.[9] Although treatment with rHuEPO in dialysis patients has been shown to have been shown to eliminate the need for red cell transfusions, improve survival, reduce cardiovascular morbidity and enhance quality of life.[9,10] However, the benefits of rHuEPO use in pre-dialysis patients are still a matter of debate. A recent Cochrane review suggested that the treatment with rHuEPO in pre-dialysis patients corrects anaemia, avoids the requirement for blood transfusions and also improves quality of life and exercise capacity.[3] Recombinant human Erythropoietin has been approved for the correction of anaemia in chronic renal failure patients, and it is required to be administered two or three times weekly in the majority of patients due to its short half-life.[11] The need for frequent dosing of rHuEPO is a considerable burden on both patients and health care staff, so long-acting ESAs have some advantages over short-acting ESA.[12] Kawahara et al. 2015 have suggested that long-acting ESAs may be more useful for pre-dialysis patients with CKD since these patients do not attend hospital frequently, unlike dialysis patients.[13]

Darbepoetin alfa (DA-α) is an erythropoiesis-stimulating glycoprotein has 3-fold longer half-life and decreased

[1]Department of Nephrology, B.L.Y. Nair Hospital, Mumbai, Maharashtra; [2]Hetero Group, Clinical Development and Medical Affairs, Hetero Corporate, Hyderabad, Telangana; [3]Hetero Group, Hetero Corporate, Hyderabad, Telangana; [4]Hetero Biopharma, Hetero Group of Pharmaceuticals, Hyderabad, Telangana; [5]Care Hospitals, Hyderabad, Telangana; [6]Department of Nephrology, Institute of Post Graduate Medical Education and Research Kolkata, West Bengal; [7]Ashwini Hospital and Ramakanth Heart Care Center, Nanded, Maharashtra; *Corresponding Author
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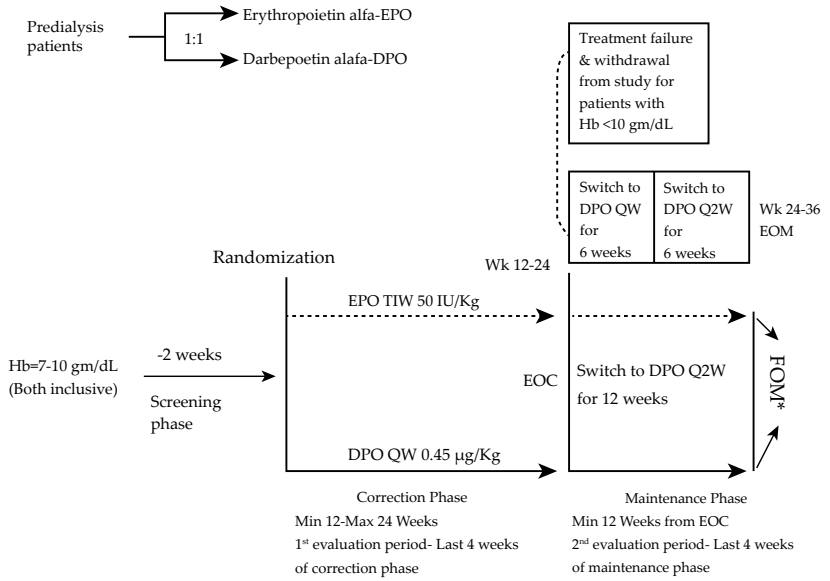

Abbreviation: EPO=Erythropoietin alfa, DPO=Darbepoetin alfa, QW= Once Weekly; TIW= Thrice weekly; Q2W= once in 2 weeks

Fig. 1: Study design. *EOM assessment - Day 1 of Week 25 or Day 1 of Week 37; #EOC=End of Correction (Min 12, Max 24 weeks); EOM=End of maintenance (Min 24, Max 36 weeks)

clearance compared to r-HuEPO in humans.[14] Darbepoetin alfa has similar mechanism for erythropoiesis as r-HuEPO. Darbepoetin alfa is indicated for less frequent administration than the epoetins/epoetin biosimilars.[9] The longer half-life enables DA-α to effectively maintain target Hb levels with less frequent dosing. The extended dosing interval of DA-α once weekly or once every 2 weeks offers many potential benefits to both patients and health care staff.[9-12] Dose requirements of DA-α has similar dose requirements for both the subcutaneous and intravenous routes which offers greater simplicity of anaemia management for physicians compared to the epoetins.[9]

Clinical studies have shown that DA-α administered once every other week was superior to weekly r-HuEPO for treatment of anaemia in pre-dialysis CKD patients, and also offered enhanced convenience.[13,14] In India, the efficacy and safety of DA-α in the treatment of renal anemia in pre-dialysis CKD patients is not yet investigated. Therefore, this study was designed to determine whether DA-α is as effective and well tolerated as Erythropoietin alfa (EPO) when administered at a reduced dose frequency for the treatment of renal anemia in Indian pre-dialysis CKD patients.

Materials and Methods

Ethics

The study was conducted in accordance with ethical guidelines outlined in Helsinki Declaration of 1964, as revised in 2013 and Indian regulatory laws governing biomedical research in human patients. Institutional ethics committee approval was obtained from each participating study centre before initiating study. Prior to any study-related screening procedures, written informed consent was obtained from each patient before enrolling in the study. The study was registered with clinical trial registry (CTRI: CTRI/2012/07/002835) before enrolment of first patient in the study.

Study Design and participants

This prospective phase III, randomized, open label, two-arm, parallel group, multi-center, active-controlled, non-inferiority clinical study was conducted at 14 centres across India from Sept 2012 to May 2014. In this study, clinically stable patients of either gender (aged 18-65 years) with pre-dialysis stage (Stage 3 and 4 with glomerular filtration rate [GFR] between 15-59 mL/min/1.73 m2) and had baseline Hb levels 7-10 gm/dL were enrolled. All the enrolled patients were either EPO - naive or on EPO (not within one week prior to screening), and had adequate transferrin saturation (≥20%) and serum ferritin (≥100 ng/mL). The patients undergoing peritoneal dialysis or have received dialysis or expected to receive dialysis in next 6 months were excluded. Pregnant women, lactating mothers, , history of uncontrolled hypertension/ diabetes, congestive heart failure, systemic haematological diseases, severe hyperparathyroidism, infections, liver disease, hypersensitive to any of the active study drug substances were excluded from this study. Study treatment period involved two phases: Correction phase (12 to 24 weeks) and maintenance phase (up to 12 weeks: 24 to 36 weeks) (Figure 1). At baseline phase, the patients who had Hb levels <10 gm/d after receiving EPO were switched to subcutaneous injection of DA-α 0.45µg/kg (X Brand name X, manufactured by Hetero Drugs Ltd, India) once weekly or EPO 50 IU/kg (Eprex®, manufactured by Cilag AG, Switzerland) thrice weekly for 12-24 weeks (correction phase) in allocation ratio of 1:1. The patients who had Hb level <10 gm/dL at the end of correction phase were considered as treatment failure and discontinued from the study. The patients with Hb levels ≥10 gm/dL at the end of correction phase were switched directly to DA-α for 12 weeks maintenance phase. The dialysis patients who had Hb level ≥ 10 gm/dL at baseline phase were directly entered into maintenance phase, and were randomized (1:1) to receive DA-α (0.45 µg/kg) once weekly or EPO (50 IU/kg) thrice weekly for 12 weeks. In each treatment group, the dose of study drug was adjusted to maintain individual patients' Hb within a target range of ≥1 gm/dL from baseline Hb and between 10-12 gm/dL throughout the 36-week study period. In correction phase, if a patient's previous Hb fell below 7 gm/dL after receiving first dose, dose was increased by 50% of the previous dose. Also if patient's previous Hb fell below 11 gm/dL after achieving the target range, the dose of study drug was increased by 25%. In maintenance phase, if a patient's Hb increased above the target range (≥11.5 gm/dL) on two consecutive weekly assessments, the dose of study drug was decreased by 25%. If a patient's previous Hb fell below 10 gm/dL after achieving the

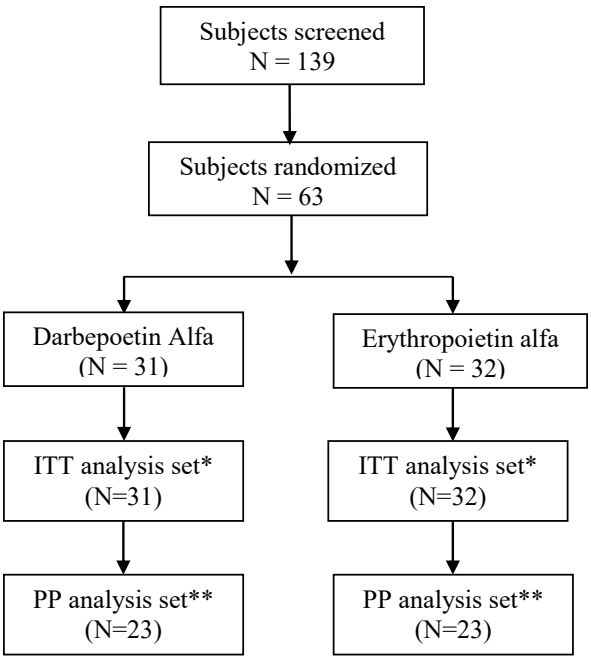

Fig. 2: Patients subjected in the analysis. *includes the patients who were randomized, and received at least one dose of study drug, had baseline and at least one efficacy assessment at the evaluation period. **Includes the patients who had completed all the study visits as per protocol without major protocol deviations.

target range (10-12 gm/dL), the dose of study drug was increased by 25%. To ensure adequate support of the erythropoietic response to study drug, IV iron therapy was required to be administered to patients with serum ferritin values <100 µg/L. The IV iron dosing regimen used for patients with low serum ferritin values (<100 µg/L) was determined by the individual center's treatment protocol.

Efficacy and safety assessment

Hemoglobin level was measured throughout the study period (correction and maintenance phase). The primary efficacy endpoint was to compare the mean change in Hb level from baseline to first evaluation visit (EOC) between EPO and DA-α. Secondary efficacy endpoints that included mean change in Hb level from baseline to Week 4 and end of second evaluation period (end of maintenance phase), Hb variability (in correction phase), mean DA-α dose, proportion of patients achieving the Hb target (defined as Hb increase of ≥1 gm/dL from baseline and Hb concentration of 10-12 gm/dL) at the end of first evaluation period and time to initial achievement of Hb target. Complete blood count, serum chemistry, and urinalysis were measured at baseline and after treatment to assess safety of EPO or DA-α. Adverse events were recorded at each study visit. Safety endpoints included the incidence of treatment-emergent adverse events (TEAEs) and immunogenicity assessment after treatment with EPO or DA-α. For immunogenicity assessment, all patients were tested for anti-drug antibody titres. DA-α /EPO antibodies sampling were performed before initial dose (Day 1 of week 1) of study medications and on Day 1 of weeks 5, 13, 25 and end of maintenance within 1 hour of dosing. Since there were various time points at which the screening, evaluation periods were ending in various subgroup of patients, the time points for immunogenicity varied accordingly in such patients. The samples were measured for relevant antibodies by ELISA method.

Statistical Analyses

Considering an estimated difference in mean change of Hb levels equal to 0.03 gm/dL for Darbepoetin versus EPO, and non-inferiority margin fixed at - 0.5 gm/dL, 88 evaluable patients in the ratio of 1:1 to either DA-α or EPO treatment groups (44 patients in each treatment group) were required to assure at least 80% power for the non-inferiority test. Taking 20% of dropout rate, a total 110 patients (55 patients in each treatment group) was required to draw conclusion of this study. Efficacy analysis was performed on intent to treat (ITT) and per protocol (PP) population. ITT population includes the patients who were randomized, and received at least one dose of study drug, had baseline and at least one efficacy assessment at the evaluation period. PP population includes the patients who had completed all the study visits as per protocol without major protocol deviations. Safety analysis was performed on safety population, which included the patients who were randomized, and received at least one dose of study drug. The mean change in Hb level from baseline to first evaluation period (EOC) between EPO and DA-α was analyzed using analysis of covariance (ANCOVA) method with treatment as main effect and baseline Hb value as covariate. Within the framework of ANCOVA, the 95% CI for difference in mean Hb of treatments was calculated to assess the non-inferiority. The non-inferiority was accepted if the lower limit of two-sided 95% CI was above the non-inferiority margin -0.5 gm/dL. Change in Hb level from baseline to Week 4 in two treatment arms was analyzed using two sample t-tests at 5% level of significance. The p-value of ≤0.05 was considered as statistically significant. Proportion of patients achieving the Hb target (≥1 gm/dL from baseline and Hb concentration of 10-12 gm/dL) at the end of first evaluation visit (EOC) was analyzed by logistic regression. The time to initial achievement of Hb target was analyzed using Kaplan-Meier. All statistical analysis was performed using SAS® Version 9.4 (SAS Institute Inc., NC, USA).

Results

Patient disposition and characteristic

A total of 139 patients not requiring dialysis were screened for anaemia (Figure 2). Of these, a total of 63 patients (31 patients DA-α and 32 patients EPO) who met eligibility criteria were enrolled and randomized (ITT population). The PP population consisted of 46 patients (23 patients in each group) . The demographics characteristic of safety population is presented in Table 1. Majority of patients were female in both the treatment groups, with the mean (SD) age of all enrolled patient was 50.3 (11.69). The mean (SD) dose of DA-α at week 1 and 12 was 25.70 (6.08 µg) and

Table 1: Patient demographics (ITT population)

Variable	Darbepoetin alfa (N=31)	Erythropoietin alfa (N=32)	Overall (N=63)
Age (years)			
Mean (SD)	50.8 (12.35)	49.8 (11.18)	50.3 (11.69)
Median (range)	56.0 (27, 65)	50.5 (29, 64)	51.0 (27, 65)
Height (cm)			
Mean (SD)	157.3 (9.69)	157.0 (9.04)	157.2 (9.29)
Median (range)	157.0 (134.6, 184)	158.5 (134, 175)	158.0 (134, 184)
Weight (kg)			
Mean (SD)	58.73 (10.64)	61.44 (10.21)	60.11 (10.43)
Median (range)	59.00 (37, 79.4)	61.20 (41.0, 86)	61.00 (35, 86)
Gender, n (%)			
Male	15 (48.39)	12 (37.50)	27 (42.86)
Female	16 (51.61)	20 (62.50)	36 (57.14)

N=number of subject at each visit; N=total number of subjects

Table 2: Mean change in hemoglobin levels from Baseline to first evaluation visit (EOC)

Statistics	ITT Population (N = 63)		PP Population (N = 46)	
	Darbepoetin alfa (n=31)	Erythropoietin alfa (n=32)	Darbepoetin alfa (n=23)	Erythropoietin alfa (n=23)
Baseline				
n	29	29	21	20
Mean (SD)	8.86 (0.89)	8.70 (0.84)	8.81 (0.99)	8.81 (0.76)
End of first evaluation visit				
n	29	29	21	20
Mean (SD)	11.28 (1.24)	11.02 (1.31)	11.43 (1.23)	11.30 (0.68)
Within group comparison				
p-value[#]	<.0001	<.0001	<.0001	<.0001
Mean change	2.42	2.32	2.62	2.50
95% CI	(1.92-2.92)	(1.78-2.87)	(2.04-3.20)	(2.08-2.91)
Between group comparison				
Mean change	0.23		0.12	
95% CI	(-0.62, 1.09)		(-0.58-0.82)	
p-value[**]	0.5837		0.7220	

N=number of subject at each visit; N=total number of subjects; [#]p-values were obtained using paired t test for mean (two tailed, α 0.05); [**]p-values were obtained using Unpaired t Test for mean change (two tailed, α= 0.05); Note: Patients taken where Hb≤10 at screening

Table 3: Mean Change in hemoglobin levels from baseline to first evaluation period (EOC) after adjusting covariates using ANCOVA model

Coefficient	Estimate	Standard error	95% CI of Mean	p-value*
ITT Population (N = 63)				
Baseline Value	-0.66698	0.193846	[-1.055--0.279]	0.0011
Darbepoetin alfa	0.202635	0.33117	[-0.461-0.866]	0.5431
Erythropoietin alfa	0.0000	-	-	-
PP Population (N = 46)				
Baseline Value	-0.63959	0.174093	[-0.992--0.287]	0.0007
Darbepoetin alfa	0.126821	0.30093	[-0.482-0.736]	0.6758
Erythropoietin alfa	0.0000	-	-	-

Model: Change in Hb levels = Treatment Group+ Site + Baseline value; [*]p-value was calculated using ANCOVA (two tailed, α= 0.05).

26.67 (11.68 µg), respectively. However there was significant dose changes in subjects assigned to EPO group.

Efficacy evaluation

Primary analysis

In ITT population, both treatment groups showed gradual increase in Hb levels from baseline at the end of first evaluation period, with the mean change in Hb levels from baseline in DA-α and EPO group was 2.42 gm/dL and 2.32 gm/dL, respectively (within group comparison, p<0.001 for each). Similar trend of increase in Hb levels from baseline at the end of first evaluation period was observed in PP population. However, the mean change in Hb from baseline to the first evaluation period was similar in the DA-α (11.28 g/dL; SD 1.24) and EPO (11.02 g/dL; SD 1.31) groups (Table 2). The difference in the mean change in Hb between these two groups was 0.23 g/dL (95% CI -0.62, 1.09, p=0.5837). This difference was not statistically significant or clinically relevant despite the reduced frequency of DA-α administration (Table 2).

After adjusting for covariates (using ANCOVA), the difference in the mean change in Hb between these two groups was 0.20 g/dL (95% CI -0.461-0.87) (Table 3). The lower limit of the two-sided 95% CI of primary endpoint was above the pre-specified non-inferiority margin of -0.5 g/dL, demonstrating that DA-α was as effective as EPO in maintaining the mean Hb in pre-dialysis patients. The robustness of the ITT analysis was confirmed by analysing the primary endpoint using the PP analysis set (Tables 2 and 3). In PP population, the lower limit of the 95% CI was -0.48, which was well above the pre-specified non-inferiority margin of - 0.50 g/dL.

Secondary analyses

The early response in increase in Hb levels at week 4 was observed in both the treatment groups. The mean change in Hb from baseline to week 4 was similar in the DA-α (1.18 g/dL; SD 0.23) and EPO (1.16 g/dL; SD 0.17) groups. The difference in the mean change in Hb between these two groups was 0.02 g/dL (95% CI --0.55, -0.59, p=0.94). This difference was not statistically significant despite the reduced frequency of DA-α administration. Similar trend of early increase in Hb levels from baseline was observed in PP population (difference in the mean change: -0.00, p=0.99). At the end of second evaluation visit, difference in the mean change in Hb levels between both the treatment was not statistically significant in ITT (p=0.5555) and PP population (p=0.8267).

In ITT population, the proportion of patients who achieved the target Hb level by the end of the first evaluation visit (EOC) was similar in both the treatment groups (DA-α vs EPO: 41.94% vs 56.25% respectively; OR [95% CI] = 0.57 [0.21 -1.54], p=0.2654). Similar trend was observed in PP analysis (DA-α vs EPO: 39.13% vs 86.95% respectively; OR [95% CI] = 0.0965 [0.02-0.42], p=0.0019). In ITT, the KM estimated median time to achieve the target Hb after DA-α and Erythropoietin alfa treatment was 6 weeks and 4.5 weeks. Similar trend was observed in PP population (DA-α: 6 weeks and Erythropoietin alfa: 4 weeks). The proportion of patients who maintained their Hb levels within the target Hb range (10-12 gm/dL) by the end of maintenance phase was statistically similar in both the treatment groups (DA-α vs EPO: 54.84% vs 65.63%, respectively; OR [95% CI] = 0.61 [0.22-1.70], p=0.3420) in ITT

analysis. Similar trend was observed in PP population (DA-α vs EPO: 71.43% vs 95.00%, respectively; OR [95% CI] = 0.131 [0.01-1.21], p=0.0735). These results demonstrate that DA-α does not increase Hb variability compared with EPO, despite the reduced frequency of dosing. Furthermore, a smaller number of dose adjustments were noted in DA-α-treated patients compared to EPO-treated patients.

Safety evaluation

Eight (25.80%) patients in DA-α group and 8 (25%) patients in EPO group experienced at least one TEAE during the study period. Most of these TEAEs were either mild or moderate in severity; one patient (3.12%) in EPO group experienced severe TEAE (cardiac failure), which was considered as a serious adverse event. None of patient in DA-α group reported TEAE that was related to the study drug. In EPO group, one patient reported a TEAE that was probably related to the study drug. Four patients (13%) in DA-α group and two patients (6%) in EPO group reported Serious TEAEs. The most commonly reported events in both the treatment group were cough (DA-α vs erythropoietin: 9.67% vs 3.12%), iron binding capacity total decreased (3.22% vs 6.25%), oedema peripheral (6.45% vs 3.12%), thrombocytopenia (3.22% vs 6.25%), and serum ferritin decreased (6.45% vs 3.12%). Clinical laboratory evaluation of haematology, biochemistry and coagulation throughout the study showed no unexpected changes that could be attributable to the study drug. Vital signs were monitored throughout the study, and no changes in mean blood pressure or heart rate were observed in either treatment group. Overall, the safety profile of DA-α was similar to that of EPO, and no antibody formation to either treatment was detected.

Discussion

To the best of our knowledge, this is the first study designed to compare the efficacy and safety of DA-α versus EPO for treating renal anemia among Indian pre-dialysis CKD patients. Our study achieved its primary efficacy endpoint demonstrating non-inferiority of DA-α compared to EPO, the most widely used comparator. The results of this randomized, active controlled study demonstrated that DA-α is as effective as EPO for treating renal anaemia in pre-dialysis patients, but at a reduced dose frequency. Darbepoetin alfa-treated patients successfully maintained Hb within the target and therapeutic ranges during the study, with a smaller number of dose adjustments as compared with the EPO -treated patients. Thus, the use of DA-α eliminates the need for frequent monitoring and dose adjustments. Also similar increases in Hb levels were seen in DA-α and EPO-treated pre- dialysis patients.

Evaluating iron availability for erythropoiesis is an important consideration when treating anaemia in CKD patients. Iron deficiency has the potential to inhibit the response to erythropoietin and DA-α and influence the measurements of efficacy. Hence, our study included iron supplementation in accordance with the clinical practice guidelines and recommendations for the correction of anemia in CKD pre-dialysis patients [15, 16]. Thus, most patients in both treatment groups received iron supplementation and maintained serum ferritin concentrations above the recommended level, and there was no difference between treatment groups with respect to serum ferritin concentrations.

The safety profile of DA-α was similar to that observed in the EPO group. The majority of adverse events were related to the underlying disease and its treatment, and only one TEAE was reported as being related to EPO; none of the reported adverse events were related to DA-α. The safety data of DA-α in the present study appears to be better than the reported trials. The tolerability data are supported by previous reports suggesting that DA-α is well tolerated, with a safety profile similar to that of EPO.[17,18]

Conclusion

Our study results demonstrate that DA-α given at a reduced dose frequency is as effective and well tolerated as EPO for treating renal anemia in Indian pre-dialysis CKD patients.

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