Egyptian Journal of Pure and Applied Science

Evaluation of the efficacy of long acting erythropoietin versus short acting erythropoietin in the treatment of anemia in Egyptian patients under hemodialysis

Nahla S. Kotb[1], Nahla E. EL-Ashmawy[2], Eman G. Khedr[3] and Fathy Salem[4]

[1,4] *National Organization for Research and Control of Biologicals, Giza, Egypt*
[2, 3] *Biochemistry Department, Faculty of Pharmacy, Tanta University, Tanta, Egypt*

ARTICLE INFO

Article history:
Received 28 October 2018
Accepted 06 March 2019

Keywords:
Anemia;
Chronic kidney disease;
Erythropoietin;
Hemodialysis.

ABSTRACT

Anemia is one of the most common complications of chronic kidney disease. Treatment of anemia in Egyptian patients with chronic kidney disease (CKD) and under hemodialysis occurs via erythropoiesis stimulating agents (ESA). A multicenter, open label randomized, prospective, parallel study was conducted in the current study to evaluate efficacy and safety of darbepoetin alfa versus epoetin alfa in patients under hemodialysis. The primary efficacy endpoint was the change in hemoglobin concentration between both treatment groups at evaluation period (weeks 20 - 24). Adverse events following administration, including pre-specified adverse event of interest, blood transfusion requirement, blood pressure and hemoglobin excursions, relation between the marker of inflammation (HS-CRP) and hemoglobin in hemodialysis patients at baseline were assessed. Only 98 patients completed the study, fifty patients received epoetin alfa and the remaining 48 patients received darbepoetin alfa (DA). The mean hemoglobin levels at evaluation period for darbepoetin alfa and epoetin alfa groups were 11.75 g/dl and 10.98 g/dl, respectively. The mean difference between two treatments was 0.77 g/dl, which was statistically significant at $p < 0.0001$. Also, the hemoglobin difference was statistically significant between the two groups starting from the eighth week to the end of the study. The most common adverse events reported during the study were hypertension 10 (21.2 %), 8 (15.4 %) and cough 8 (15.4 %), 10 (21.2 %) for darbepoetin alfa and epoetin alfa, respectively. The difference in incidence of adverse event between two groups was not statistically significant. A negative correlation was observed between serum CRP and hemoglobin level in hemodialysis patients. In conclusion Treatment with darbepoetin alfa was more efficient in achieving target hemoglobin level with lower time than epoetin alfa. Furthermore, CRP could be used as a marker for ESA hypo-responsiveness.

Introduction

Chronic kidney disease (CKD) is highly prevalent and a growing global health concern. Anemia is one of the most common complications of CKD especially in end stage renal disease patients (ESRD) under regular hemodialysis. There are many different causes for anemia but it is mainly due to deficiency of endogenous erythropoietin (EPO) production by the failing kidney [1]. The vast majority of ESRD patients require exogenous erythropoietin to achieve and maintain target hemoglobin Level, as well as decreasing the need of blood transfusion and improve quality of life [2-4]. In the Egyptian market there are four available erythropoiesis stimulating agents (ESA), classified into short and long acting ESA, including epoetin alfa and epoetin beta as short acting and darbepoetin alfa and methoxy polyethylene glycol epoetin beta as long acting. The ESAs distributed through the Egyptian Health Insurance are darbepoetin alfa and the locally manufactured erythropoietin epoetin alfa. The vast majority of CKD patients are covered by health insurance scheme and the

two mentioned ESAs are listed in the health insurance. This addresses the following question, what is the prioritization of administrating both products? The answer will be based on controlled management of the resources through affording the most effective product and excluding products with low quality which will increase the quality of life of CKD patients.

The short acting erythropoietin epoetin alfa is a recombinant human erythropoietin (RHuEPO), which has proven efficacy in treating anemia in CKD patients. Its dose is usually administered two or three times weekly [5]. By contrast, long acting darbepoetin alfa is a glycoprotein analog of erythropoietin. It is created by introducing five amino acid changes into the primary sequence of erythropoietin produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology to create two extra consensus N-linked carbohydrate addition sites.

Darbepoetin alfa stimulates erythropoiesis as both endogenous erythropoietin (EPO) and recombinant human erythropoietin. However, due to the additional carbohydrate chains, darbepoetin alfa has an approximately 3-fold longer terminal half-life and longer in vivo biological activity than RHuEPO, allowing therefore darbepoetin alfa to be administered at extended intervals compared to RHuEPO. Accordingly, darbepoetin alfa dose is once every week (QW) or once every two weeks (Q2W) or once per month (QM) [6-8].

Inflammation is common among haemodialysis patients. Over several inflammatory markers investigated, the most widely one is serum C-reactive protein (CRP). Two third of hemodialysis patients are chronically inflamed (C-reactive protein > 10 mg/dl). The causes of inflammation usually result from graft or fistula infections, incompatible dialysis membrane, dialysate and endotoxin exposure. All dialysis facilities in Egypt do not routinely measure CRP although several studies have shown a relationship between serum C-reactive protein and anemia [9-12].

The objective of the present study was to evaluate efficacy and safety of darbepoetin alfa, administered once every week, versus epoetin alfa, administered three times per week, for the treatment of anemia among Egyptian CKD patients under hemodialysis.

Subjects and Methods

Patients

Eligible patients met the following criteria: clinically stable patients ≥ 18 years of age, both genders, had a diagnosis of ESRD defined as glomerular filtration rate (GFR) less than 15 ml/min/1.73 m^2 on regular hemodialysis had hemoglobin level < 10 g/dl during screening, adequate iron store defined as transferrin saturation (TSAT) ≥ 20 % or serum ferritin level > 100 ng/ml. Patients were excluded according to the following criteria: uncontrolled hypertension, had a diagnosis of myocardial infarction, human immunodeficiency virus (HIV) or hepatitis B infection, systemic hematological disease (sickle cell anemia or hemolytic anemia), androgen or immunosuppressive therapy administration before enrollment, pregnancy or breast feeding, gastrointestinal bleeding, life expectancy less than 12 months, aluminum toxicity, scheduled to receive a kidney transplant and uncontrolled secondary hyperparathyroidism.

Drugs

Investigational products were provided for subcutaneous administration [13,14]. The initial dose was determined using the weight-based calculation of 0.45 µg/kg once every week for darbepoetin alfa (Aranesp; Amgen, USA) group and 100 IU /kg three times weekly for epoetin alfa (SEDICO, Egypt) group. Doses were adjusted to achieve and then maintain hemoglobin level with a target range of 10.0 - 12.0 g/dl based on the hemoglobin rate of rise. The dose was reduced by 25 % if the hemoglobin rate of rise in a 4-week period exceeded 2 g/dl.

Treatment was interrupted if hemoglobin exceeded 14 g/dl. In order to support the erythropoietic response for the two treatments, supplementation of iron therapy was recommended.

Study Design

The study was conducted at three centers in Egypt; two centers in Benha and one center in Zefta from January 2015 to June 2015. This study was approved by the Research Ethics Committee at the Faculty of Pharmacy (Tanta University, Egypt). All patients (104 enrolled patients) provided written informed consent to participate in the study, which was carried out in accordance with the Helsinki declaration**.**

Eligible patients were randomized and allocated to the two treatment groups in a 1:1 ratio using permuted block randomization with a block size of four. This was an open label study; therefore the treatment assignment was not masked **Fig. 1**.

Analysis and Methods

Blood samples were collected once monthly (QM) for measuring complete blood count (CBC), transfusion requirements, adverse events and blood pressure were recorded at each visit. Reticulocyte count, serum ferritin and transferrin saturation (TSAT) were measured every 12 weeks, as well as high sensitive serum C-reactive protein (HS-CRP) at baseline and at the end of the study. Parathyroid hormone, calcium and phosphorus were also measured. Efficacy of dialysis was measured by (Kt/v) and urea reduction ratio (URR).

The primary efficacy endpoint in the current study was the change in hemoglobin concentration between both treatment groups during the evaluation period (Weeks 20-24), while the secondary efficacy end points included the percentage of patients who successfully achieved hemoglobin levels ≥ 10, 11 g/dl over the study period in both treatment groups, adverse events following administration of ESAs including pre-specified adverse event of interest such as blood transfusion requirement, blood pressure and hemoglobin excursions (> 12.0, > 13.0, or > 14.0 g/dl), as well as relation between the marker of inflammation (HS-CRP) and hemoglobin in hemodialysis patients at baseline and evaluating the effect of ESAs on HS-CRP level in ESRD.

Statistical analysis

With a two-sided 5 % significance level and a power of 80 %, a sample size of 51 patients per group was necessary to find difference in mean hemoglobin concentration between two groups of 0.5 g/dl within-groups standard deviation. One hundred four patients (who were fulfilling the study inclusion criteria) were recruited.

Continuous variables are expressed as mean ± standard deviations, categorical variables as numbers and percentages in brackets. Comparison between two treatments was done by independent sample *t* test or Mann-Whitney's U test depending on the normality assumption, chi-square test or Fischer's exact test for qualitative date, one-way analysis of variance to test difference of hemoglobin between groups during the study period.

Descriptive statistics for secondary end point, weakly dose derived from the received dose and the frequency of administration, ratio of dose calculated by dividing the weekly dose during the evaluation period by the initial weekly dose, the time to first hemoglobin level ≥ 10, 11 g/dl was estimated by Kaplan-Meier method, subjects not achieving the end-point were censored at their last hemoglobin assessment. Correlation was assessed by Spearman's or Pearson correlation coefficient as appropriate .

Adverse events were tabulated, and the comparison was conducted between two treatments using Fischer's exact or chi square tests, percentage of patients with a Hb excursion > 12 g/dl were summarized descriptively. SPSS version 20 (IBM) was used for analysis. The level of significance was at $p < 0.05$.

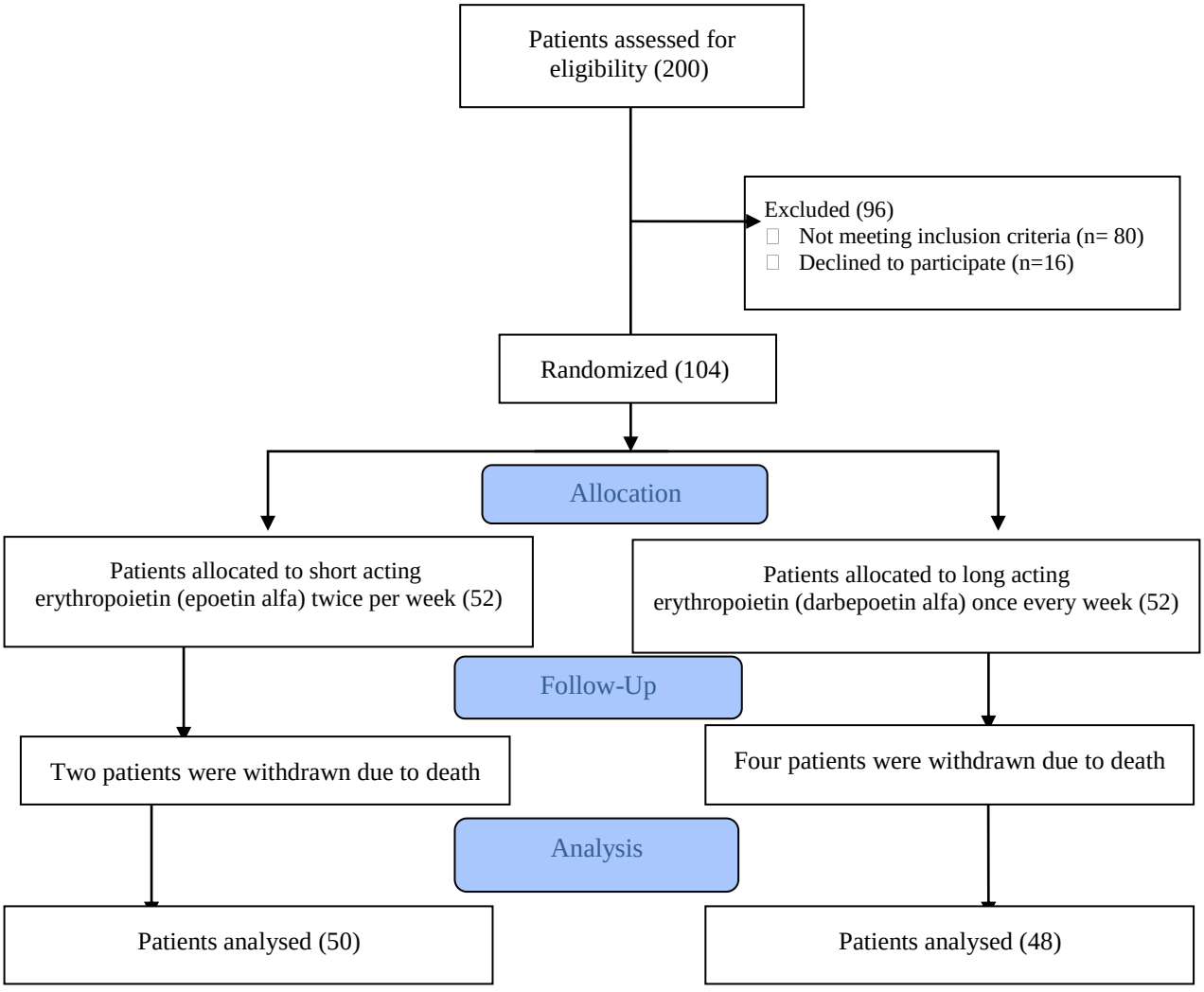

Fig. 1: A representative scheme for the study design.

Results

A total of 104 patients were enrolled in the study, where 98 patients completed the study, 48 patients in darbepoetin alfa and 50 patients in epoetin alfa **Fig. 1**. Baseline demographics and clinical characteristics were similar between two groups. There was no significant difference between the two groups in the studied parameters at baseline except for the body weight **Table 1.**

The most primary causes of ESRD in darbepoetin alfa and epoetin alfa groups were diabetes 16 (30.8 %), 14 (26.9 %) and hypertension 12 (23 %), 11 (21.2 %), respectively, whereas 100 % of patients in both groups had arteriovenous fistula as vascular access.

The higher percentage of patients 60 (57.6 %) were HCV positive; 33 (55 %) in darbepoetin alfa and 27 (45 %) in epoetin alfa groups, respectively, while 44 patients (42.3 %) were HCV negative .

During the study period there was no significant difference in iron parameters between the two treatment groups **Table 2**. The percentage of patients who received concomitant iron treatment were 26 (50 %) in darbepoetin alfa and 24 (46.1 %) in epoetin alfa groups.

Table 1: Patient demographics and clinical characteristics at baseline

Variables	Darbepoetin alfa (N=52)	Epoetin alfa (N=52)	*p* value
Age (Years)	48.4 ± 13.39	51 ± 10.56	NS
Gender			
Female	22 (42 %)	23 (44 %)	
Male	30 (58 %)	29 (56 %)	NS
Weight (Kg)	77.14 ± 6.99	73.05 ± 7.71	0.02
Iron supplementation	26 (50 %)	24 (46.1 %)	NS
Etiology of kidney disease			
Diabetes	16 (30.8 %)	14 (26.9)	NS
Hypertension	12 (23.1 %)	11 (21.2 %)	NS
Polycystic kidney disease	4 (7.7 %)	3 (5.8 %)	NS
Glomerulonephritis	6 (11.5 %)	7 (13.5 %)	NS
Interstitial nephritis	4 (7.7 %)	6 (11.5 %)	NS
Unknown	10 (19.2 %)	11 (21.2 %)	NS
Systolic BP (mmHg)	128.571 ± 15.366	127 ± 20.367	NS
Diastolic BP (mmHg)	79.714 ± 9.54	82 ± 10.635	NS
Albumin (g/dl)	3.75 ± 0.310	3.68 ± 0.282	NS
Ferritin (ng/ml)	625.7 ± 354	612 ± 338	NS
TSAT (%)	25.5 ± 8.07	26.5 ± 7.65	NS
Hemoglobin (g/dl)	8.63 ± 0.99	8.62 ± 0.83	NS
Calcium (mg/dl)	9.44 ± 1.1	9.14 ± 0.61	NS
Phosphate (mg/dl)	4.40 ± 0.63	4.71 ± 0.70	NS
CRP (mg/dl)	13.34 ± 7.84	11.31 ± 8.54	NS
Reticulocytes (%)	0.73 ± 0.22	0.72 ± 0.21	NS
Hematocrit (%)	26.26 ± 2.85	26.38 ± 2.25	NS
Red blood cells (10^6/mm^3)	2.952 ± 0.31	2.882 ± 0.25	NS
White blood cells (10^3/mm^3)	7.900 ± 1.3	7.897 ± 1.48	NS
Platelets (%)	215.411 ± 37.65	216.617 ± 31.31	NS
PTH (pg/ml)	324.3 ± 178.5	293.2 ± 137.5	NS
Vascular access			
AVF	52 (100 %)	52 (100 %)	NS

BP: blood pressure; **TSAT:** transferrin saturation; **CRP:** C-reactive protein; **PTH:** parathyroid hormone; **AVF:** Arteriovenous Fistula
NS: Non-significant, *p* value < 0.05 is considered significant

Table 2: Comparison between the two groups regarding iron parameters during the study period

Iron parameters	Darbepoetin alfa	Epoetin alfa	*p* value
Ferritin at baseline	625.7 ± 354	612 ± 338	NS
Ferritin at 12 weeks	709.1 ± 296	638.7 ± 287.3	NS
Ferritin at 24 weeks	627.2 ± 208.7	607.9 ± 223.9	NS
TSAT at baseline	25.5 ± 8.07	26.5 ± 7.65	NS
TSAT at 12 weeks	26.8 ± 7.3	26.8 ± 5.6	NS
TSAT at 24 weeks	27.7 ± 7.6	25.8 ± 5.2	NS

NS: Non-significant, *P* value < 0.05 is considered significant

Efficacy

The mean hemoglobin level at the end of the evaluation period (24 weeks) was 11.75 g/dl for darbepoetin alfa group and 10.98 g/dl for epoetin alfa group. The mean difference between the two treatments was 0.77 g/dl, which was statistically significant at $p < 0.0001$. In addition, the hemoglobin difference was statistically significant between the two groups starting from the eighth week to the end of the study.

The mean hemoglobin change from baseline to evaluation period was 3.12 g/dl and 2.36 g/dl for darbepoetin alfa and epoetin alfa groups, respectively **Fig. 2**.

Secondary end point

Forty-nine patients (94.2 %) in the darbepoetin alfa group achieved hemoglobin level ≥ 10 g/dl, whereas 46 patients (88.5 %) in epoetin alfa group achieved hemoglobin level ≥ 10 g/dl. The percentage difference between two the treatments was not statistically significant $p = (0.35)$. The proportion of patients who achieved hemoglobin ≥ 11 g/dl was higher in patients treated with darbepoetin alfa [44 of 52 (84.6 %)] than those treated with epoetin alfa [27 of 52 (51.9 %)]. The difference was statistically significant ($p < 0.001$).

The mean time to achieve hemoglobin level ≥ 10 g/dl in darbepoetin alfa and epoetin alfa groups was 9.69 ± 6.8 and 12.38 ± 7.33 weeks, respectively **Fig. 3.** The mean time to achieve hemoglobin level ≥ 11 g/dl in darbepoetin alfa and epoetin alfa groups was 16.1 ± 7.58 and 20.2 ± 6.44 weeks, respectively ($p = 0.001$) **Fig. 4.**

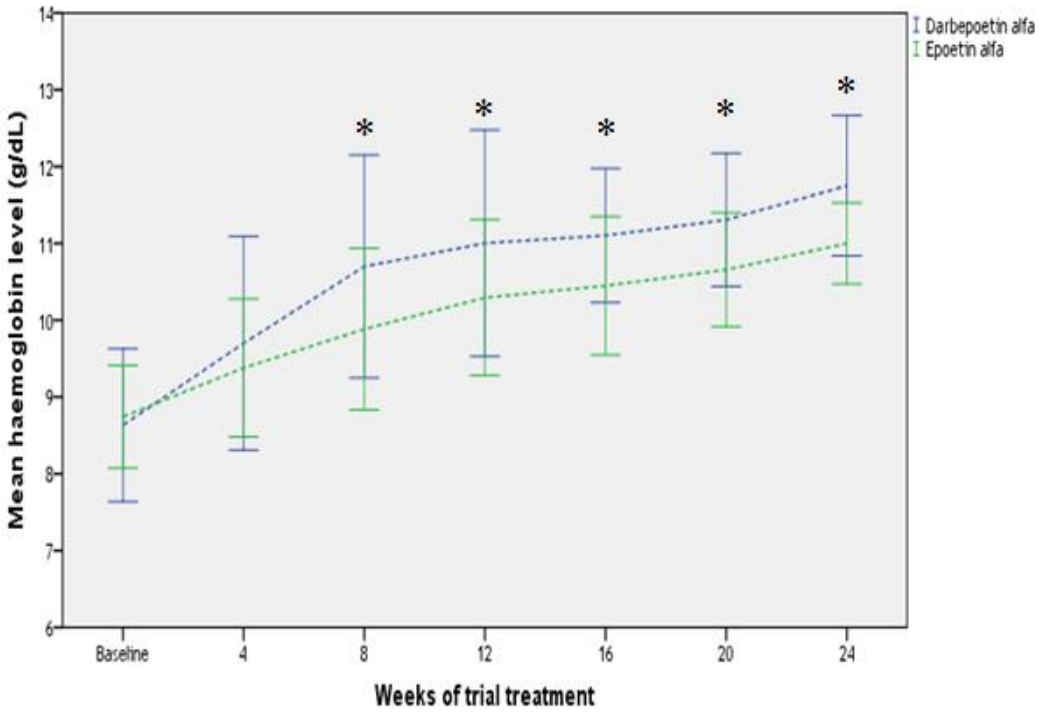

Fig. 2: Mean hemoglobin levels change over the study period in hemodialysis patients receiving either darepoetin alfa or epoetin alfa.

***** Difference between groups was significant ($p < 0.001$).

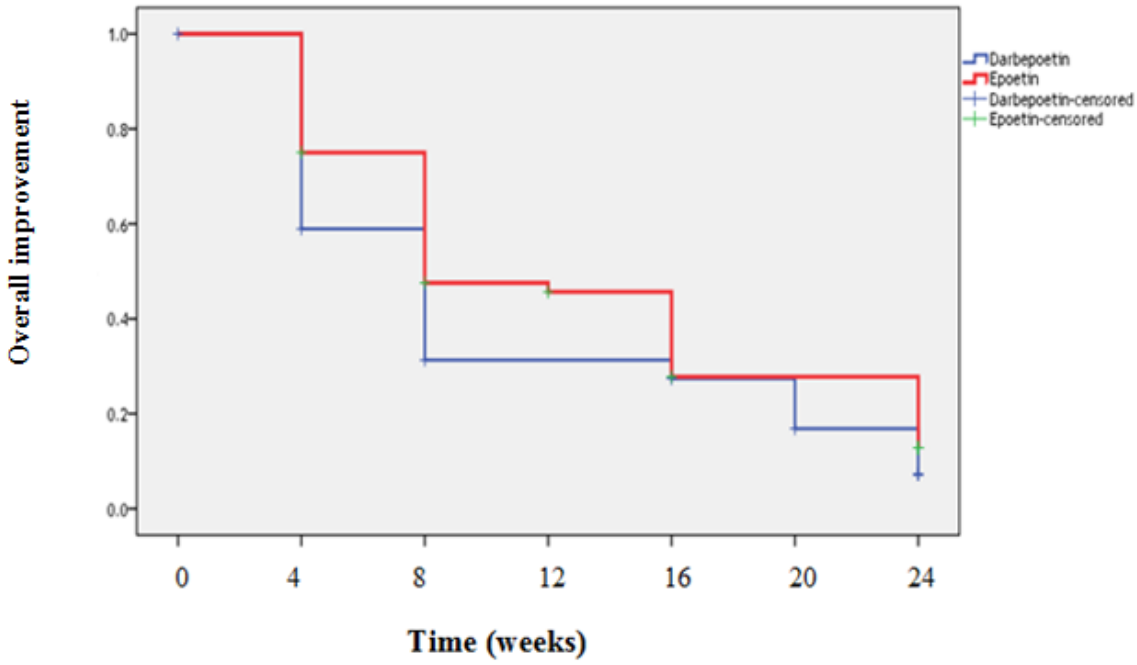

Fig. 3: Kaplan- Meier plot of overall improvement of hemoglobin (Hb ≥ 10) in darbepoetin alfa and epoetin alfa groups though the treatment period.

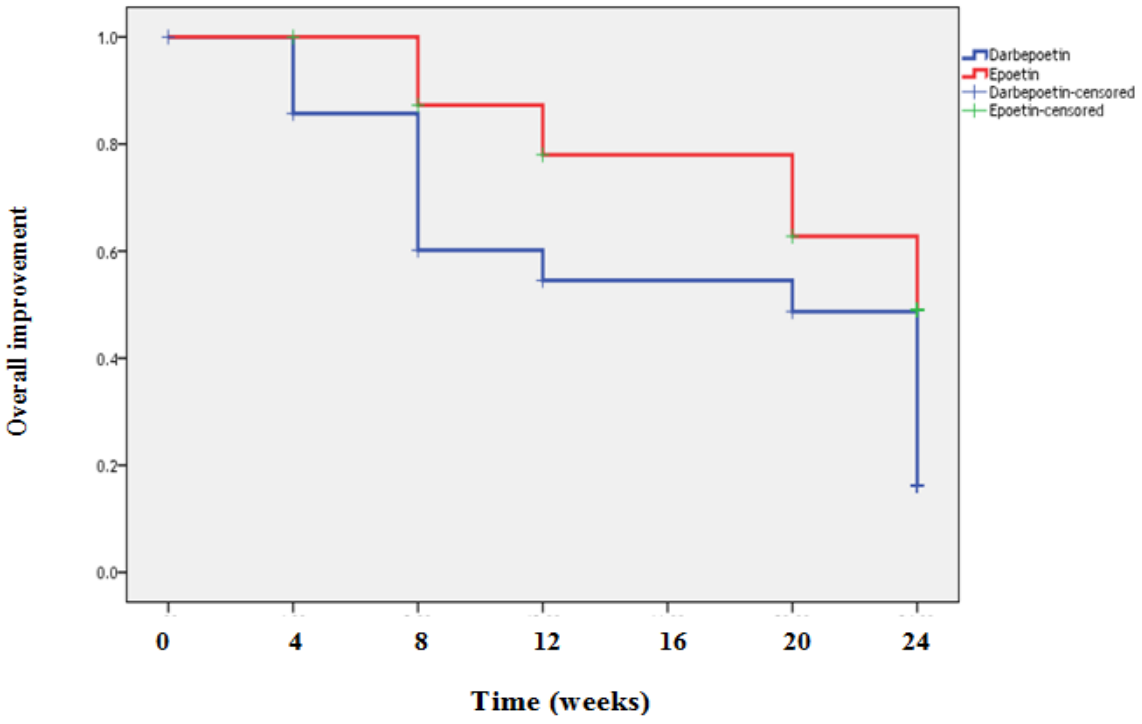

Fig. 4: Kaplan- Meier plot of overall improvement of hemoglobin (Hb ≥ 11) in darbepoetin alfa and epoetin alfa groups though the treatment period.

The mean weekly equivalent dose at baseline was 40.6 ± 2.57 µg for darbepoetin alfa and 8896.5 ± 1012.2 IU for epoetin alfa. The mean weekly equivalent dose at evaluation period (20 - 24 weeks) was 29.3 ± 5.9 µg for darbepoetin alfa and 7862 ± 1597.4 IU for epoetin alfa. The average weekly doses ratio was decreased by 0.88 ± 0.13 and 0.738 ± 0.15 from baseline to evaluation period for epoetin alfa and darbepoetin alfa, respectively.

The ratio of darbepoetin alfa and epoetin alfa dose at evaluation period to the baseline was 0.72 and 0.88 respectively.

There was a significantly negative correlation between hemoglobin level and high sensitive C-reactive protein ($r = -0.493$, $p < 0.001$) in hemodialysis patients at baseline **Fig. 5.**

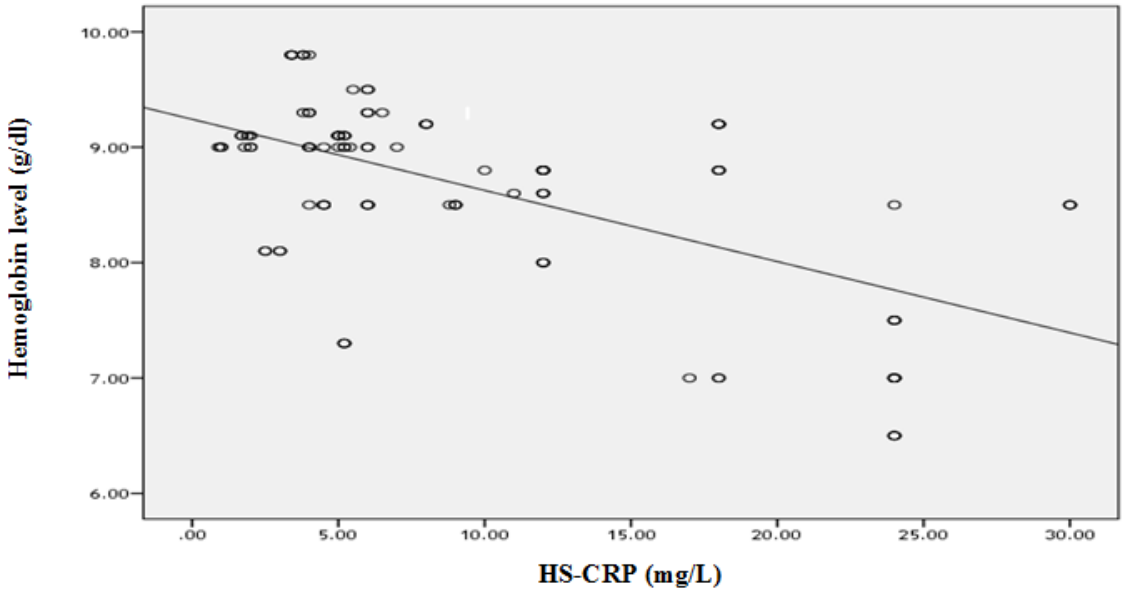

Fig. 5: Correlation between highly sensitive C-reactive protein (HS-CRP) and hemoglobin level in hemodialysis patients at baseline (55 patients). At the end of the study there was no significant difference in serum CRP level between the two treatment groups.

Adverse events

During the study, a total of 40 patients (77 %) in darbepoetin alfa group and 50 (96 %) patients in epoetin alfa group reported at least one adverse event, one patient might manifest more than one event.

Table 3 demonstrates the adverse events reported during the study period and hemoglobin excursion. The most common adverse events reported during the study were hypertension 10 (21.2 %), 8 (15.4 %), cough 8 (15.4 %), 10 (21.2 %) and pain at site of injection 8 (15.4 %), 12 (23.2 %) for darbepoetin alfa and epoetin alfa groups, respectively. Adverse events of interest were vascular access thrombosis 2 (3.8 %) & 5 (9.6 %), stroke 3 (5.8 %) & 7 (13.5 %) and myocardial infarction 2 (3.8 %) & 2 (3.8 %) for darbepoetin alfa and epoetin alfa groups, respectively. Four patients (7.6 %) in darbepoetin alfa group and two patients (3.8 %) in epoetin alfa group died during the study. The fetal adverse events were not considered related to treatment as determined by the investigator. The difference in incidence of adverse events between the two groups was not statistically significant.

Hemoglobin excursion

Ten patients (19.3 %) and 4 patients (7.7 %) in darbepoetin alfa and epoetin alfa groups, respectively had hemoglobin value > 12.0 g/dl during the study (p = 0.085). Only one patient in darbepoetin alfa group had hemoglobin > 13.0 g/dl and another patient in the same group had hemoglobin > 14.0 g/dl.

Blood pressure

No significant difference was recorded between the two groups in systolic and diastolic blood pressure during the study.

Blood transfusion

Five patients (9.6 %) in the darbepoetin alfa group and 6 patients (11.5 %) in epoetin alfa group received blood transfusion during the study period. The difference in blood transfusion between two groups was not statistically significant.

Discussion

The Canadian Society of Nephrology (CSN) work group recommends that for CKD patients, with anemia on erythropoiesis-stimulating agents (ESAs), an acceptable range for Hb is 9.5 - 11.5 g/dl with a target of 10-11 g/dl and does not support the use of ESAs to target Hb > 11.5 g/dl [15], whereas the National Kidney Foundation Kidney Disease Outcome Quality Initiative (KDOQI) recommends targeting Hb between 11.0 and 12.0 g/dl [16]. It is desirable to determine the target Hb in dialysis patients depending on their ages, comorbidities and the patient's disease state. In the current study, we have chosen the target of 10 - 12 g/dl according to current international literature [17]. It is important to use ESA therapy to generally maintain diabetic CKD patients with Hb level ranging between 10 and 12 g/dl [18]. Erythropoiesis stimulating agent (ESA) treatments targeting mild anemia (10 - 12 g/dl) can decrease the risk of occurrence of cardiovascular disease (CVD) in patients with hypertension and diabetes mellitus. Two systematic reviews suggested that improvements in quality of life are maximized when Hb level ranges between 10 - 12 g/dl [19,20].

This study is conducted to evaluate the efficacy and safety of darbepoetin alfa versus the locally manufactured epoetin alfa, which is also distributed through health insurance in Egypt to correct anemia in patient under hemodialysis.

Table 3: Adverse event reported during the study and hemoglobin excursion

Adverse events	Darbepoetin alfa	Epoetin alfa	*p* value
Hypertension	10 (21.2 %)	8 (15.4 %)	NS
Vascular access thrombosis	2 (3.8 %)	5 (9.6 %)	NS
Stroke	3 (5.8 %)	7 (13.5 %)	NS
Myocardial infarction	2 (3.8 %)	2 (3.8 %)	NS
Pain at site of injection	8 (15.4 %)	12 (23.1 %)	NS
Vomiting	6 (11.5 %)	5 (9.6 %)	NS
Diarrhea	1 (1.9 %)	0 (0 %)	NS
Procedural hypotension	6 (11.5 %)	9 (17.3 %)	NS
Cough	8 (15.4 %)	10 (21.2 %)	NS
Edema	3 (5.8 %)	4 (7.7 %)	NS
Death	4 (7.6 %)	2 (3.8 %)	NS
Hb excursion			
Hb > 12 (g/dl)	10 (19.3 %)	4 (7.7 %)	NS
Hb > 13 (g/dl)	1 (1.9 %)	0 (0 %)	NS
Hb >14 (g/dl)	1 (1.9 %)	0 (0 %)	NS

NS: Non-significant

Demographical baseline and other baseline characteristics showed a balance between the two treatment groups. The drugs were administrated to achieve and maintain hemoglobin level within the target of 10 - 12 g/dl.

Analysis of primary efficacy results demonstrated that darbepoetin alfa is more efficient in achieving target Hb than epoetin alfa. There was a significant difference ($p < 0.001$) in mean hemoglobin levels at evaluation period for patients in darbepoetin alfa group, compared to those in epoetin alfa group which is greater than 0.5 g/dl. This difference is considered clinically relevant [21] and is not demonstrated before. The result from meta-analysis published in 2014 concluded that there is currently insufficient evidence to suggest the superiority of any ESA formulations on each other [22].

The mean initial rates of Hb concentration in the first four weeks were 1.1 g/dl (95 % CI 0.7 - 1.6) and 0.7 g/dl (95 % CI 0.4 - 1) in darbepoetin alfa and epoetin alfa groups respectively. This is consistent with the finding in ESA trials of CKD-associated anemia where the mean initial rates of Hb concentration increase were of 0.7 to 2.5 g/dl in the first 4 weeks [17]. The proportion of patients who achieve hemoglobin ≥ 11 g/dl was higher in patients treated with darbepoetin alfa [44 of 52 (84.6 %)] Than with epoetin alfa [27 of 52 (51.9 %)] where the difference was statistically significant ($p < 0.001$). However, a rise in Hb of greater than 2.0 g/dl over a 4-week period should be avoided [23]. Eight (15.4 %) and two (3.8 %) patients had hemoglobin increases ≥ 2 g/dl/4 weeks in darbepoetin alfa and epoetin alfa groups, respectively

Longer time needed to reach the target hemoglobin was associated with significantly higher risk of hospitalization and mortality [24]. The mean time to achieve the predefined lower limits of 10 g/dl was lower in darbepoetin group than epoetin alfa group with no significant difference but mean time to achieve hemoglobin ≥ 11 was lower in darbepoetin alfa and the difference was statistically significant. Another study concluded also that switching from TIW epoetin to QW darbepoetin provided saved time and effort that can be used by the nursing team in different activities aimed to improve patient care, less frequent administration of darbepoetin alfa offer advantage over epoetin alfa for patient and health care team in term of convenience, flexibility and improved compliance [25]. The findings of the current study, was also in agreement with the results of a published study, which concluded that darbepoetin is more effective in increasing hemoglobin and reducing creatinine levels than erythropoietin in a mean difference [26].

The frequencies of adverse events were similar between two treatments. In agreement with other finding, no significant difference was observed between the two treatment groups regarding the number of adverse events reported during the study period [26]. The most common adverse events were hypertension, cough and pain at site of injection, which agree with the results of a previously published study [27]. We therefore focused on cardiovascular adverse event (stroke and myocardial infarction) and vascular access thrombosis. One patient in darbepoetin alfa group and two patients in epoetin alfa group died during the study. The cause of death was not related to trial treatment by the investigator.

It was observed that serum CRP is negatively correlated with hemoglobin level in hemodialysis patients, which may be associated with relative erythropoietin resistance in hemodialysis patients. Our findings support the first direct evidence that inflammation, which is closely related to protein-energy malnutrition in hemodialysis patients [28], might affect anemia toward its intensification. This indicates association between inflammation, ESA hypo-responsiveness, and the requirement for higher ESA doses which agrees with the result finding in trials conducted to assess this relationship [29].

Conclusion

In summary, treatment with darbepoetin alfa Q weekly is more efficient than epoetin alfa in achieving target hemoglobin, with lower time. The clinical importance of serum high CRP concentration in hemodialysis patients as observed in the present study is dependent on the potential of serum CRP in predicting response to ESA therapy; therefore, CRP should be included in routine laboratory in dialysis center in Egypt.

Limitation of the study includes the potential bias in assessment which is inherent to all open label clinical trials.

Role of funding source

The author received fund from National Organization for Research and Control of Biologicals (NORCB).

Conflict of interest

No conflict of interest.

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