The Efficacy of Monthly Administration of Darbepoetin Alfa in Saudi Hemodialysis Patients

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BACKGROUND: Erythropoiesis-stimulating agents have improved the outcome and quality of life in patients with chronic kidney disease.

OBJECTIVE: We investigated the efficacy and safety of conversion of hemodialysis patients from epoetin beta to darbepoetin alfa administered once a month.

PATIENTS AND METHODS: The study included 26 patients. Their mean age was 47.0 ± 17.13 years with a mean hemodialysis duration of 55.8 ± 14.0 months. The study was carried out in 2 consecutive phases of 12 weeks each. The mean initial dose of darbepoetin was 57 ± 10.0 μg biweekly. After maintaining target hemoglobin (Hgb) levels—(11–12 g/L)—with the biweekly injections, we shifted our patients to a once-monthly dose schedule.

RESULTS: The mean weekly darbepoetin dose increased from 28.75 ± 4.2 μg during the biweekly phase to 38.5 ± 3.9 μg after switching to the monthly protocol (the mean conversion ratio changed from 309:1 to 256:1). The mean Hgb level was 10.81 ± .86 g/L at the start of the study and 10.86 ± .76 g/L at the end of 6 months.

CONCLUSION: Our experience with darbepoetin alfa reveals that it is effective and safe for the treatment of anemia in hemodialysis patients even at monthly dose intervals.

Renal anemia is considered an essential contributing factor to the reduction of quality of life and to the increase in cardiovascular morbidity in patients with advanced chronic renal failure.[1] The management of uremic anemia was revolutionized in the late 1980s by the commercial availability of recombinant human erythropoietin (rhEPO).[2] To be effective, however, rhEPO needs to be given as frequently as 3 times per week. This frequency of administration is a burden for both patients and healthcare providers.

The advent of darbepoetin alfa, a modified erythropoietin with 2 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 alfa is increased 2 to 3-fold relative to conventional erythropoietin after either subcutaneous or intravenous (IV) administration both in adults and children.[3] Several studies have demonstrated that the interval of subcutaneous darbepoetin alfa 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 chronic kidney disease (CKD) patients receiving once weekly rhEPO to receiving once-every-2-week darbepoetin alfa injections maintains target hemoglobin (Hgb) 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 dosing. As found by others,[9,10] in Saudi Arabia, Shaheen et al[11] experienced gratifying results in hemodialysis patients by switching 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 alfa to maintain Hgb levels with biweekly and monthly dosing in hemodialysis patients for more convenience and savings.

Patients and Methods

This single center prospective exploratory study is to evaluate the efficacy and safety of darbepoetin alfa therapy administered at extended dosing intervals to maintain Hgb concentrations in chronic hemodialysis patients at Prince Salman Center for Kidney Diseases. The study was conducted

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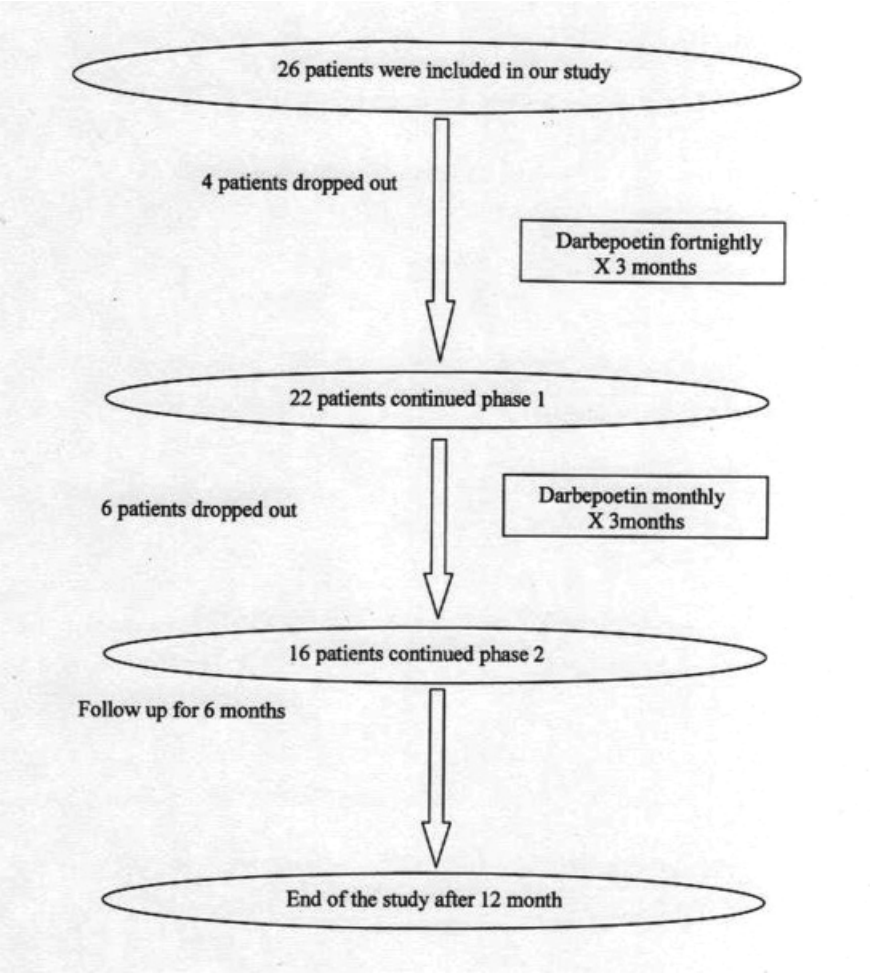

FIGURE 1. *Patient's disposition and evaulability.*

from November 2006 to November 2007. Patients were eligible for the trial if they were treated with erythropoietin for renal anemia, had stable Hgb concentrations for at least 12 weeks before the study, and were optimally dialyzed for at least 6 months prior to initiating darbepoetin alfa as judged by the 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 folic acid, vitamin B_{12}, or iron deficiency, had 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 pregnant or 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 exam 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 in 2 consecutive phases. The study design is presented schematically in *Figure 1*.

Phase 1

In the first phase of the study, patient treatment was converted from intravenous erythropoietin beta, which was administered in our center twice or three times weekly, to intravenous fortnightly darbepoetin alfa. The latter was injected into the venous line during the remaining 10 minutes of the dialysis session. This was based on recommended conversion rates and both frequency and route of administration as per the recommendations provided by Corwin et al[12]; the dosage conversion from erythropoietin beta to darbepoetin alfa was calculated as a 350 units of erythropoietin beta to 1 μg of darbepoetin alfa.

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

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 remaining 12 weeks, and Hgb/iron status was monitored for a period of 3 months.

The darbepoetin alfa dose was adjusted when 2 consecutive weekly Hgb values were outside the target range. Dose adjustments were made by ±25% of the baseline dose. Intravenous iron supplementation was administered to maintain serum ferritin in the range between 200 and 600 mg/L. Our aim was to maintain an Hgb of between 11 and 12 g/dL. If the Hgb concentration exceeded 14 gm/L, the erythropoiesis-stimulating agent (ESA) was withheld for 2 weeks and reinstituted at 75% of the original dosage. If the Hgb fell 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 ➲

TABLE I. Patient demographics prior to conversion from epoetin beta to darbepoetin alfa.

Demographics	Mean/Numbers
Age (yrs)	47.04 ± 17.13
Sex	
Male	17
Female	9
Original renal disease	
Diabetes mellitus	10
Hypertension	8
Hypoplastic kidney	1
Unknown	7
Weight (kg)	67.77 ± 18.19
Dialysis duration (mo)	55.8 ± 14.0
Type of vascular access	
AV fistula	21
AV graft	3
Perm-cath	2
Kt/V	1.37 ± .14
Iron (umol/L)	14.67 ± 9.57
Iron saturation (%)	32.94 ± 15.84
nPCR	1.08 ± .08

Abbreviations: nPCR, normalized protein catabolic rate.

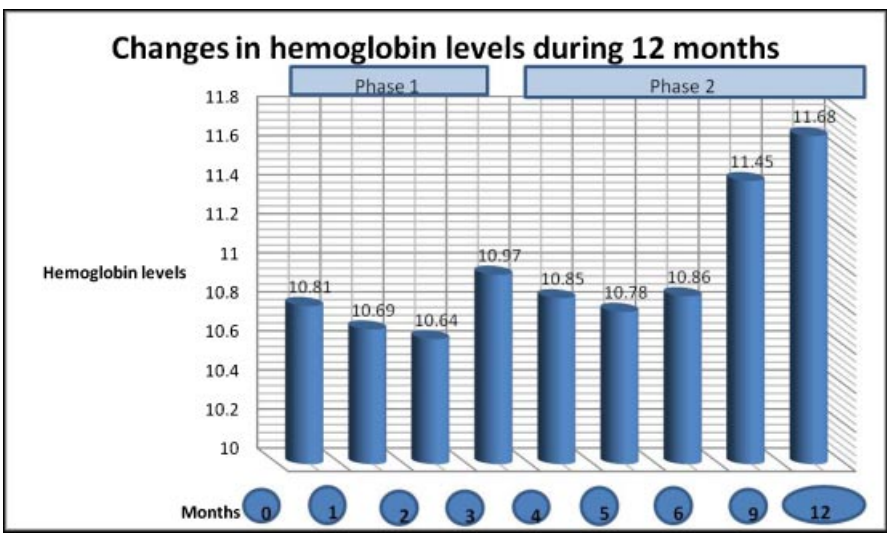

FIGURE 2. *Changes in mean Hgb concentrations after switching from epotien beta to fortnightly darbepotien alfa and monthly darbepotien.*

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 Hgb 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.

Statistical Analysis

Variables are given as mean ± standard deviation (SD) unless otherwise stated. An χ^2 test was used to compare the prevalence of non-parametric variables while differences between variables were analyzed by a paired student's *t*-test. A *p* value of <.05 was considered statistically significant. All analysis was performed using the Statistical Package for Social Science (SPSS, Chicago, Ill.) 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 hemodialysis was 55.8 ± 14.0 months. The etiology of renal disease was diabetes mellitus in 10 (38.5%) patients, hypertensive nephropathy in 8 (31.5%) patients, unknown etiology in 7 (27%) patients, and hypoplastic kidneys in 1 (3%) patient. The mean body weight was 67.77 ± 18.19 kg (data are shown in *Table I*).

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 baseline (31.4% ± 3.04% versus 33.9% ± 3.55%, respectively). The baseline SpKt/V was 1.37 ± .14 and the normalized protein catabolic rate (nPCR) was 1.08 ± .08.

Darbepoetin Dose and Hgb Concentrations

Because there is not much data in the literature about the monthly use of darbepoetin

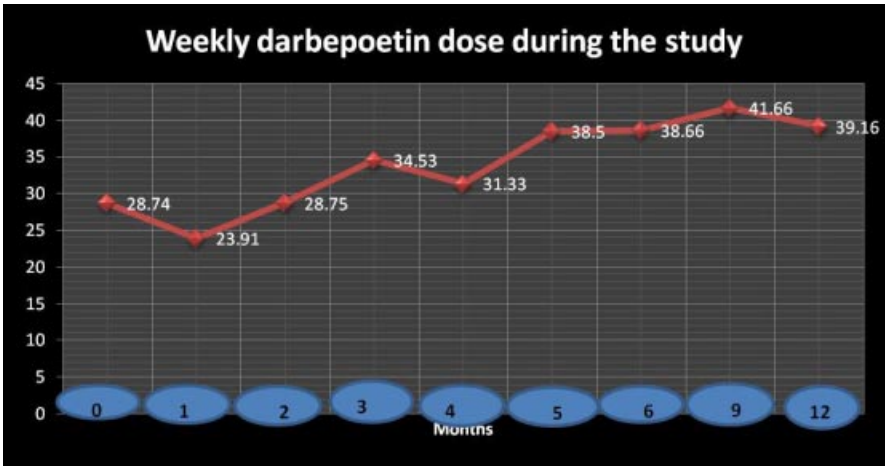

FIGURE 3. *The mean weekly doses of darbepoetin alfa during the study.*

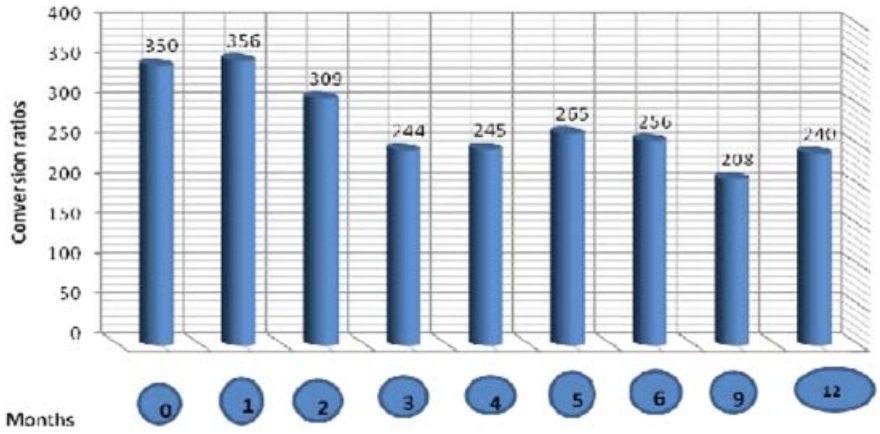

FIGURE 4. *Changes in the conversion ratio from epotien beta to darbepotien alfa over the study period.*

in hemodialysis patients and maintaining target Hgb levels, this study was designed to include 2 phases with a gradual shift of patients from Phase 1 to Phase 2

Phase 1: Conversion from erythropoietin beta to darbepoetin alfa: During Phase 1 of the present study, patient treatment was converted from twice weekly (n = 11) or 3 times per week (n = 15) intravenous administration of erythropoietin beta to darbepoetin alfa. The Hgb concentrations remained within the target range during the subsequent 3 month period (10.69 ± .98, 10.64 ± .95, and 10.79 ± .91, respectively) following the conversion (*Figure 2*).

Following the conversion from erythropoietin beta, there was an initial decrease from the starting dose weekly dosage of 28.47 ± 5.02 to 23.91 ± 6.65 μg during the first month, however this was followed by an increased dose of darbepoetin alfa to 28.75 ± 9.75, 34.53 ± 10.72 μg during the second and third months, respectively, required to maintain the same target Hgb concentration (*Figure 3*).

The equivalent conversion rate when changing from erythropoietin beta to darbepoetin alfa 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/μg respectively *(Figure 4)*.

Phase 2: Conversion from fortnightly to monthly intravenous darbepoetin alfa: Following 3 months of fortnightly intravenous darbepoetin alfa, patients were switched to a monthly dosing regimen. During that period of follow-up, an attempt was made to maintain Hgb (*Figure 2*) and target serum iron concentration and saturation (*Table I*) within the intended range. Target Hgb levels were maintained (10.85 ± .62, 10.78 ± .56, and 10.86 ± .58 gm/dL) on the expense of a protocol-driven increase in the weekly required dosage of darbepoetin alfa to 31.13 ± 14.16, 38.5 ± 15.25, and 38.66 ± 14.10 μg, respectively (*Figure 3*).

The equivalent conversion rate when changing from fortnightly to monthly darbepoetin alfa administration decreased to 245, 265, and 265 units/μg during the second phase of the study. *(Figure 4)*.

Results After 12 Months of Starting Darbepoetin

The mean Hgb levels remained within the predetermined range with no statistically significant change at the end of 12 months relative to baseline (11.68 ± .91 gm/dL). The mean weekly darbepoetin dose increased from 38.65 ± 14.1 μg—at the end of phase 2—to 39.16 ± 21.75 μg at the end of the study. So the conversion ratio changed from 265—at the end of the 6 month period—to 240 at the end of the study. Intravenous 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 Rate

Six patients discontinued the study; 2 patients due to gastrointestinal tract bleeding, 3 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 2 treatment periods. None of the treatment-related adverse events led to study discontinuation for any of the patients.

Discussion

The results of our study revealed that target Hgb levels could be maintained by darbepoetin alfa administration at longer intervals; from once every 2 weeks to once a month in our hemodialysis patients; however this is achieved with a continuous increase in its dose. Chronic renal failure patients often require rhEPO to stimulate bone marrow to produce red blood cells.[13] However, rhEPO usually has to be administered 2 to 3 times per week to obtain maximum efficacy due to its short circulating half-life.[14] After nearly 2 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 hEPO has 3 N-linked carbohydrate side chains, whereas darbepoetin alfa has 5. The increased carbohydrate content of darbepoetin alfa delays drug clearance, thereby increasing serum half-life and biological activity when compared with rhEPO. Darbepoetin alfa has been shown to have a serum half-life 3-fold longer than that of rhEPO in dialysis patients, which allows for extended dosing intervals.[16] This allows for reduced dosing frequency and the expectation that there was dosage equivalence, whether administered intravenously or subcutaneously.[17] Epoetin alfa has a 4.3-fold higher binding affinity for the erythropoietin receptor than darbepoetin alfa in vitro. Although darbepoetin alfa has reduced receptor affinity in relation to epoetin alfa, 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 2 erythropoietic agents is the different biological activity of these 2 agents. Recently, it has been observed that epoetin alfa is more effective than darbepoetin alfa 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 alfa was about 10-fold lower than darbepoetin alfa.[19] Darbepoetin alfa has been demonstrated to be efficacious in clinical trials, allowing once weekly dosing intervals. The fact that darbepoetin alfa 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 IV administration of ESAs to dialysis patients.[15] Several earlier studies demonstrated that darbepoetin alfa can be given once every 2 weeks and maintains Hgb levels in hemodialysis patients. In 2006, the results of the study done by Carrera et al,[20] fully supported the practical use of the once every-2-week IV darbepoetin alfa regimen in stable HD patients switched from once-weekly dosing.

Our results are not in agreement with what was reported by Shaheen et al,[21] who observed an increase of the initial conversion ratio from short-acting erythropoietin to darbepoetin alfa from 200 to 1 μg to an equivalent conversion ratio of 361 IU: 1 μg after 12 weeks of weekly injection. Furthermore, the conversion ratio increased to 400 to 500 IU:1 μg when 60% of patients were administered darbepoetin alfa every 2 weeks while maintaining the Hgb level within the previously defined range. The differences in the study design (since we did not start with the weekly injection protocol) were in the route of injection—all our patients received darbepoetin alfa IV while in the Shaheen et al study both IV and subcutaneous routes were tried, and finally, the difference in follow-up period—12 months in our study versus 12 weeks may in part explain the inconsistencies in the results.

Monthly administration of darbepoetin alfa 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 IV administration.[21]

Our results are not in agreement with what was reported by Jadoul et al[22] where 38 patients were converted to darbepoetin alfa administered once every 4 weeks. Of these, 36 patients were considered evaluable and 30 (83%) of those evaluable patients successfully maintained the target Hgb with no or minimal dose increase required to maintain the required Hgb concentration while their conversion regimen was unsuccessful in 6 patients. It was concluded that darbepoetin alfa, administered once monthly, maintained Hgb effectively and safely in most dialysis patients stabilized previously on once-every-2-week dosing. However, the median weekly dose of darbepoetin alfa increased from 15 units, (confidence interval [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 an 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 Hgb concentrations rather than the absolute dose of darbepoetin alfa required to achieve that target.[23,24] Conversely, the higher dosage required to maintain target Hgb 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 alfa dosing frequency can be safely reduced to once every two weeks. However, this advantage was lost when patients were switched from an every-2-week to a once-every-month regimen. The average dosage of darbepoetin alfa rose again to 39.16 μg/week by the twelfth month. This may represent a less efficacious dosing regimen or a reduced impact of changes made to darbepoetin alfa dosing on subsequent Hgb concentrations.

Hiramatsu et al[25] suggests that in peritoneal dialysis patients, treatment fre-

quency 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 Hgb concentration by monthly administration after an initial period of weekly administration. Furthermore, in a recent review of 867 predialysis patients receiving epoetin alfa or darbepoetin alfa, there was a significantly greater percentage of patients reaching target Hgb 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 Hgb concentration, serum ferritin and transferrin saturation levels, and better dialysis adequacy test results, as measured by urea reduction ratio or Kt/V, than patients who received darbepoetin alfa.[26]

In our study, 12 months after darbepoetin alfa 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 United States have revised the dose conversion ration and have changed it to 260:1.[30] Anemia is strongly predictive of complications and death from cardiovascular causes in patients with CKD. Several studies have demonstrated that the correction of anemia in patients with CKD improves the quality of life and exercise tolerance while reducing the need for transfusion.[31] In 2000, a panel of the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation recommended that the target level of Hgb should be 11.0 to 12.0 g per deciliter in patients with CKD, whether or not they were receiving dialysis.[32] A recent update of guidelines regarding anemia in such patients expanded the target range to 11.0 to 13.0 g per deciliter. The lower limit of the Hgb level was set at 11.0 g per deciliter as an "evidence-based recommendation," whereas the upper limit was set at 13.0 g per deciliter as a "clinical practice recommendation." The committee concluded that there was insufficient evidence to recommend the routine maintenance of a Hgb level of 13.0 g per deciliter or higher in patients being treated with erythropoiesis-stimulating agents.[33]

The adverse effects were minimal in our study patients. 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.[34,35] This was most likely due to maintenance of Hgb at the lower recommended levels of 11 g/L, since most of the side effects are usually secondary to the high levels of Hgb (>13 g/L). The 2 study dropouts were not related to drug administration since neither showed 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 caretakers and patients. We concluded that our experience with darbepoetin alfa reveals that it is effective and safe for the treatment of anemia in hemodialysis patients and maintaining target Hgb levels 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 more convenient for patients and caretakers in comparison with the currently used short-acting ESAs. Larger studies of a longer duration are warranted.

Preliminary data on once monthly dosing of darbepoetin alfa are interesting, but all studies reported to date are non-randomized and uncontrolled. There is a pressing need for more robust scientific studies, such as the TREAT trial investigating the efficacy of once-monthly dosing of darbepoetin alfa. D&T

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