

Monthly Administration of Darbepoetin Alpha in Saudi Hemodialysis Patients: is it a Practical Regimen?



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ABSTRACT

Aim: In this study, we investigated the efficacy and safety of conversion of stable hemodialysis patients from the current short-acting r-HuEPO (EPO beta) to the long-acting darbepoetin.

Method: The study included 12 months of darbepoetin administration. The mean initial conversion ratio was 350 IU of short acting r-HuEPO to 1 microgram of darbepoetin. We adjusted the dose of darbepoetin to maintain hemoglobin levels between 11-12 g/dL. The study was carried out on 2 consecutive phases of 12 weeks each. Success with the extended dosing interval was defined as maintenance of mean hemoglobin >10.0 g/dl during each phase.

Result: There were 26 patients who fulfilled the entry criteria. Their mean age was 47.0 ± 17.13 years, and the mean duration on hemodialysis was 55.8 ± 14.0 months. The mean weekly dose increased from $28.75 \pm 4.2 \mu\text{g}$ in the biweekly frequency of dosing to $38.5 \pm 3.9 \mu\text{g}$ after switching to the monthly protocol. The hemoglobin levels were maintained at therapeutic range without statistically significant change throughout the study; the mean hemoglobin levels was $10.81 \pm .86 \text{ g/L}$ at start of the study and $10.86 \pm .76 \text{ g/L}$ at the end of 6 months. Continuing the darbepoetin in 12 patients for one year disclosed no significant change of the conversion ratio of the drug, and the mean of hemoglobin levels remained within the targeted limits.

Conclusion: Darbepoetin alpha is effective and safe for the treatment of anemia in hemodialysis patients even at monthly dose intervals and for long-term. With the the above mentioned conversion ratio and current prices, darbepoetin seems more expensive than the short acting erythropoetin beta by 15%, 58 % for the biweekly and monthly doses respectively. However, the longer dosing intervals are certainly much better convenience to patients and care takers in comparison with the currently used short acting ESAs.

Key words: Darbepoetin alpha, hemodialysis, monthly

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INTRODUCTION

Renal anemia is considered as an essential contributing factor to reduce the quality of life and to increase the cardiovascular morbidity in patients with advanced chronic renal failure (1). The management of uraemic anemia was revolutionized in the late 1980s by the commercial availability of recombinant human erythropoietin (r-HuEPO) (2). To be effective, however, rHuEPO needs to be given as frequent as three times per week. This frequency of administration is a burden for both patients and health care providers.

The advent of darbepoetin-alpha, a modified Epo with two additional glycosylation chains and extra sialic acid residues, has directed clinical interest to the modification of dosing intervals. The plasma disappearance half-life of darbepoetin- alpha is increased 2 to 3-fold relative to conventional Epo after either subcutaneous or intravenous administration both in adults and children (3). Several studies indeed demonstrated that the interval of subcutaneous darbepoetin- alpha injections can be extended to 2 weeks in dialysis patients and up to 4 weeks in patients with chronic renal failure (4,5). Data from clinical trials suggest that switching CKD patients receiving once weekly rHuEPO to once every 2 weeks darbepoetin alpha maintains target hemoglobin (Hb) concentration (6-8) . However, there is little reported evidence, if any, of switching hemodialysis patients directly from fortnightly darbepoetin alfa dosing to monthly darbepoetin alfa. As found by others (9,10) recently in Saudi Arabia, Shaheen FA et al (11) experienced gratifying results in hemodialysis patients switched to darbepoetin once weekly with more convenience of administration, and less frequency of dosing. The aim of our study is to establish the efficacy and safety of darbepoetin- alpha to maintain hemoglobin levels with biweekly and monthly dosing in hemodialysis patients for more convenience and savings.

MATERIAL AND METHODS

This single centre prospective exploratory study was conducted in Prince Salman Center for Kidney Diseases from November 2006 to November 2007. Patients were eligible for the trial if they were treated with erythropoietin for renal anemia, had stable hemoglobin concentrations for at least 12 weeks before the study, and were optimally dialyzed for at least 6 months prior to initiating darbepoetin alpha as judged by usual dialysis and serum chemistry parameters (SpKT/V: >1.2). Dialysis prescription and adequacy were not changed during the study period.

Patients with severe congestive heart failure (New York Heart Association Class III or IV), uncontrolled hypertension (pre-dialysis diastolic blood pressure >100 mmHg), grand mal epilepsy, clinical evidence of uncontrolled hyperparathyroidism or systemic hematologic disease were excluded from the study. Patients were also excluded if they had other causes of anemia such as folate, vitamin B12, or iron deficiency, undergone major surgery or if they had evidence of active blood loss or blood transfusions within 12 weeks before the study period. All female patients had a negative pregnancy test and were not breast-feeding at the time of entry into the study. The patients were not on drugs that could affect erythropoiesis. Each patient signed an informed consent and had a comprehensive history and physical examination at the beginning and at the end of the study. The patients continued the same medications they were taking prior to the beginning of the study including antihypertensives and iron supplements. The study was carried out on 2 consecutive phases: (The study design is presented schematically in Figure 1)

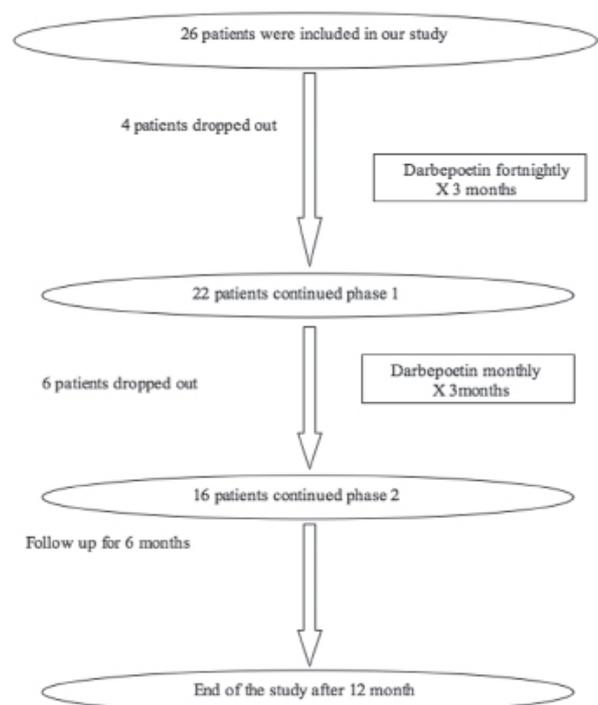


Figure 1. Patients disposition and evaluability.

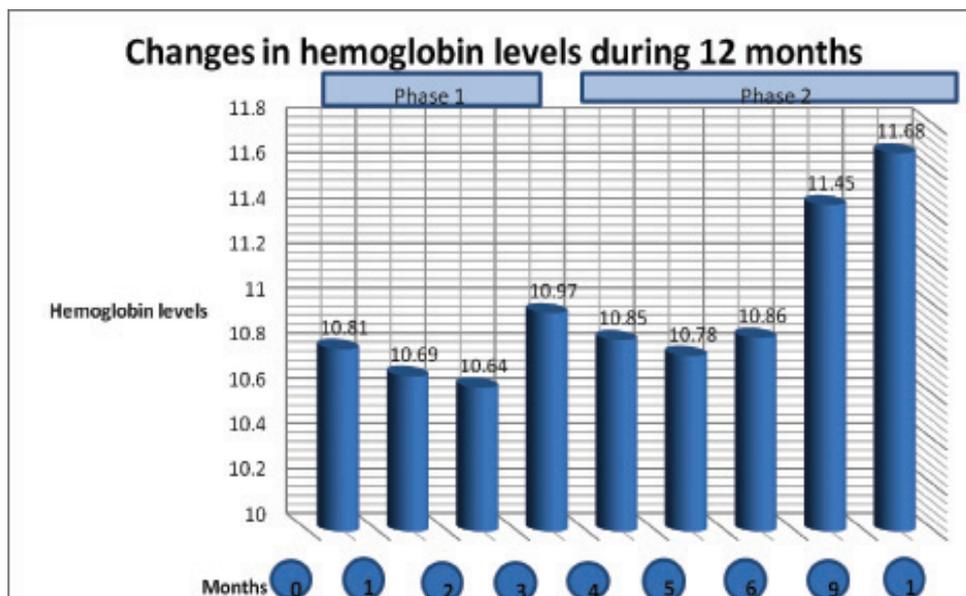


Figure 2. Changes in mean hemoglobin concentrations after switching from epoetin beta to Fortnightly darbepoetin and monthly darbepoetin .

PHASE 1

In the first phase of the study, patient treatment was converted from intravenous erythropoietin beta - given twice or three times weekly - intravenous fortnightly darbepoetin alpha. The latter was injected into the venous line during the remaining 10 minutes of the dialysis session. This was based on the recommended conversion rates and both frequency and route of administration as per the recommendations provided by Corwin HL et al (12); the dosage conversion from epoetin beta to darbepoetin alpha was calculated as a 350 units of erythropoietin beta to 1microgram of darbepoetin.

After a 12 week dose titration period (to maintain hemoglobin concentration within >1.0 to 1.5 g/dl of the baseline value and between 10.0 and 13.0 g/dl), patients entered evaluation period 1 (weeks 13-14) to choose those who are eligible to be included in phase 2 trial.

PHASE 2

In the second phase of the trial, patients were maintained on intravenous darbepoetin alfa, they were switched from a fortnightly frequency administration to monthly injection, but at the same total dose for a further 12 weeks, and hemoglobin/iron status was monitored for the subsequent period of 3 months.

Darbepoetin alpha dose was adjusted when two consecutive weekly hemoglobin values were outside the target range. Dose adjustments were made by $\pm 25\%$ of the baseline dose. Intravenous iron supplementation was administered to maintain serum ferritin in the range between 200-600 mg/l. Our aim was to maintain hemoglobin of between 11 and 12 g/dL. If the hemoglobin concentration exceeded 13 g/dL, ESA was withheld for 2 weeks and reinstated at 75% of the original dosage. If the hemoglobin fall below 11 g/L, the dosage was increased by 25%.

Laboratory investigations, which included estimation of dialysis adequacy (SpKT/V urea), electrolytes, calcium, phosphate, liver function tests (total proteins, albumin, ALT and AST) , cholesterol, alkaline phosphatase , iron stores tests (iron, ferritin, total iron binding capacity, transferrin saturation), parathyroid hormone level and glucose, were performed at entry, every 4 weeks and at the end of the study. Complete blood count tests were performed on a biweekly basis to monitor hemoglobin levels. Incidence of all adverse events (including serious adverse events, the use of antihypertensive medications, IV iron medications, and access related events) were reported by the investigators as related to the study drug.

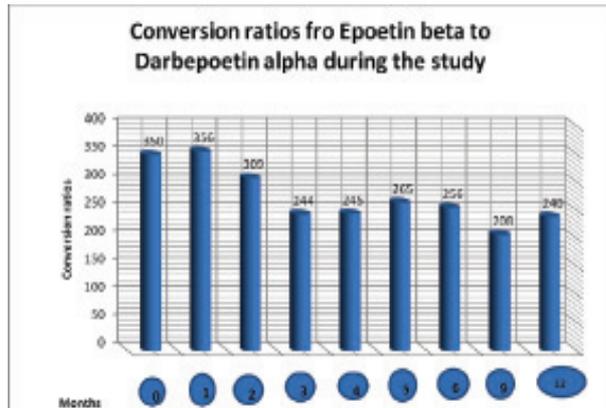


Figure 3. Changes in the conversion ratio from epotien beta to darbepoetin alpha over the study period

Statistical analysis

Variables are given as mean \pm standard deviation (SD) unless otherwise stated. Chi-squared test was used to compare the prevalence of non-parametric variables while differences between variables were analyzed by paired Student's t-test. p- Value of < 0.05 was considered statistically significant. All analysis was performed using the Statistical Package for Social Science (SPSS, Chicago) version 10.0 for windows.

RESULTS

Patients' demographics

At the commencement of the present study, 26 patients fulfilled the entry criteria, 17 men and 9 women, the mean age was 47.0 ± 17.1 years, and the mean duration on HD was 55.8 ± 14.0 months. The etiology of renal disease was diabetes mellitus in 10 (38.5%) patients, hyper-tensive nephropathy in 8 (31.5%), unknown etiology in 7 (27%) and hypoplastic kidneys in 1 (3%) patient. The mean body weight was 67.77 ± 18.19 kg. (Data are shown in Table 1).

Laboratory data

The clinical and laboratory parameters were compatible with adequate iron stores, reasonable mineral and bone management and adequate dialysis at baseline. There was no significant decrease in the mean percentage of transferrin saturation at the end of the study compared with the base line ($31.4 \pm 3.04\%$ vs. $33.9 \pm 3.55\%$ respectively). The baseline Sp KT/V was 1.37 ± 0.14 and normalized protein catabolic rate (nPCR) 1.08 ± 0.08 .

Darbepoetin dose and hemoglobin concentrations:

1-Phase 1: Conversion from epoetin beta to darbepoetin- alpha:

During phase one of the present study, patient treatment was converted from twice weekly (n:11) or three times per week (n:15) intravenous administration of epoetin beta to darbepoetin alpha.

The hemoglobin concentrations remained within the target range during the subsequent 3 month period (10.69 ± 0.98 , 10.64 ± 0.95 and 10.79 ± 0.91 respectively) following the conversion (Figure 2).

Following the conversion from epoetin beta, there was an initial decrease from the starting weekly dosage (28.47 ± 5.02 to 23.91 ± 6.65 Microgram during the first month) , however this was followed by an increased dose of darbepoetin- alpha to (28.75 ± 9.75 , 34.53 ± 10.72 Microgram during the second and third months respectively) required to maintain the same target hemoglobin concentration.

The equivalent conversion rate when changing from epoetin beta to darbepoetin alpha increased from 350 at the start of the study to 356 during the first month, however it decreased to 309, 244 during the second and third month units/ μ g respectively .

2-Phase 2: Conversion from fortnightly to monthly intravenous darbepoetin- alpha :

Following 3 months of fortnightly intravenous darbepoetin- alpha, patients were switched to a monthly dosing regimen. During that period of follow up, an attempt was made to maintain hemoglobin (Figure 2) and target serum iron concentration and saturation (Table 1) within the intended range. Target hemoglobin levels were maintained (10.85 ± 0.62 , 10.78 ± 0.56 , and 10.86 ± 0.58 gm/dl) on the expense of a protocol-driven increase in the weekly required dosage of darbepoetin- alpha to 31.13 ± 14.16 , 38.5 ± 15.25 and 38.6 ± 14.1 Microgram, respectively.

The equivalent conversion rate when changing from fortnightly to monthly darbepoetin- alpha administration decreased to 245, 265 and 265 U/ μ g during the second phase of the study

Results after 12 months from starting darbepoetin:

The mean hemoglobin levels remained within the pre-determined range with no statistically significant change at the end of 12 months relative to base line (11.68 ± 0.91 gm/dl) . The mean weekly darbepoetin dose increased from 38.65 ± 14.1 Microgram- at the end

Table 1: Patient demographics and dialysis data prior to conversion from epoetin beta to darbepoetin alpha

Demographics	Mean/numbers
Age (years)	47.04±17.13
Sex	
Male	17
Female	9
Original renal disease	
Diabetes mellitus	10
Hypertension	8
Hypoplastic kidney	1
Unknown	7
Dialysis duration (months)	55.8 ± 14.0
Type of vascular access (patient's number)	
AV Fistula	21
AV Graft	3
Perm-cath	2
SpKt/V	1.37±.14
Iron (ug/dl)	14.67±9.57
Iron saturation (%)	32.94±15.84
nPCR	1.08 ±.08

of phase 2- to 39.16±21.75 Microgram at the end of the study. So the conversion ratio changed from 265- at the end of six months period to 240 at the end of the study. I.V iron supplementation was maintained according to the iron stores tests, and none of the patients required blood transfusions during the study period.

Patient's drop out

Six patients discontinued the study; two patients due to GIT bleeding, three patients lost follow-up at our center, and 1 patient received a renal transplant. Therefore, the data available for the remaining 16 patients were analyzed. No significant adverse reactions were reported during the study period in the rest of the patients.

Safety analysis

Darbepoetin-alfa was well tolerated during the 1-year study period; no signs suggestive of pure -red cell aplasia were noted in our study population. Adverse events were consistent with those typically found in the dialysis population and there were no differences observed between the two treatment periods. None of the treatment-related adverse events led to study discontinuation in any of the patients.

DISCUSSION

The results of our study revealed that hemoglobin levels

could be maintained by darbepoetin alpha administration at longer interval from in our hemodialysis patients, however this is achieved with a continuous increase in its dose. CRF patients often require recombinant human EPO (rHuEPO) to stimulate bone marrow to produce red blood cells (13). However, rHuEPO usually has to be administered 2-3 times per week to obtain maximum efficacy due to its short circulating half-life (14).

After nearly two decades of experience with ESAs, it has become increasingly common to administer ESAs at not only a reduced dosage, but also on a less frequent administration routine (15). Recombinant HuEPO has three N-linked carbohydrate side chains, whereas darbepoetin alpha has five. The increased carbohydrate content of darbepoetin- alpha delays drug clearance, thereby increasing serum half-life and biological activity when compared with rHuEPO. Darbepoetin-alpha has been shown to have a serum half-life 3-fold longer than that of rHuEPO in dialysis patients, which allows for extended dosing intervals (16). This allowed reduced dosing frequency and the expectation that there was dosage equivalence, whether administered intravenously or subcutaneously (17).

Epoetin alpha has a 4.3-fold higher binding affinity for the erythropoietin receptor than darbepoetin alpha in vitro. Although darbepoetin- alpha has reduced receptor affinity in relation to epoetin alpha, biological potency is enhanced secondary to a longer serum half-life. This suggests that the latter is a more important determinant of subsequent erythropoietic response (18) .

Another factor that may account for the differences between the two erythropoietic agents is the different biological activity of these two agents. Recently, it has been observed that epoetin alpha is more effective than darbepoetin alpha in supporting the in vitro growth of erythroid burst-forming units (19). In human bone marrow cells derived from healthy donors, the EC50 of epoetin alpha was about 10-fold lower than darbepoetin-alpha (19). Darbepoetin- alpha has been demonstrated to be efficacious in clinical trials, allowing once weekly dosing intervals.

The fact that darbepoetin alpha can be administered less frequently to HD patients may offer considerable benefit to both patients and their healthcare providers, especially in view of the current recommended guidelines for i.v. administration of ESAs to dialysis patients (15). Several earlier studies demonstrated that darbepoetin-alpha can be given once every 2 weeks (Q2W) and maintains hemoglobin levels in hemodialysis

patients , in 2006 the results of the study done by Carrera et al (20), fully support the practical use of the i.v. Q2W darbepoetin- alpha regimen in stable HD patients switched from once weekly dosing.

Our results are not in agreement with what reported by Shaheen F A et al 2006 (11) , who observed an increase of the initial conversion ratio from short-acting erythropoietin to darbepoetin alpha from 200 to 1 microgram to an equivalent conversion ratio of 361 IU: 1 microgram after 12 weeks of weekly injection . Furthermore, the conversion ratio increased to 400-500 IU:1 microgram when 60% of patients were administered darbepoetin every 2 weeks while maintaining the hemoglobin level within the previously defined range. The differences in the study design since we did not start with the weekly injection protocol , the difference in the route of injection - all our patients received darbepoetin IV while in that study both IV and SC routes were tried, and finally, the difference in follow up period-12 months in our study versus 12 weeks in Shaheen,s et al study may in part explain the inconsistencies in the results.

Monthly administration of darbepoetin was primarily studied in predialysis patients with chronic renal failure, however few data are available for hemodialysis patients and there is no consensus on conversion ratios among different studies. Furthermore, the majority of these studies used subcutaneous administration, and only a limited number of studies have been conducted using intravenous administration (21).

Our results are not in agreement with what reported by Jadoul et al. 2004 (22) where 38 patients were converted to darbepoetin- alpha administered once every 4 weeks. Thirty (83%) of those evaluable patients successfully maintained the target haemoglobin with no or minimal dose increased required to maintain the required hemoglobin concentration , while their conversion regimen was unsuccessful in 6 patients and was concluded that darbepoetin- alpha administered once monthly, maintained hemoglobin effectively and safely in most dialysis patients stabilized previously on once every 2 weeks dosing however the median weekly dose of darbepoetin- alpha increased from (15 units , CI =11.5-20) at the start of the study to (21.88 units, CI =12.31-31.25) . This may be explained by the difference in our study design from Jadoul, s design since we did not include a once injection every 3 weeks in our study.

This controversy between different studies can be explained by the fact that the current published trials

that explore increased dosing interval regimens often refer to the percentage of patients achieving target hemoglobin concentrations rather than the absolute dose of darbepoetin alpha required to achieve that target (23-24).

Conversely, the higher dosage required to maintain target hemoglobin levels may reflect the delay in initiating the change in dosage; in a dialysis unit, it may take up to 2 weeks for the next increased strength injection dose to be administered rather than being administered within a week's time.

This exploratory study has demonstrated that darbepoetin alpha dosing frequency can be reduced to once every two weeks. However, this advantage was lost when patients were switched from every two weeks to once monthly regimen. The average dosage of darbepoetin- alpha rose again to 39.16 microgram /week by the twelve month. This may represent a less efficacious dosing regimen or a reduced impact of changes made to darbepoetin dosing on subsequent hemoglobin concentrations.

Hiramatsu et al (25) suggests that in peritoneal dialysis patients, treatment frequency could be further extended to once every 4 weeks in many patients with an adjustment of the dose and it may be feasible to maintain the hemoglobin concentration by monthly administration after an initial period of weekly administration .

Furthermore , in a recent review of 867 predialysis patients receiving epoetin alpha or darbepoetin - alpha, there was a significantly greater percentage of patients reaching target hemoglobin levels (110 g/L) when on epoetin alfa than when on darbepoetin-alfa at weeks 4, 8 and 12. On average, patients receiving epoetin alfa had higher hemoglobin concentration, serum ferritin and transferrin saturation levels and better dialysis adequacy test results, as measured by URR or Kt/V, than patients received darbepoetin alpha (26) .

In our study, twelve months after darbepoetin administration , the conversion ratio decreased from 350 to 240, it should be mentioned that no consensus on the conversion ratio from epoetin to darbepoetin among different studies and different dose ratios were reported in different countries. In the United Kingdom, a dose ratio of 200:1 is recommended in the Medicines Compendium (27) . The European Medicines Agency also recommends a dose ratio of 200:1 (28). Recently, it was observed that in Australian hemodialysis patients

who switched from IV epoetin alfa to IV darbepoetin alfa, the dose ratio was approximately 200:1 (29). Our findings are also in keeping with a recent report as some funding bodies in the USA have revised the dose conversion ration and have changed it to 260:1 (30).

The adverse effects were minimal in our study patients. The blood pressure did not need further management during the study period. This also was the experience of others in the trials of the drug on mixed populations of hemodialysis patients and CKD patients (31-32). This was most likely due to maintenance of hemoglobin at the lower recommended levels of 11 g/L, since most of the side effects are usually secondary to the high levels of hemoglobin (above 13 g/L). The two phases study dropouts were not related to the drug administration since both did not show any thrombotic events during dialysis and had stable blood pressure levels during the study period.

The limitations of our study include the small number of patients and the trial of both biweekly and monthly intervals of dosing instead of adherence to a single protocol. However, the convenience of longer intervals of dosing is still appealing for the care takers and patients.

We conclude that our experience with darbepoetin reveals that it is effective and safe for the treatment of anemia in hemodialysis patients even at monthly dose intervals and for long-term. The expected savings are definite with the biweekly dose frequency and reasonable though less savings with the monthly dosing. Furthermore, the longer dosing intervals are certainly much better convenience to patients and care takers in comparison with the currently used short acting ESAs.

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