

Conversion from Recombinant Human Erythropoietin to Once Every 4 Weeks Darbepoetin Alfa for Treatment of Renal Anemia in CAPD Patients

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Background: Darbepoetin alfa is a new erythropoietic protein with a three-fold longer half-life than recombinant human erythropoietin (rHuEPO), allowing for an extended dosing interval of once every 2 weeks in patients with chronic renal failure. The objective of this study was to investigate the possibility of further extending the dose interval of this erythropoietic agent to once every 4 weeks in the treatment of renal anemia in dialysis patients.

Methods: A prospective study was carried out in 14 continuous ambulatory peritoneal dialysis (CAPD) patients stably maintained on subcutaneous rHuEPO with hemoglobin level of 10–13 g/dL. They were switched to subcutaneous darbepoetin alfa administered once every 4 weeks for a period of 24 weeks. The starting dose was 40 µg. The dose of darbepoetin alfa was then adjusted to maintain a target hemoglobin level between 10 and 13 g/dL. When darbepoetin alfa was increased by 100%, the dosing interval was shortened to maintain the target hemoglobin. Evaluation was done during the last 4 weeks.

Results: Of the 14 patients recruited, 11 patients completed the study. Of these 11 patients, 9 (82%) successfully maintained the target hemoglobin with once every 4 weeks darbepoetin alfa. For those successful patients, the mean hemoglobin level during the evaluation period was 11.13 ± 2.04 g/dL (mean \pm standard deviation), and the mean change in hemoglobin level from baseline was -1.03 g/dL (95% CI: $-2.34, 0.27$). The mean weekly darbepoetin alfa dose requirement during the evaluation period was 12.33 ± 4.80 µg/week, and the mean change in weekly dose from baseline was $+2.33$ µg/week (95% CI: $-1.35, 6.02$). No serious adverse event related to darbepoetin alfa occurred during the study.

Conclusion: Darbepoetin alfa administered once every 4 weeks effectively maintained hemoglobin level in most CAPD patients after conversion from previously stabilized rHuEPO treatment. Darbepoetin alfa is safe and well tolerated, allowing for less frequent dosing. [*Hong Kong J Nephrol* 2007;9(2):77–81]

Key words: continuous ambulatory peritoneal dialysis, darbepoetin alfa, end-stage renal failure, erythropoietin, renal anemia

背景：Darbepoetin alfa 是一種新型的促紅細胞生成素，相比於重組人體促紅細胞生成素 (rHuEPO)，其半衰期長達 3 倍，可供慢性腎衰竭患者以每 2 週一次的間隔使用。本研究旨在調查於接受透析的腎性貧血患者間，darbepoetin alfa 的使用間隔是否可以延長至每 4 週一次。

方法：研究採前瞻性方式，對象為 14 位接受可攜帶式連續腹膜透析 (CAPD) 及穩定劑量 rHuEPO 皮下注射的病人，其血紅素為 10–13 g/dL，轉換至 darbepoetin alfa 每 4 週一次皮下注射至 24 週，起始劑量 40 µg，後續的劑量調整以血紅素達到 10–13 g/dL 為目標。若 darbepoetin alfa 劑量增幅達 100%，則容許縮短施藥間隔以達血紅素目標。結果的評估於最後的 4 週進行。

結果：共 11 人完成研究，其中 9 人 (82%) 在每 4 週一次的 darbepoetin alfa 使用間隔下仍可達到血紅素目標，評估期間其平均血紅素為 11.13 ± 2.04 g/dL，相比於基線值平均變幅為 -1.03 g/dL (95% CI: $-2.34, 0.27$)。評估期間，darbepoetin alfa 的每週平均劑量為 12.33 ± 4.80 µg/week，相比於基線值

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的變幅則為 +2.33 $\mu\text{g}/\text{week}$ (95% CI: -1.35, 6.02)。在 darbepoetin alfa 治療期間，並未發生相關的嚴重不良作用。

結論：CAPD 接受者從穩定劑量 rHuEPO 療程轉換至 darbepoetin alfa 每 4 週一次之後，大部分人的血紅素水平均保持穩定。Darbepoetin alfa 所需的施藥頻率較低，且兼具良好的安全與耐受性。

INTRODUCTION

Anemia secondary to chronic renal failure has been associated with cardiovascular complications including left ventricular hypertrophy [1] and congestive heart failure [2], reduced cognitive function [3], decreased quality of life [3,4] and, more importantly, mortality [5]. Recombinant human erythropoietin (rHuEPO) has been the mainstay therapy of renal anemia since its introduction over two decades ago [6,7]. However, rHuEPO needs to be administered frequently up to three times a week to be effective.

Darbepoetin alfa is a new erythropoietic protein which stimulates erythropoiesis by the same mechanism as endogenous erythropoietin and rHuEPO. Research has indicated that sialic acid-containing carbohydrate of erythropoietin determines its serum half-life [8]. Recombinant HuEPO has three N-linked carbohydrate side chains, while darbepoetin alfa has five. The increased carbohydrate content of darbepoetin alfa results in a longer terminal half-life when compared with rHuEPO. In dialysis patients, darbepoetin alfa has been shown to have a serum half-life three times longer than that of rHuEPO, accommodating extended dosing intervals [9].

The efficacy and safety of administering darbepoetin alfa once weekly or once every 2 weeks has been demonstrated in patient with end-stage renal failure [10]. The objective of this study was to investigate the possibility of further extending the dose interval of darbepoetin alfa to once every 4 weeks in the treatment of renal anemia in dialysis patients.

PATIENTS AND METHODS

A prospective open-label study was carried out in 14 end-stage renal failure patients receiving continuous ambulatory peritoneal dialysis (CAPD). The study was approved by the research ethics committee of Princess Margaret Hospital, Hong Kong. All patients gave written informed consent before recruitment into the study. Patients eligible for recruitment were those on CAPD, and receiving subcutaneous rHuEPO with hemoglobin level stably maintained between 10 and 13 g/dL for the past 3 months. Patients with uncontrolled hypertension (defined as diastolic blood pressure ≥ 110 mmHg), New York Heart Association

Class III or IV congestive heart failure, grand mal epilepsy, any kind of blood loss causing iron depletion, vitamin B12 or folate deficiency, aluminium toxicity and severe hyperparathyroidism (defined as parathyroid hormone level > 20 times normal) were excluded from the study. The presence of infection within the past 3 months, inflammatory conditions, malignancies, any type of thalassemia and hematologic diseases that might interfere with the erythropoietic response, were also exclusion criteria. Those who had received blood transfusion within 3 months before the screening period, and pregnant and lactating females were also excluded.

Darbepoetin alfa was supplied by the hospital pharmacy as a sterile protein solution in pre-filled syringes containing 20 μg and 40 μg of the drug. The 14 enrolled patients were switched from subcutaneous rHuEPO to subcutaneous darbepoetin alfa which was administered once every 4 weeks. The starting dose was 40 μg , which was equivalent to an average weekly dose of 10 μg . The dose of darbepoetin alfa was adjusted to maintain a target hemoglobin level between 10 and 13 g/dL. Dose adjustments were made by 20 μg increments or decrements when the hemoglobin levels were outside the target range. If the hemoglobin level was still below the target range after the darbepoetin alfa dose had been increased by 100%, the dose interval was reduced by 1 week. Subjects were followed-up for a period of 24 weeks. Evaluation was done during the last 4 weeks of the study. Complete blood count, transferrin saturation, serum ferritin, albumin, urea and creatinine levels were monitored every 4 weeks. Any requirement for blood transfusion was recorded. Blood pressure and adverse events were closely monitored.

The primary end point of the study was the percentage of patients who were able to maintain the target hemoglobin level of 10–13 g/dL with once every 4 weeks dosing during the evaluation period. The secondary end points were the mean changes in hemoglobin level and weekly dose of darbepoetin alfa from baseline to evaluation period in those patients who successfully maintained the target hemoglobin.

Statistical analysis

The number and percentage of patients who completed the study and successfully maintained hemoglobin above the target level (hemoglobin level ≥ 10 g/dL) during the evaluation period are presented. The mean changes in hemoglobin level and weekly darbepoetin

alfa dose from baseline to evaluation period for those successful patients are presented, with two-sided 95% confidence intervals (CIs). The non-parametric Wilcoxon signed rank test was used to compare the means of transferrin saturation and serum ferritin level at baseline and evaluation period. A p value < 0.05 was regarded as statistically significant.

RESULTS

Fourteen patients were enrolled in the study. Eleven of the 14 patients completed the study. Of the three patients who withdrew from the study prior to completion, one died of infection, one inadvertently injected conventional rHuEPO and one chose to discontinue before completion of the study because of mild elevation of blood pressure after receiving the drug. For the 11 patients who completed the study, the mean dose requirement of rHuEPO before entering the study was 55.42 ± 21.01 U/kg/week (range, 27.78 ± 91.91 U/kg/week). Their primary renal pathologies included unknown pathology (6 patients), diabetic nephropathy (3 patients), polycystic kidney disease (1 patient) and IgA nephropathy (1 patient). The demographic data and baseline characteristics of the patients are shown in Table 1.

Table 1. Demographic and baseline characteristics of patients ($n = 11$)*

Sex	
Male	9 (82)
Female	2 (18)
Race	
Chinese	11 (100)
Age (yr)	60.0 ± 12.9
Dialysis modality	
Peritoneal dialysis	11 (100)
Baseline rHuEPO dose (U/kg/wk)	55.42 ± 21.01
Frequency of rHuEPO	
Once per wk	5 (45)
Once every 10 d	4 (36)
Once every 2 wk	2 (18)
Baseline hemoglobin level (g/dL)	12.20 ± 1.43
Transferrin saturation (%)	44.45 ± 11.95
Ferritin (ng/mL)	785 ± 672

*Data are presented as n (%) or mean \pm standard deviation. rHuEPO = recombinant human erythropoietin.

During the evaluation period, nine of the 11 patients (82%) successfully maintained the target hemoglobin level with once every 4 weeks darbepoetin alfa. The two unsuccessful patients required an increase in the frequency of darbepoetin alfa to once every 3 weeks to maintain the target hemoglobin level. For the nine successful patients, the mean hemoglobin level during the evaluation period was 11.13 ± 2.04 g/dL, and the mean change in hemoglobin level from baseline was -1.03 g/dL (95% CI: $-2.34, 0.27$) (Table 2, Figure 1). The mean weekly darbepoetin alfa dose requirement during the evaluation period was 12.33 ± 4.80 μ g/week, and the mean change in weekly dose from baseline was $+2.33$ μ g/week (95% CI: $-1.35, 6.02$) (Table 3, Figure 2). From Table 1, six of the 11 studied patients were receiving rHuEPO less frequently than once weekly before entering the study. One of these six patients belonged to the unsuccessful group. In the successful group, four patients were receiving rHuEPO with frequency not less than once weekly.

No significant changes in transferrin saturation and serum ferritin level were observed during the evaluation period (Table 3). No intravenous iron was required during the study period. None of the patients had blood transfusion given during the study. No serious adverse events occurred during the study period. One death occurred during the study due to infection which was not considered to be related to darbepoetin alfa. No clinically significant changes in other laboratory values were observed. None of the patients had any change in the peritoneal dialysis dose during the study period.

DISCUSSION

Recombinant HuEPO has been the mainstay therapy in the treatment of renal anemia. However, due to its relatively short half-life, rHuEPO needs to be administered frequently up to three times a week. Darbepoetin alfa has a three-fold longer half-life than rHuEPO. This unique characteristic allows it to be administered in an extended dose interval that is more convenient for patients. Previous studies have demonstrated the efficacy of darbepoetin alfa when given once weekly [10–15] or once every 2 weeks [10, 14–17] to both dialysis and pre-dialysis chronic renal failure patients with renal anemia. These studies also found that, in contrast to rHuEPO, there was no difference in intravenous and subcutaneous dose requirements for darbepoetin alfa [10,14].

The present study aimed to evaluate the efficacy of subcutaneous darbepoetin alfa in CAPD patients when further extending the dose interval to once every 4 weeks. The majority (82%) of our patients successfully maintained the target hemoglobin level after conversion from rHuEPO to darbepoetin alfa. There was only

Table 2. Changes in hemoglobin level and weekly darbepoetin alfa dose from baseline to evaluation period in successful patients (*n* = 9)

	Baseline (mean ± SD)	Evaluation period (mean ± SD)	Mean change (95% CI)
Hemoglobin (g/dL)	12.17 ± 1.47	11.13 ± 2.04	-1.03 (-2.34, 0.27)
Weekly darbepoetin alfa dose (µg/wk)	10.00 ± 0.00	12.33 ± 4.80	+2.33 (-1.35, 6.02)

SD = standard deviation; CI = confidence interval.

Table 3. Serum transferrin saturation and ferritin levels at baseline and the evaluation period in successful patients (*n* = 9)*

	Baseline	Evaluation period	<i>p</i>
Transferrin saturation (%)	45.2 ± 13.1	51.4 ± 12.3	0.207
Ferritin (ng/mL)	701 ± 702	854 ± 470	0.214

*Data are presented as mean ± standard deviation.

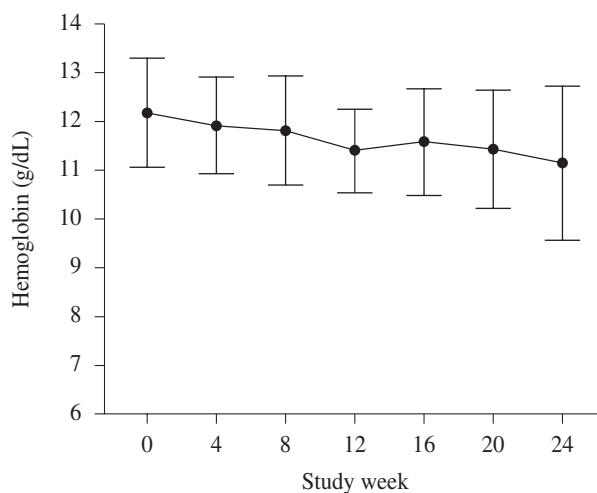


Figure 1. Mean hemoglobin level in successful patients. The bars represent 95% confidence intervals.

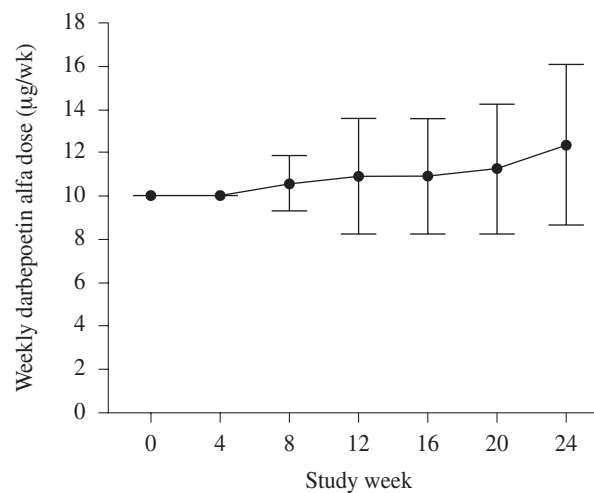


Figure 2. Mean weekly darbepoetin dose in successful patients. The bars represent 95% confidence intervals.

minimal increase in darbepoetin alfa dose requirement towards the end of the study. Since 50% of the unsuccessful patients were receiving rHuEPO less frequently than once weekly and 44% of the successful patients were receiving rHuEPO with frequency not less than once weekly before recruitment, it is unlikely that the less frequent rHuEPO dosing in some of our patients could account for the successful switching to darbepoetin alfa once every 4 weeks. The mean baseline rHuEPO dose requirement (55.42 U/kg/week) was low in our patients. This is speculated to be due to race effects, since Chinese patients may have a lower erythropoietin requirement.

Recently, two studies have demonstrated that a monthly dosing interval of darbepoetin alfa effectively maintained hemoglobin level in dialysis patients [18, 19]. In one of the studies by the Darbepoetin Alfa

20000144 Study Group, the median weekly dose of darbepoetin alfa required at the end of the study was 22 µg/week [18]. In the other study by Theodoridis et al [19], a 200 IU rHuEPO to 1 µg darbepoetin alfa ratio was used to calculate the weekly starting dose, in accordance with the novel erythropoiesis-stimulating protein (NESP) usage guidelines group [20]. In the current study, the starting dose (average weekly dose) of darbepoetin alfa was 10 µg/week, which was lower than that used in the above two studies. The weekly dose conversion ratio was approximately 275 IU rHuEPO to 1 µg darbepoetin alfa. The same starting dose was used in all patients. The dose requirement was then adjusted to maintain the target hemoglobin level, and the final mean weekly darbepoetin alfa dose at the evaluation period was 12 µg/week, which was still below the doses used in the above two studies.

The iron status in our patients was not affected by conversion to darbepoetin alfa. Both the transferrin saturation and serum ferritin level remained unchanged and no intravenous iron therapy was required by the patients. No serious adverse events related to darbepoetin alfa had occurred.

This prospective study demonstrated that darbepoetin alfa administered once every 4 weeks effectively maintained hemoglobin in most CAPD patients after conversion from previously stabilized rHuEPO treatment. Darbepoetin alfa is safe and well tolerated, allowing for less frequent dosing, which may confer significant advantages to patients by decreasing the number of injections required. Nevertheless, the present study, although prospective, was not a randomized, controlled and large-scale study, and the follow-up period did not exceed 6 months. Therefore, a long-term, large-scale, randomized study is warranted to confirm the results.

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