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Darbepoetin alfa administered once monthly maintains hemoglobin concentrations in patients with chronic kidney disease

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Key words
anemia – chronic renal insufficiency – glycoprotein – drug therapy – safety

Abstract. Background: Darbepoetin alfa is an erythropoiesis-stimulating glycoprotein that functions by the same mechanism as recombinant human erythropoietin (rHuEPO), but has a three-fold longer serum half-life. Reduction in the frequency of darbepoetin alfa administration would be beneficial to patients with renal disease and their healthcare providers. This study evaluated the effect of extending the darbepoetin alfa dosing interval to once monthly in patients with chronic kidney disease (CKD) not receiving dialysis. Methods: This study was a multicenter, open-label study of 97 patients with CKD not on dialysis. Patients receiving stable subcutaneous doses of darbepoetin alfa once every two weeks were converted to darbepoetin alfa once monthly for 29 weeks. The proportion of patients who successfully maintained hemoglobin concentrations between 10.0 and 12.0 g/dl and the mean darbepoetin alfa dose were evaluated. Safety measurements (e.g. adverse events, laboratory parameters, blood pressure) and seroreactivity were assessed. Results: Hemoglobin concentration was maintained within the target range in 79% (95% confidence interval (CI) = 71% to 87%) of all patients receiving darbepoetin alfa and in 85% (95% CI = 78% – 93%) of patients who completed the study period. The mean ± standard deviation monthly darbepoetin alfa dose was similar between baseline (88.7 ± 49.9 g) and the evaluation period (86.6 ± 78.8 g). The safety profile for monthly darbepoetin alfa administration was comparable with that previously observed with more-frequent administration. Conclusion: Patients with CKD who are clinically stable on darbepoetin alfa administered once every two weeks can be safely and effectively converted to darbepoetin alfa administered once monthly.

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Introduction

Anemia is highly prevalent among the more than ten million Americans with chronic kidney disease (CKD) [Coresh et al. 2003]. Most patients with CKD develop anemia because of reduced renal production of erythropoietin. Anemia usually begins in the early stages of CKD and generally becomes progressively more severe as renal function deteriorates [Hsu et al. 2002, Walters et al. 2002]. Anemia of renal disease has been associated with diminished quality of life, increased rates of red blood cell transfusions and hospitalizations, and contributes to the increased morbidity and mortality from cardiovascular disease that is associated with CKD [Culleton et al. 1999, Foley et al. 1995, Klang et al. 1996, Levin 2001, Pereira 2000, Working Party 1999]. Current evidence suggests that the enhanced burden of cardiovascular morbidity and mortality develops early on in patients with CKD and is already established and relatively advanced by the time dialysis becomes necessary [Barrett et al. 1997].

Darbepoetin alfa (Aranesp, Amgen Inc., Thousand Oaks, California, USA) acts in a manner similar to both endogenous and recombinant human erythropoietin (rHuEPO) [Macdougall 2000], but has a three-fold longer serum half-life than rHuEPO [Egrie et al. 2003], and is, therefore, effective with less-frequent administration. Clinical studies have shown that darbepoetin alfa safely and effectively corrects anemia in patients with CKD using once-weekly [Locatelli et al. 2001, Nissenson et al. 2002] or once every two weeks [Suryani et al. 2003] dosing schedules.

A further reduction in the frequency of darbepoetin alfa injections to once monthly would facilitate the management of anemia of CKD for patients and their healthcare providers. The current study was undertaken to determine whether hemoglobin concentrations could be maintained in patients with CKD not on dialysis after extension of the dosing interval from once every two weeks dosing to once monthly administration.

Patients and methods

Study population

The institutional review board or independent Ethics Committee for each of the participating study centers approved the protocol, and all study patients gave written informed consent, before any study-related procedures were done. Study patients were at least 18 years of age, had CKD with a creatinine clearance calculated by the Cockroft-Gault formula [Cockroft and Gault 1976] between 15 and 40 ml/min (representing stage 3 and 4 CKD) [National Kidney Foundation 2004] were not receiving or expected to initiate dialysis for the duration of the study and were receiving subcutaneous darbepoetin alfa, with stable dosages administered once every two weeks for at least the six weeks preceding enrollment. A stable dose was defined as 25% change in darbepoetin alfa dose over the six-week period before enrollment. Eligible patients had hemoglobin concentrations (measured from two samples obtained at least one week apart and within six weeks of enrollment) within the range of 10.0 – 12.0 g/dl. Patients had serum ferritin levels 100 g/l, or a transferrin saturation (Tsat) 19.5%, or both; both vitamin B_{12} and folate levels were to be above the lower limit of the normal range. Patients were excluded if they had undergone or anticipated kidney transplantation, had uncontrolled hypertension, severe hyperparathyroidism, or significantly abnormal liver function tests, were infected with human immunodeficiency virus or hepatitis B virus, received red blood cell transfusions or androgen therapy within eight weeks of study enrollment, or were pregnant, actively bleeding, or known to be hypersensitive to human serum albumin.

Study design and treatment schedule

This study was a multicenter, single-group study in which patients with CKD not on dialysis who were receiving subcutaneous darbepoetin alfa administered once every two weeks were converted to subcutaneous darbepoetin alfa administered once every four weeks. Darbepoetin alfa was administered within 14 days of enrollment by subcutaneous injection. The initial dose was equivalent to the total dose administered during the month preceding study enrollment. The first dose was administered at week one (by definition) and the final dose at week 25. Darbepoetin alfa was administered once every four weeks. Hemoglobin concentrations, hematocrit values and blood pressure measurements were assessed every two weeks. The baseline hemoglobin value was obtained on the day the first dose of study drug was administered. Darbepoetin alfa dose adjustments of 25% of the previous dose were allowed to maintain hemoglobin concentration within the target range of 10.0 – 12.0 g/dl. Doses were withheld per protocol when the hemoglobin result obtained two weeks earlier was > 12.0 g/dl and were imputed as zero at such time points. Iron could be administered according to clinic policy for patients who had a serum ferritin < 100 g/l or transferrin saturation < 19.5% at any time during the study. The use of iron supplements was not evaluated in this study. Red blood cell transfusion events were recorded at each study visit. Seroreactivity for anti-erythropoietin antibodies was assessed for all patients.

Efficacy endpoints

The efficacy of darbepoetin alfa, administered once monthly, was primarily assessed by the proportion of patients maintaining a mean hemoglobin concentration of 10.0 – 12.0 g/dl during the evaluation period (i.e. study weeks 21 – 29). Secondary endpoints included the proportion of patients maintaining a mean hemoglobin concentration of 10.0 – 13.0 g/dl during the evaluation period, the proportion of patients who received a red blood cell transfusion, the mean change from baseline in hemoglobin concentration and darbepoetin alfa dose.

Table 1. Baseline demographics and clinical characteristics of enrolled patients.

	Darbepoetin alfa n = 98
Sex n (%)	
Men	54 (55)
Women	44 (45)
Race n (%)	
White	43 (44)
Black	34 (35)
Hispanic	18 (18)
Asian	2 (2)
Other	1 (1)
Age, years	
Mean (SD)	66 (12)
Median	69
Range	44 – 91
Weight, kg	
Mean (SD)	82 (19)
Hemoglobin, g/dl	
Mean (SD)	11.1 (0.55)
Darbepoetin alfa dose, g/month	
Mean (SD)	88.7 (49.9)
eGFR (ml/min/1.73 m^2)	
Mean (SD)	22 (8)

SD = standard deviation, eGFR = estimated glomerular filtration rate.

Safety endpoints

The safety profile of darbepoetin alfa was evaluated by adverse events, changes in blood pressure and serum chemistry parameters, the presence of anti-erythropoietin antibodies and the hemoglobin rate of rise and proportion of patients with hemoglobin rate of rise > 4 g/dl/month.

Statistical analyses

The proportion of patients who maintained a mean hemoglobin concentration between the target range (i.e. 10.0 and 12.0 g/dl) during the evaluation period (i.e. weeks 21 – 29) was calculated by dividing the number of patients maintaining a mean hemoglobin concentration within the target range during the evaluation period by the total number of patients. The primary analysis was a modified intent-to-treat (mITT) analysis, which included only those patients who entered the study and received at least one dose of darbepoetin alfa. Of the 98 patients enrolled into the study, 97 were included in the mITT analysis. Those patients who did not complete the study were classified as not having achieved target hemoglobin value. In a secondary completers analysis, patients who received the last dose of darbepoetin alfa at week 27 and had a hemoglobin result during the last study week (i.e. week 29) also were evaluated. A 95% confidence interval (CI) for the proportion of responders was calculated using the normal approximation to the binomial distribution. Summary statistics were computed for the number of patients with red blood cell transfusion events, the mean hemoglobin concentration and the darbepoetin alfa dose from baseline through the evaluation period. Two-sided 95% CIs were calculated for the mean changes from baseline in hemoglobin concentration and darbepoetin alfa dose through the evaluation period.

Safety was evaluated for all patients who received at least one dose of darbepoetin alfa (the primary analysis group). The patient incidences of adverse events and deaths were summarized. Changes in laboratory and blood pressure evaluations and the development of anti-erythropoietin antibodies were summarized.

Results

Patient demographics and disposition

Ninety-eight patients were enrolled into the study. Study participants were typical of the population of patients with CKD not receiving dialysis, with a mean baseline creatinine clearance of 22.1 ml/min/1.73 m^2 (Table 1). The mean age was 66 years and 55% of the patients were men and patients were predominantly white (44%), black (35%), or Hispanic (18%).

One patient did not receive darbepoetin alfa and was excluded from the primary end-

point analysis. Of the 97 patients who received at least one dose of darbepoetin alfa during the study, 86 (89%) completed the study (Figure 1). Eight patients discontinued the study due to initiation of dialysis (4%), adverse event (3%), or withdrawal of consent (1%). Two patients (2%) died during the study. One patient (1%) completed darbepoetin alfa dosing, but was lost to follow-up before end of study assessments and was considered a non-completer.

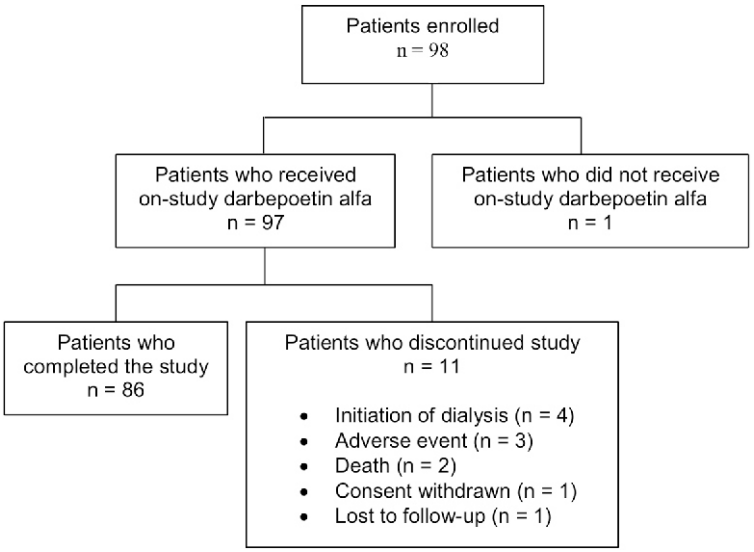

Figure 1. Patient disposition.

Efficacy

Of the 97 patients who received at least one dose of darbepoetin alfa, 77 (79% ± 95% CI = 71% – 87%) successfully maintained mean hemoglobin concentrations within the 10.0 – 12.0 g/dl target range and 83 (86% ± 95% CI = 79% – 93%) maintained mean hemoglobin concentrations within the 10.0 to 12.0 g/dl range during the evaluation period. Among the 86 patients who completed the evaluation period, the proportion of patient achieving the hemoglobin 10.0 – 12.0 g/dl target was 85% (95% CI = 78% – 93%).

Three patients (3%) received red blood cell transfusions. One of these patients received the transfusion within 40 days of the evaluation period and was classified as not having achieved the target hemoglobin concentration. The two remaining transfusion events occurred more than 40 days before the evaluation period.

Mean ± SD hemoglobin concentration remained stable during the study (11.1 ± 0.6 g/dl at baseline versus 11.1 ± 0.7 g/dl during the evaluation period), with mean ± SD hemoglobin change between baseline and the evaluation period of 0.0 ± 0.9 g/dl and mean percent hemoglobin change of –0.1% (95% CI = –1.9% – 1.6%) (Figure 2).

The mean ± SD monthly darbepoetin alfa dose administered was 88.7 ± 49.9 g at baseline and 86.6 ± 78.8 g during the evaluation period (Figure 3, Table 2). The mean change

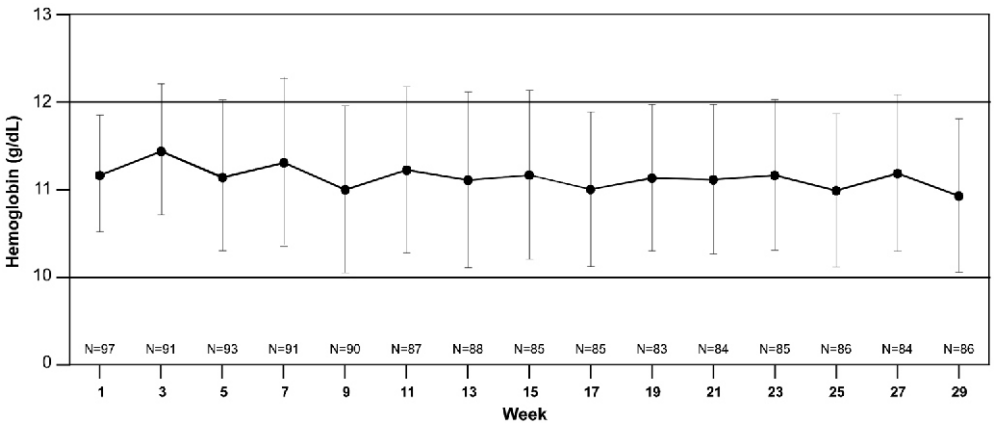

Figure 2. Mean hemoglobin concentrations by study week (modified intent-to-treat analysis). Numbers equal number of observations at each time point. Vertical lines represent one standard deviation above and below the mean. Horizontal bars represent limit of hemoglobin target range (10.0 – 12.0 g/dl). Week 29 results include measurements taken after study week 29.

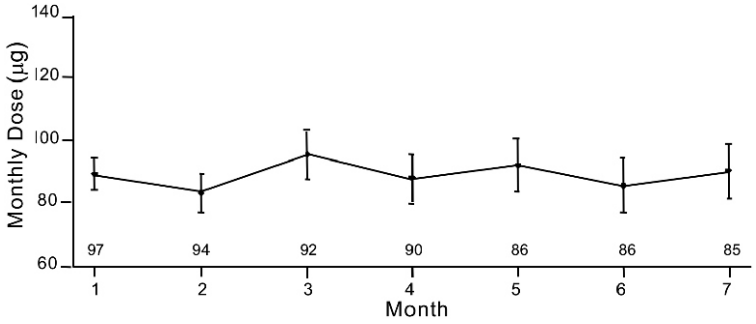

Figure 3. Dose summary by study month (modified intent-to-treat analysis). Numbers equal number of observations at each time point. Vertical lines represent standard error of the mean. Study month 1 represents dose at baseline.

± SD in monthly darbepoetin alfa dose between baseline and the evaluation period was –1.4 ± 59.9 g and the mean percent dose change during this period was –2.7% (95% CI = 14.7% – 9.2%). The range of doses was 16.0 – 250.0 g/month at baseline and 0.0 – 500.0 g/month over the evaluation period.

Table 2. Darbepoetin alfa dose at baseline and over the evaluation period.

	Darbepoetin alfa n = 97
Baseline/ month 1 dose (g)	
n	97
Mean	88.7
SD	49.9
Q1, Q3	50.0, 120.0
Range	16.0 – 250.0
Dose over evaluation period (g)	
n	86
Mean	86.6
SD	78.8
Q1, Q3	37.5, 105.0
Range	0.0 – 500.0

n = number of patients administered drug (i.e. mITT analysis set), Q1 = first quartile, Q3 = third quartile, evaluation period = weeks 21 – 29.

Safety

Darbepoetin alfa was well-tolerated when administered once monthly, and the overall safety profile was consistent with that expected for a population of anemic patients with CKD who are not receiving dialysis. Adverse events were reported for 87% of study patients. Hypertension (26%), peripheral edema (11%), fatigue (11%), and upper respiratory infection (10%) were the most frequently reported adverse events. Three patients (3%) withdrew from the study due to adverse events (myocardial infarction, respiratory insufficiency, erythema multiforme). Of these events, erythema multiforme was considered related to darbepoetin alfa. Two patients (2%) died of adverse events (cardiac arrest, diabetic ketoacidosis) that were considered unrelated to darbepoetin alfa.

Blood pressure remained stable throughout the study. No significant changes were observed in laboratory parameters, including red or white blood cell counts, platelet count, serum calcium, creatinine, phosphorus, ferritin or liver function tests and transferrin saturation. No anti-erythropoietin antibodies were detected.

The hemoglobin rate of rise was stable over the study period, with a mean ± SD of –0.04 ± 1.36 for all patients at all study visits. Four patients (4%) had a hemoglobin rate of rise of > 2 g/dl over any two-week interval during the study. The adverse event profile for these four patients was comparable with that of other patients in the study.

Discussion

This report, in which patients with CKD not receiving dialysis (stage 3 or 4 CKD) were studied, demonstrates that most patients successfully maintained mean hemoglobin concentrations within the 10.0 – 12.0 g/dl target range after converting from once every two weeks to once monthly darbepoetin alfa administration. The mean darbepoetin alfa dose in the month preceding baseline and the mean dose administered throughout the evaluation period were comparable. These data suggest that the total monthly darbepoetin alfa dose required to maintain hemoglobin concentrations within

the target range is similar when the dosing interval was increased from once every two weeks to once monthly.

Previous studies have demonstrated the efficacy and safety of initiating treatment with darbepoetin alfa at doses of 0.75 g/kg administered once every two weeks in anemic patients with CKD [Suryani et al. 2003]. The results of this study support a novel darbepoetin alfa dosing paradigm and demonstrate that patients with CKD who are stable on darbepoetin alfa administered once every two weeks can be safely and effectively converted to once monthly darbepoetin alfa administration by doubling the once every two weeks dose. The use of a once monthly darbepoetin alfa dosing schedule, and the resultant reduction in the frequency of visits to a healthcare provider, may improve compliance and quality of life for patients with CKD and their caregivers. These practical benefits could result in better overall management of renal anemia in this population.

Less frequent dosing did not reduce the efficiency of darbepoetin alfa in this study. In addition, monthly darbepoetin alfa administration was well-tolerated in this study, with a safety profile comparable with that reported with once weekly [Locatelli et al. 2001] and once every two weeks administration [Suryani et al. 2003]. The hemoglobin rate of rise observed in this study is consistent with that observed in other studies in patients with CKD evaluating darbepoetin alfa administered once weekly [Locatelli et al. 2001] or once every two weeks [Suryani et al. 2003].

In the setting of CKD, the recommended dosing frequency for epoetin alfa is three times a week. Recent studies, however, have evaluated the clinical effectiveness of less frequent dosing regimens for maintenance [Germain et al. 2003, Provenzano et al. 2004a] and treatment [Provenzano et al. 2004b] of anemia of CKD. The patient populations in these studies were similar to our patient population. All patients were at least 18 years of age and were not receiving dialysis and were not scheduled to receive dialysis during the course of the study. The Germain et al. [2003], Provenzano et al. [2004a], and the Provenzano et al. [2004b] studies, however, enrolled patients with all stages of CKD, while our study enrolled only patients with stage 3 or stage 4 disease. Baseline hemoglobin concentrations were not reported by Germain et al. [2003] but were reported to be 11.9 g/dl in the Provenzano et al. [2004a] study and 11.1 ± 0.55 g/dl in our study. The target hemoglobin concentration was reported to be 11.0 ± 0.5 g/dl in the Germain et al. [2003] study and 10.0 – 12.0 g/dl in our study. The weekly epoetin alfa dose requirements necessary to maintain target hemoglobin ranged from 10 000 – 12 000 units [Germain et al. 2003, Provenzano et al. 2004a,b]. These data have supported the clinical use of epoetin alfa administered once weekly.

In comparison, the current study results suggest that darbepoetin alfa can maintain hemoglobin concentrations when administered at a mean (SE) monthly dose of 86.6 ± 8.31 g or 22 g/week. Results from this study supported the expanded marketing authorization by the European Union for darbepoetin alfa to be administered once monthly for the treatment of anemia in patients with CKD.

CKD is associated with an increased risk for cardiovascular morbidity and mortality [Culleton et al. 1999, Foley et al. 1995, Levin 2001]. Recent data indicate that patients with CKD are much more likely to die than progress to end-stage renal disease [Gilbertson et al. 2003]. Some associative data suggest that anemia is an independent risk factor for cardiovascular disease and mortality [Foley et al. 1996, Levin et al. 1996, Mann 1994] and support that treatment of anemia with rHuEPO may reduce the risk of cardiovascular disease in patients with CKD [Besarab and Levin 2000, Fink et al. 2001, London 2001, Portoles et al. 1997, Silverberg et al. 2003]. However, a large proportion of patients with CKD who are not on dialysis do not receive rHuEPO [Kausz et al. 2000, Obrador et al. 2001]. Undertreatment of renal anemia in this population may be due, in part, to the need for frequent injections of rHuEPO. This study supports extended dosing regimens for the treatment of anemia in patients with CKD, which, by improving compliance and convenience, may increase the proportion of patients treated.

This study has some potential limitations, which should be taken into consideration. The study was a single-arm, non-randomized study in which all patients acted as their own control.

Although the study was only 24 weeks in duration, it was similar to other studies evaluating ESP therapy in patients with CKD [Germain et al. 2003, Locatelli et al. 2001, Provenzano et al. 2004a,b]. Our study did not collect data concerning iron status of the patients or iron use during the follow-up period; therefore, it is possible that patients who received darbepoetin alfa on a once every four week schedule may have received iron supplementation, but this is probably unlikely.

In conclusion, in most patients with CKD, the darbepoetin alfa dosing interval can be safely and effectively extended from once every two weeks to once monthly without reduction in mean hemoglobin concentrations or diminished efficacy. Less frequent dosing may improve convenience and compliance for patients and facilitate management of renal anemia for healthcare providers.

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