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Once-weekly darbepoetin alfa is as effective as three-times weekly epoetin

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ABSTRACT

Background: This study was designed to evaluate whether haemoglobin levels can be maintained in haemodialysis patients after switching from three-times weekly dosing with intravenous epoetin to once-weekly dosing with darbepoetin alfa.

Patients and methods: Eligible patients were stabilized on three-times weekly epoetin therapy for a 6-month initial period. At Month 0, patients were randomized either to continue with three times weekly intravenous epoetin (control group) or to switch to once-weekly intravenous darbepoetin alfa (darbepoetin alfa group) for a period of 10 months. 200 IU:1 µg was used to start patients who were switched from epoetin to darbepoetin alfa. Throughout the study, doses of epoetin or darbepoetin alfa were titrated to maintain haemoglobin in the range 11.0–12.5 g/dL. The primary efficacy parameter was the level of Hb at Month 10 in the darbepoetin alfa group, compared with the control group.

Results: Twenty-four patients were randomized to the darbepoetin alfa group and 20 to the control group. At Month 10, mean haemoglobin levels in the darbepoetin alfa and control groups were 12.03 g/dL (95% CI: 11.57, 12.50 g/dL) and 12.41 g/dL (11.55, 13.27 g/dL), respectively (P = 0.38), representing a mean change in haemoglobin from Month 0 to Month 10 of 0.12 g/dL (95% CI: –0.72, 0.96 g/dL) in the darbepoetin alfa group and 0.05 g/dL (–1.13, 1.23 g/dL) in the control group (P = 0.91).

Conclusions: Once-weekly dosing with IV darbepoetin alfa is as effective as three-times

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weekly dosing with IV epoetin in maintaining Hb levels in patients receiving haemodialysis.

Key words: epoetin, Darbepoetin alfa, haemodialysis, anaemia, erythropoietic therapy

INTRODUCTION

The treatment of anaemia in patients with end-stage renal disease (ESRD) was revolutionized with the introduction of recombinant human erythropoietin (epoetin) therapy in the late 1980s[1,2]. The partial correction of anaemia in ESRD patients has well-documented benefits, including improvements in patients' quality-of-life, exercise tolerance and cardiac function, and there is strong evidence supporting the total correction of anaemia in these patients[3]. European Best Practice Guidelines recommend that at least 85% of patients should have haemoglobin (Hb) level of > 11 g/dL[4].

For patients with ESRD receiving haemodialysis (HD), the intravenous (IV) route of epoetin administration is the preferred choice, reducing patient discomfort and the nursing time associated with subcutaneous (SC) administration. Epoetin has a short half-life, however, particularly when administered via the IV route, which necessitates frequent dosing, typically two or three times per week[4,5]. Although there is some evidence that Hb can be maintained with less-frequent dosing (once weekly) with SC epoetin[6,7], there is no evidence that once-weekly dosing with epoetin via the IV route is effective[8].

The most-recently developed erythropoietic agent, darbepoetin alfa, was developed by glycoengineering techniques using site-directed mutagenesis. This allowed the introduction of two additional *N*-linked carbohydrate chains to the epoetin molecule, increasing its sialic acid content. Consequently, darbepoetin alfa has increased *in vivo* bioactivity and a three-fold longer serum half-life, compared with epoetin[9,10]. Moreover, a single dose of darbepoetin alfa, administered via either the IV or SC route, has been shown to remain at a serum concentration above the erythropoietic threshold for longer than an equivalent dose of epoetin[9].

Previous studies have shown that darbepoetin alfa can correct and maintain Hb at extended dosing intervals compared with epoetin[11-14]. In addition, darbepoetin alfa can be used SC or IV with the same or equivalent Hb responses and dosing[15]. However, there are relatively few data on patients treated exclusively by the IV route. In a case report of three patients with chronic renal failure receiving HD, we have previously reported that once-weekly treatment with IV darbepoetin alfa can result in clinically meaningful increases in Hb concentrations, compared with more frequent dosing with epoetin[16].

Therefore, the aim of the present study was to expand on these findings, by evaluating whether Hb levels can be maintained in a larger group of patients with ESRD receiving HD, after switching from three-times weekly dosing with IV epoetin to once-weekly dosing with IV darbepoetin alfa.

METHODS

Study design

This randomized study was designed to evaluate whether Hb levels can be maintained in patients with ESRD receiving HD after switching from three-times weekly dosing with epoetin to once-weekly dosing with darbepoetin alfa.

In order to be included in this study, patients had to be ≥ 18 years of age, have ESRD and be maintained on HD, with no evidence of active bleeding, infection or inflammation. Patients eligible for study inclusion were stabilized on epoetin therapy for an initial period of 6 months (Months –6 to 0). Epoetin was administered three-times weekly by the IV route, with the dose titrated to maintain Hb levels within the range 11.0–12.5 g/dL (maximum permitted Hb = 13 g/dL).

At Month 0, patients were randomized either to continue treatment with three-times weekly IV epoetin (control group), or to switch to once-weekly treatment with IV darbepoetin alfa (darbepoetin alfa group; Figure 1). A dose conversion ratio of epoetin 200 IU: darbepoetin alfa 1 µg was used initially for patients switching to darbepoetin alfa. Patients were followed up for a further period of 10 months, during which time the dose of epoetin or darbepoetin alfa was titrated to maintain Hb levels in the range 11.0–12.5 g/dL, as before.

Hb levels were monitored once monthly. Iron status was monitored every 3 months throughout the study and all patients were prescribed iron supplements as necessary.

Efficacy parameters

The primary efficacy parameter was Hb level at study evaluation (Month 10) in the darbepoetin alfa group, compared with the control group. Secondary efficacy parameters were comparisons between the two groups in the change in dose of erythropoietic agent (darbepoetin alfa or epoetin) from Month 0 to Month 10, safety, tolerability, and the need for blood transfusion.

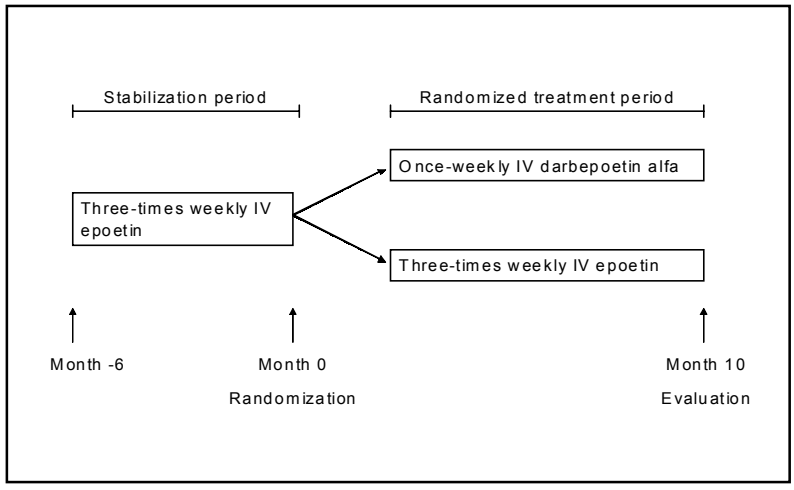

Figure 1. Study design.

TABLE 1
Patient demographics

Characteristic	Darbepoetin alfa group (n = 18)	Control group (n = 13)
Mean age (years [± SD])	57.7 (± 11.78)	61.5 (± 22.66)
Gender (n [%])		
Male	16 (88.9)	7 (53.8)
Female	2 (11.1)	6 (46.2)
Race (n [%])		
Caucasian	17 (94.4)	13 (100)
Black	1 (5.6)	0 (0)
Time on dialysis (months [±SD])	70.8 (± 59.14)	60.7 (± 64.07)
Aetiology of ESRD (n [%])		
Alport	1 (5.6)	0 (0)
Diabetic nephropathy	1 (5.6)	3 (23.1)
Chronic glomerulonephritis	9 (50)	3 (23.1)
Hypertension	1 (5.6)	0 (0)
Polycystic kidney	0 (0)	1 (7.7)
Obstructive uropathy	0 (0)	1 (7.7)
Paramyloidosis	0 (0)	1 (7.7)
Psoriasis	1 (5.6)	0 (0)
Reflux nephropathy	0 (0)	1 (7.7)
SLE	1 (5.6)	0 (0)
Unknown	4 (22.2)	3 (23.1)

ESRD = end-stage renal disease; SLE = systemic lupus erythematosus

Statistical analyses

Two-sided *t*-tests were used to compare normally distributed continuous variables, and 95% confidence intervals (CIs) of the mean were obtained. For continuous variables that were not normally distributed, log transformations were performed, two-sided *t*-tests were conducted using the transformed values, and 95% CIs of the geometric means were obtained. The Fisher's exact test was used to compare categorical variables.

RESULTS

Patient characteristics

In total, 55 patients were screened for possible study inclusion and 44 were randomized to enter the study, 24 to the darbepoetin alfa group and 20 to the control group. In the darbepoetin alfa group, 6 patients did not complete the study: 2 died, 2 received transplants and 2 were hospitalized for surgery. In the control group, 7 patients did not complete the study: 3 died, 1 re-

TABLE 2

Clinical characteristics of patients

Characteristic	Darbepoetin alfa group	Control group	*P*-value
Mean Hb level (g/dL [95% CI])			
Month 0	11.91 (11.37, 12.46)	12.36 (11.69 13.03)	0.27
Month 10	12.03 (11.57, 12.50)	12.41 (11.55, 13.27)	0.38
Change from Month 0 to Month 10	0.12 (-0.72, 0.96)	0.05 (-1.13, 1.23)	0.91
Mean[a] Kt/V (95% CI)			
Month 0	1.49 (1.43, 1.56)	1.48 (1.40, 1.57)	0.80
Month 10	1.46 (1.38, 1.53)	1.49 (1.40, 1.58)	0.56
Mean[a] iron dose at Month 0 (mg [95% CI])	192.0 (157.5, 234.1)	215.9 (129.3, 360.3)	0.65
Mean[a] dose of erythropoietic agent			
Month 0	35.7 (26.9, 47.4)*	5837 (3670, 9281)†	
Month 10	20.1 (14.9, 27.2)*	6540 (4649, 9199)†	
Mean % change from Month 0 to Month 10	-31.08 (-56.47, -5.69)	24.48 (-26.92, 75.88)	0.03

[a]Geometric mean; *µg/week;

ceived a transplant, and 3 were hospitalized for surgery. We report here on the 31 patients (18 from the darbepoetin alfa group and 13 from the control group) who completed the study.

The two treatment groups were well matched with respect to age, aetiology of ESRD and time on dialysis (Table 1). There was, however, an excess of male patients in the darbepoetin alfa group. There were no statistically significant differences between the darbepoetin alfa group and the control group at Month 0 in terms of Hb concentration (mean values [95% CIs]: 11.91 g/dL [11.37, 12.46 g/dL] *versus* 12.36 g/dL [11.69, 13.03 g/dL]; *P* = 0.27; Table 2 and Figure 2), iron dose (mean* values [95% CI]: 192.0 mg [157.5, 234.1 mg] *versus* 215.9 mg [129.3, 360.3 mg]; *P* = 0.65; Table 2), or Kt/V (mean* values [95% CI]: 1.49 [1.43, 1.56] *versus* 1.48 [1.40, 1.57]; *P* = 0.80; Table 2).

Primary efficacy parameter

The mean Hb levels in the darbepoetin alfa and control groups at Month 10 were 12.03 g/dL (95% CI: 11.57, 12.50 g/dL) and 12.41 g/dL (11.55, 13.27 g/dL), respectively (*P* = 0.38; Table 2 and Figure 2). This represents a mean change in Hb from Month 0 to Month 10 of 0.12 g/dL (95% CI: –0.72, 0.96 g/dL) in the darbepoetin alfa group, and 0.05 g/dL (–1.13, 1.23 g/dL) in the control group. The difference between the two groups was not significant (*P* = 0.91).

Secondary efficacy parameters

In the darbepoetin alfa group, the mean* doses of darbepoetin alfa at Month 0 and Month 10 were 35.70 µg/week (95% CI: 26.90, 47.40

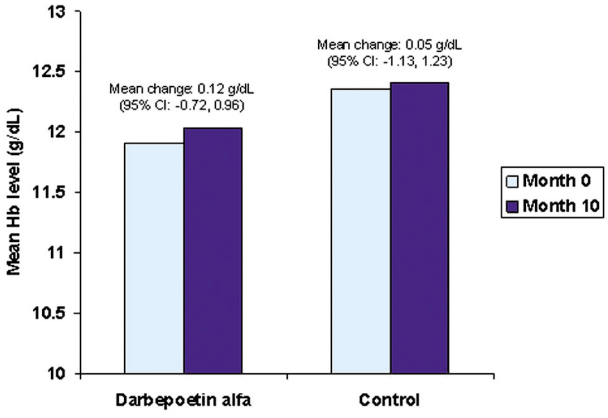

Figure 2. Mean Hb levels at Month 0 and Month 10 in the darbepoetin alfa and control groups.

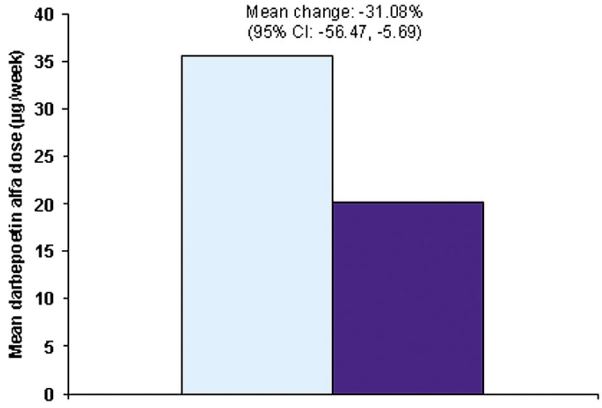

Figure 3. Mean* weekly dose of darbepoetin alfa at Month 0 and Month 10 in the darbepoetin alfa group.
* Geometric mean.

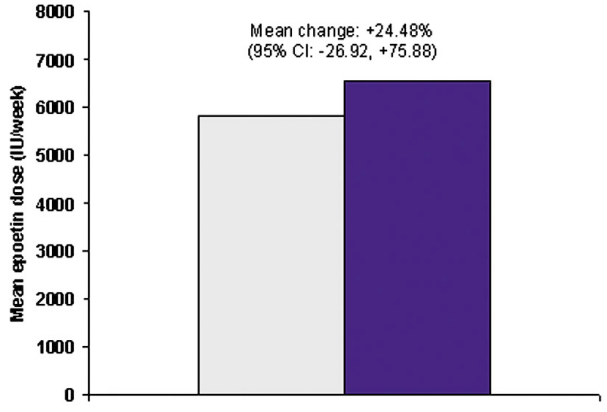

Figure 4. Mean* weekly dose of epoetin at Month 0 and Month 10 in the control group.
*Geometric mean.

µg/week) and 20.10 µg/week (95% CI: 14.90, 27.20 µg/week), respectively. This corresponds to a mean change in weekly darbepoetin alfa dose from Month 0 to Month 10 of –31.08% (95% CI: –56.47, –5.69%; Table 2, Figure 3).

In the control group, the mean* doses of epoetin at Month 0 and Month 10 were 5837 IU/week (95% CI: 3670, 9281 IU/week) and 6540 IU/week (95% CI: 4649, 9199 IU/week), respectively. This corresponds to a mean change in weekly epoetin dose from Month 0 to Month 10 of +24.48% (95% CI: –26.92, +75.88%; Table 2, Figure 4).

There was a significant difference between the two groups in mean percentage change in weekly dose from Month 0 to Month 10 ($P = 0.03$; Table 2).

One patient from the darbepoetin alfa group required blood transfusion during the course of the study, as a result of prostatectomy, and received 1 unit of packed red blood cells. Similarly, a patient from the control group required blood transfusion during the last month of the study, because of gynaecological surgery, and received a total of 3 units of packed red blood cells.

Serum ferritin was adequate for erythropoiesis in both the darbepoetin alfa and control groups throughout the study (Table 3).

Two patients in the darbepoetin alfa group,

TABLE 3
Mean serum ferritin levels (ng/ml [95% CI]) in the darbepoetin alfa and control groups at Month -5, Month -2 and Month 10

Month	Darbepoetin alfa group	Control group
-5	317.3 (198.4, 436.1)	375.4 (232.4, 518.4)
-2	329.3 (233.3, 425.2)	520.8 (293.0, 748.5)
10	438.2 (355.8, 520.6)	476.2 (339.4, 613.0)

and 3 from the control group, died before study completion. In no case was the cause of death thought to be related to treatment. No treatment-related adverse events were recorded.

* Geometric mean

DISCUSSION

This study demonstrates that once-weekly dosing with darbepoetin alfa by the IV route is as effective as three-times weekly dosing with IV epoetin in maintaining Hb levels in patients receiving HD. This study also shows that treatment with darbepoetin alfa resulted in a mean Hb increase of 0.12 g/dL, compared with an increase of 0.05 g/dL in the control group, and this was accompanied by a significant reduction in dose requirements for darbepoetin alfa. Taken together, these results suggest that darbepoetin alfa might be more effective than epoetin. Should this prove to be the case it means that treating anaemia in HD patients is considerably less expensive when using Darbepoetin alfa than epoetin via the i.v. route. Larger, appropriately powered studies are required to clarify these findings further.

Patients in both treatment groups remained iron replete throughout the study period. This indicates that the observed differences between the treatment groups were not related to iron deficiency and are more likely to result from the erythropoietic agent used.

The Novel Erythropoiesis-Stimulating Protein (NESP) Usage Guidelines recommend that Hb levels in patients switched from epoetin to darbepoetin alfa be monitored every 1–2 weeks during the titration phase[17]. The present study demonstrated that the frequency of Hb monitoring can be reduced to once monthly with no effect on patient outcomes.

Finally, extended dose intervals result in a reduction in the staff time required to manage renal anaemia, suggesting that darbepoetin alfa might, once again, reduce further specific costs of anaemia management.

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