

*Original Article*

## The efficacy of intravenous darbepoetin alfa administered once every 2 weeks in chronic kidney disease patients on haemodialysis

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### Abstract

**Background.** It is becoming increasingly more common to administer intravenous (i.v.) darbepoetin alfa to haemodialysis (HD) patients at less frequent dosing intervals in routine clinical practice. This study investigated extending the dosing interval for i.v. darbepoetin alfa treatment from once a week (QW) to once every 2 weeks (Q2W) at the same dose in order to maintain target haemoglobin (Hb) concentrations (11–13 g/dl).

**Methods.** Stable HD patients in routine clinical practice receiving i.v. darbepoetin alfa QW for a period of 6 months ( $n=105$ ) (treatment period 1) were switched to i.v. Q2W darbepoetin alfa for a further 6 months (treatment period 2) ( $n=90$ ). The dose of i.v. darbepoetin alfa was titrated to maintain Hb concentrations between 11 and 13 g/dl throughout the full 12-month study period.

**Results.** The mean change in Hb for treatment period 2 was  $0.04 \pm 1.1$  g/dl ( $\pm$ SD), which was not clinically relevant ( $11.7 \pm 0.8$  g/dl vs  $11.7 \pm 1.0$  g/dl;  $P=0.8$ ). The mean weekly doses of darbepoetin alfa were similar throughout the treatment periods ( $34.0 \pm 17.1$   $\mu$ g/week vs  $32.1 \pm 17.3$   $\mu$ g/week;  $P=0.3$ , respectively for QW and Q2W dosing). Intravenous darbepoetin alfa was well tolerated.

**Conclusions.** The treatment of renal anaemia in HD patients with i.v. Q2W darbepoetin alfa effectively and safely maintains Hb concentrations at a less frequent dosing regimen than observed with QW administration. Dose requirements for i.v. darbepoetin alfa administered QW or Q2W were not different. The results of this study demonstrate that i.v. darbepoetin alfa administered Q2W is an effective regimen for HD patients requiring anaemia treatment in routine clinical practice.

**Keywords:** darbepoetin alfa; frequency of administration; haemodialysis (HD); intravenous dosing; once every 2 weeks dosing (Q2W); renal anaemia

### Introduction

The treatment of renal anaemia using erythropoiesis stimulating agents (ESAs) [darbepoetin alfa and recombinant human erythropoietin (rHuEPO) alfa or beta] is now a common clinical practice in patients with chronic kidney disease (CKD), regardless of their dialysis status, such that there is an increasing need for consensus and guidelines on their use [1]. Despite their established role in the management of CKD patients, it remains important to further investigate how to utilize these agents in order to fully gain both the clinical and the economical benefits they can afford to in this ever-expanding patient population.

After nearly two decades of experience with these drugs, it has become increasingly common to administer ESAs at not only a reduced dosage, but also on a less frequent administration routine [1]. Clearly, this benefits both the patient and their healthcare providers, however, there is little reported experience from outside the clinical trial setting as to how such treatment regimens would routinely impact renal anaemia clinical practice in general.

In haemodialysis (HD) patients, darbepoetin alfa is usually administered once a week (QW) [1,2]. There are data from clinical trials to suggest that switching CKD patients receiving QW rHuEPO to once every 2 weeks (Q2W) darbepoetin alfa maintains target haemoglobin (Hb) concentration, without the need for an increase in dose [3–7]. However, there is little reported evidence, if any, of switching patients directly from QW darbepoetin alfa dosing to i.v. Q2W darbepoetin alfa, especially from a single dialysis centre during routine clinical practice.

The results of the present study offer an evaluation of stable HD patients being treated in routine clinical practice with i.v. darbepoetin alfa QW, who were

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subsequently converted to a Q2W treatment regimen in a dialysis centre over a 12-month treatment period.

### Subjects and methods

This single centre, open label, prospective study in 105 patients (selected from a total of 111) with end-stage renal disease (ESRD) receiving HD evaluated the efficacy and safety of unit doses of darbepoetin alfa administered i.v. Q2W for the treatment of renal anaemia to patients previously receiving i.v. darbepoetin alfa QW. The study design is presented schematically in Figure 1. Clinically stable ESRD patients ( $\geq 18$  years of age) with mean Hb concentrations between 11 and 13 g/dl receiving HD for at least 3 months were recruited from a single Portuguese dialysis centre (Eurodial, Leiria). The study protocol required that the patients were receiving a stable dose of i.v. darbepoetin alfa QW for 6 months (treatment period 1) prior to switching to the same dose of i.v. darbepoetin alfa Q2W for a further 6 months (treatment period 2). A stable dose is defined as  $\leq 25\%$  change in darbepoetin alfa dose over the 6-week period immediately prior to enrolment and with less than one missed dose over this period. To ensure adequate iron stores for supporting erythropoiesis, serum ferritin was required to be in the range 200–600  $\mu\text{g/l}$ .

The principal exclusion criteria for the study were: New York Heart Association class III or IV congestive heart failure, uncontrolled hypertension (diastolic blood pressure  $\geq 110$  mmHg prior to HD), concomitant infection, haematological disorders, inflammatory disease and epilepsy. Patients were also excluded if they had undergone major surgery or blood transfusions within 12 weeks before the 12-month study period, or were pregnant or lactating.

Prior to switching to i.v. darbepoetin alfa Q2W, patients received unit doses of i.v. darbepoetin alfa QW to maintain Hb concentrations between 11 and 13 g/dl for a period of 6 months. Human serum albumin-free darbepoetin alfa was available for administration at the following unit doses: 10, 15, 20, 30, 40, 50, 60, 80, 100 or 150  $\mu\text{g}$ . After this initial 6-month treatment period, patients were switched from a QW frequency administration to Q2W, but at the same total weekly dose (i.e. no dose adjustment) for a further 6 months. Intravenous iron supplementation was administered to maintain serum ferritin in the range 200–600  $\mu\text{g/l}$ .

Darbepoetin alfa dosing was adjusted to maintain each patient's Hb concentration within a target range of  $-1.0$  to  $+1.5$  g/dl of the mean baseline Hb and between 11 and 13 g/dl throughout the 12-month study period.

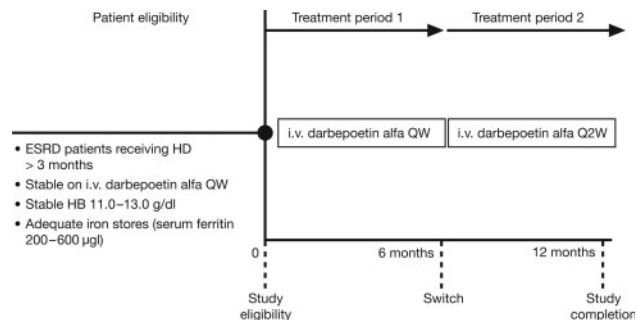


Fig. 1. Study design.

Dose increases or decreases were made according to the NESP guidelines [2]. If a patient's Hb fell below the target range on two consecutive assessments, then the dose of darbepoetin alfa was increased to the next higher unit dose. Conversely, if a patient's Hb increased above the target range on two consecutive assessments then the dose of darbepoetin alfa was decreased to the next lower unit dose. Any change in dose was one step up or down in the list of provided unit doses. Blood samples for Hb, serum ferritin and transferrin saturation measurements were taken monthly throughout the study period. Laboratory parameters were also monitored. There were no changes in HD format (conventional HD), dialysis membranes or the dialysis machine throughout the study period.

The primary efficacy endpoints were the change in Hb between the switch from QW to Q2W administration, and the dose of darbepoetin alfa administered during the study. Safety variables assessed the nature, frequency, severity, relation to treatment and the outcome of all adverse events.

### Statistical analysis

In this analysis, variables were expressed as mean values with SD for continuous parameters and frequencies with percentages for categorical parameters. Changes in Hb and darbepoetin alfa mean values were evaluated using a paired *t*-test. Categorical parameters association was evaluated using the  $\chi^2$  test. Analyses were conducted in the per-protocol and intent-to-treat (ITT) patient populations.

For all comparisons a *P*-value  $< 0.05$  was considered statistically significant. Statistical analyses were performed using SPSS v13.0.

### Results

In total, 107 patients from our unit were considered eligible for study inclusion (Figure 2). Of these patients, two were not included because they had concomitant severe haematological disease. Therefore, 105 patients were subsequently included in the 12-month study period. Patient demography and

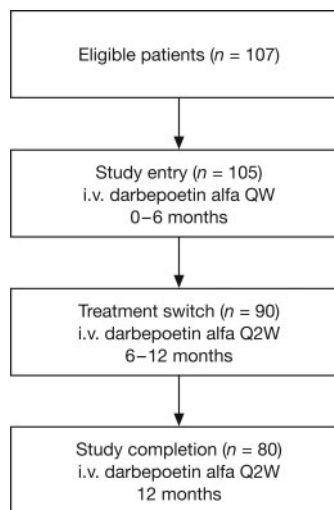


Fig. 2. Patient disposition.

baseline characteristics are shown in Tables 1 and 2. In total, 80 patients completed the study. Discontinuations were due to death (17 patients) and also transfusions relating to either gastrointestinal bleeding (two patients) or major surgery (six patients). All deaths were considered to be unrelated to study treatment. Ten of the 17 deaths occurred during the QW period and seven occurred during the Q2W period. Of the eight patients who discontinued the study because of blood transfusions, five withdrew in the QW period and three in the Q2W period.

The mean Hb concentration at the outset for patients included in the study population was  $11.75 \pm 1.66$  g/dl (mean  $\pm$  SD;  $n = 105$ ). At the end of the first treatment period (treatment period 1) during which patients received darbepoetin alfa QW, Hb was  $11.46 \pm 1.6$  g/dl (mean  $\pm$  SD). After switching to Q2W dosing and completing the 12-month study period, the Hb concentration in these patients was  $11.54 \pm 1.6$  g/dl (mean  $\pm$  SD). For comparison, mean changes in Hb concentration from baseline to the end of each treatment period in the protocol population are shown in Table 3.

Hb concentrations were effectively maintained above 11 g/dl throughout the study period both after QW dosing ( $11.7 \pm 0.8$  g/dl), and Q2W dosing

( $11.7 \pm 1.0$  g/dl), with no statistically significant changes from the study outset or at the end of the study period (Figure 3) ( $P = 0.8$ ). The percentage of evaluable patients who successfully maintained Hb concentrations in the required range was 65% [95% confidence interval (CI), 55–75%] for treatment period 1 and 81% (95% CI, 71–88%) for treatment period 2.

During dose adjustment, increases or decreases of darbepoetin alfa never exceeded 25% of the previous dose. There were no statistically significant differences in the mean weekly dose of i.v. darbepoetin alfa ( $34.0 \pm 17.1$  vs  $32.1 \pm 17.3$   $\mu$ g/week;  $P = 0.3$ ) over the study period, even when adjusted for body weight [ $0.56 \pm 0.36$  vs  $0.51 \pm 0.33$   $\mu$ g/week;  $P =$  not significant (NS)] (Figure 4). The median weekly dose of darbepoetin alfa was 30.0  $\mu$ g at the beginning of the study, at the end of treatment period 1 and at the end of treatment period 2, using both per-protocol and ITT analyses. Therefore, no difference was observed between the 80 patients who completed the study and the 105 patients who commenced the study.

Mean serum ferritin levels were  $443 \pm 220$   $\mu$ g/l at the study outset and were maintained above 200  $\mu$ g/l throughout the study period ( $565 \pm 216$   $\mu$ g/l at the final evaluation). Intravenous iron was received by 90.5% (95/105) and 95.6% (86/90) of patients during treatment period 1 and 2, respectively (ITT population;

**Table 1.** Patient demography

	Intravenous darbepoetin alfa ( $n = 105$ )
Sex	
Male	62 (59%)
Female	43 (41%)
Race	
White	105 (100%)
Age (years) <sup>a</sup>	64.4 ( $\pm 15.8$ )
Weight (kg) <sup>a</sup>	65.3 ( $\pm 13.4$ )

<sup>a</sup>Mean ( $\pm$ SD).

**Table 2.** Patient baseline characteristics

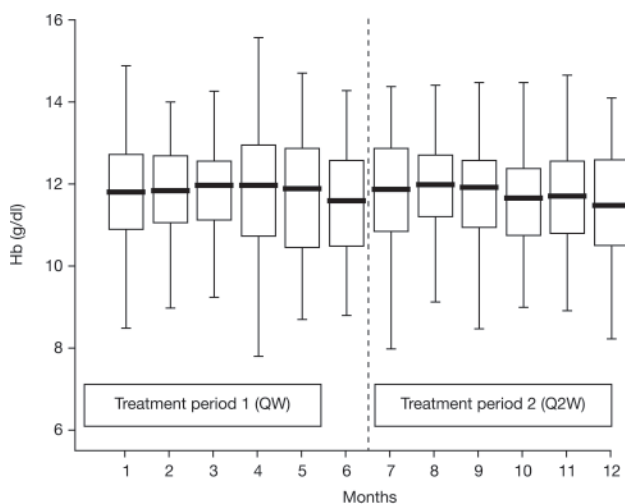
	Intravenous darbepoetin alfa ( $n = 105$ )
Cause of CKD	
Hypertension	29 (28%)
Diabetic nephropathy	20 (19%)
Glomerulonephritis	13 (12%)
Urological	6 (6%)
Pyelonephritis	12 (11%)
Autosomal dominant polycystic kidney disease	4 (4%)
Chronic graft rejection	3 (3%)
Unknown/other <sup>a</sup>	17 (17%)
Time since first dialysis (months) <sup>b</sup>	43 $\pm$ 37
Baseline darbepoetin alfa ( $\mu$ g/kg) <sup>b</sup>	0.5 $\pm$ 0.4
Baseline Hb concentration (g/dl) <sup>b</sup>	11.75 $\pm$ 1.66
Serum ferritin ( $\mu$ g/l) <sup>b</sup>	443 $\pm$ 220

<sup>a</sup>Unknown category includes 'suspected' unconfirmed cases.

<sup>b</sup>Mean ( $\pm$ SD).

**Table 3.** Variation of Hb concentration in the total population during the study

	Baseline ( $n = 105$ )	End of treatment period 1 ( $n = 90$ )	End of treatment period 2 ( $n = 80$ )	<i>P</i> -value
Mean (g/dl)	11.75	11.79	11.70	NS
Median (g/dl)	11.80	11.80	11.67	NS
SD	1.61	1.57	1.30	



**Fig. 3.** Mean ( $\pm$ SD) haemoglobin concentration overtime.

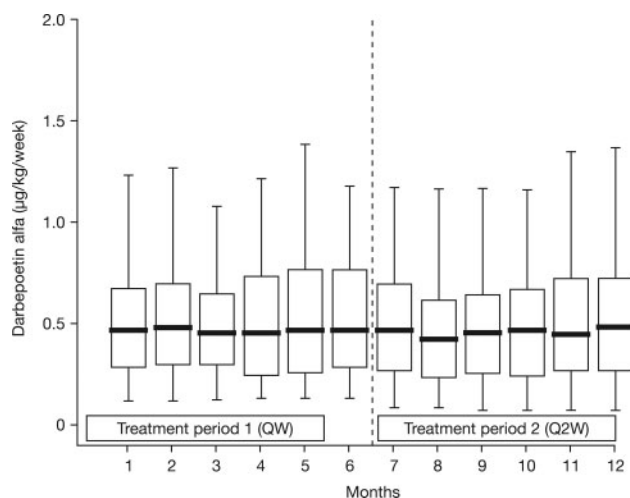


Fig. 4. Mean ( $\pm$ SD) weekly dose of darbepoetin alfa ( $\mu\text{g}/\text{kg}/\text{week}$ ).

$P = \text{NS}$ ). This is compared with 92.5% (74/80) and 96.3% (77/80) of patients, respectively, in the per-protocol population ( $P = \text{NS}$ ). Mean doses of iron were 120 mg/month during treatment period 1 and 100 mg/month during treatment period 2 for both the ITT and per-protocol populations ( $P = \text{NS}$ ).

#### Stability of Q2W darbepoetin alfa treatment

The stability of Hb concentrations for patients receiving Q2W darbepoetin alfa was determined in two ways: (i) the proportion of patients who did not require a switch back to QW administration of darbepoetin alfa and (ii) the proportion of patients receiving darbepoetin alfa who required a dose adjustment. Overall, 100% of patients (80/80) maintained the Q2W frequency. Of these patients, 26% (21/80) did not require any dose adjustments. Similarly, during the QW phase, 30% (24/80) of patients did not require any dose adjustments ( $P = \text{NS}$ ).

#### Safety analysis

Darbepoetin alfa was well tolerated during the 1-year study period, consistent with previous clinical experience at the centre. No pure red-cell aplasia was reported 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. Overall, 67% of patients reported at least one adverse event. The most commonly occurring adverse events were hypertension (22%), arthralgia (12%), vascular access complication (11%), upper respiratory tract infection (10%), hypotension (9%), diarrhoea (7%) and asthenia (5%). None of the treatment-related adverse events led to study discontinuation for any of the patients.

C-reactive protein levels (mean  $\pm$  SD 1.47  $\pm$  1.87 and 0.91  $\pm$  0.74 mg/dl in treatment periods 1 and 2,

respectively) remained consistent throughout the study period, as did serum protein(s) (7.0  $\pm$  0.42 and 6.9  $\pm$  0.40 g/dl, respectively), parathyroid hormone (432  $\pm$  195 and 383  $\pm$  101 pg/ml, respectively) and Kt/V dosage (1.47  $\pm$  0.34 and 1.46  $\pm$  0.26, respectively). No significant differences in these laboratory parameters were observed between treatment periods 1 and 2.

## Discussion

It is now commonplace to administer ESAs to CKD patients with renal anaemia, regardless of their dialysis status, with less frequent administration than the regimens used immediately following their introduction in the 1980s [1]. This has occurred mostly from the practical use of such agents, but also with hindsight from large, randomized, clinical and controlled trials. As is the case in many areas of medicine, the results of in-clinic experience of less frequent administration of ESAs are rarely fully reported; thus the ability to administer ESAs at both reduced dosage and frequency remains a topic of continuing research and vigorous debate despite the plethora of published data showing the beneficial effects of ESAs in CKD patients, which has resulted in guidelines for their usage [1,2]. In our own unit, it has become regular practice to administer ESAs on dosing schedules less frequent than the initially approved three-times-per-week regimens used a decade ago. Our recent experience suggests not only can we routinely treat patients QW with ESAs, but that we can also obtain the same results and outcomes in patients administered Q2W with i.v. darbepoetin alfa. The results of our current investigation indicate clearly that switching CKD patients on HD from darbepoetin alfa QW to Q2W dosing effectively maintains stable Hb concentrations without any need for an increase in dose. However, we must place these results against the data currently published on other ESAs to further understand and maximize the benefits of reduced dosing in CKD patients, especially those receiving HD. The data for the use of i.v. rHuEPO at reduced frequency of QW in HD patients is largely anecdotal, limited and inconclusive, moreover, there are no studies or clinical reports for Q2W dosing regimen following i.v. rHuEPO administration.

The results of the present study fully support the practical use of the i.v. Q2W darbepoetin alfa regimen in stable HD patients switched from QW dosing. 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 i.v. administration of ESAs to dialysis patients [1].

If, as suggested from the present results, darbepoetin alfa can be given Q2W to CKD patients on HD, what does the future hold in terms of extended dosing frequency and adequacy? The area remains the subject



of considerable research, but recent results suggest that it may be entirely feasible to administer darbepoetin alfa once monthly in order to maintain stable Hb concentrations in CKD patients. In one study [8], clinically stable dialysis patients ( $n=38$ ) receiving stable Q2W darbepoetin alfa were converted to darbepoetin alfa once every 3 weeks for 20 weeks, and then (if Hb concentrations were maintained between 10 and 13 g/dl) to darbepoetin alfa once monthly for a further 20 weeks. In another study [9], CKD patients ( $n=97$ ) not on dialysis receiving stable subcutaneous Q2W darbepoetin alfa were converted to darbepoetin alfa once monthly for 29 weeks. In both studies darbepoetin alfa administered once monthly effectively and safely maintained Hb levels in patients previously stabilised on Q2W dosing. Nevertheless, whatever the outcome of future clinical investigations, the present results from routine clinical practice confirm that Q2W administration of i.v. darbepoetin alfa is an effective and well-tolerated treatment in CKD patients on HD.

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*Conflict of interest statement.* F.C. is a scientific consultant for Amgen (Europe). None of the other authors have any conflict of interest to declare.

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