ORIGINAL ARTICLE

Randomized Study of Darbepoetin Alfa and Recombinant Human Erythropoietin for Treatment of Renal Anemia in Chronic Renal Failure Patients Receiving Peritoneal Dialysis

Wen-Yi Li,[1] Tzong-Shinn Chu,[2,3] Jenq-Wen Huang,[2] Ming-Shiou Wu,[2] Kwan-Dun Wu[2]*

Background/Purpose: Darbepoetin alfa can be administered less frequently than recombinant human erythropoietin (r-HuEPO) for the treatment of anemia in chronic renal failure (CRF) patients. We aimed to confirm that darbepoetin alfa at a reduced dosing schedule can safely maintain a target hemoglobin level in CRF patients undergoing peritoneal dialysis.

Methods: Forty-five PD patients receiving r-HuEPO were randomized in a 1:1 ratio to continue r-HuEPO or to change to darbepoetin alfa (open-label). Patients were maintained within a target range of hemoglobin for 5.5 months by adjusting the dose and then the frequency of darbepoetin alfa and r-HuEPO over the initial 4 months. The evaluation period was the final 1.5 months. A total of 37 patients completed the study.

Results: During the evaluation period, the hemoglobin of the darbepoetin alfa group was higher than that in the baseline period (10.46 ± 0.22 g/dL *vs.* 9.98 ± 0.18 g/dL, $p < 0.05$). Hemoglobin remained similar in the r-HuEPO group. The average dose in the darbepoetin alfa group was 93.0 μg/month, while the average dose in the r-HuEPO group was 18,339.9 units/month. The dosing frequency was less in the darbepoetin alfa group (3.9 times/month *vs.* 9.2 times/month). We divided the darbepoetin alfa group into low-dose (< 70 μg/month) and high-dose (≥ 70 μg/month) subgroups. The body weight in the high-dose group was higher than that in the low-dose group (66 ± 11 kg *vs.* 52 ± 4.4 kg, $p < 0.01$).

Conclusion: Both darbepoetin alfa and r-HuEPO safely maintain hemoglobin levels within the target range in peritoneal dialysis patients. [*J Formos Med Assoc* 2008;107(11):843–850]

Key Words: anemia, chronic renal failure, darbepoetin alfa, erythropoietin, peritoneal dialysis

Kidney damage, as seen in chronic renal failure (CRF), frequently leads to anemia. Anemia can significantly affect patient morbidity, mortality and quality of life. The anemia of renal disease is primarily caused by deficient production of erythropoietin.[1] Recombinant human erythropoietin (r-HuEPO) is licensed worldwide for the treatment of anemia in CRF patients. r-HuEPO produces an increase in red cell mass, eliminates the need for red blood cell transfusions and mitigates the symptoms associated with anemia.[2,3] It is recommended that r-HuEPO is administered two or three times per week[4] due to its relatively short circulating half-life.

[1]Department of Internal Medicine, National Taiwan University Hospital Yun-Lin Branch, Yun-Lin, [2]Department of Internal Medicine, National Taiwan University Hospital, and [3]Department of Primary Care Medicine, National Taiwan University College of Medicine, Taipei, Taiwan.

Received: August 8, 2007
Revised: April 2, 2008
Accepted: May 26, 2008

***Correspondence to:** Dr Tzong-Shinn Chu, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 100, Taiwan.
E-mail: tschu@ntu.edu.tw

Research has indicated that the sialic acid-containing carbohydrate of erythropoietin determines its serum half-life.[5] Darbepoetin alfa differs from r-HuEPO by alteration of five amino acids in the primary protein structure and two additional carbohydrate chains allowing for an increase of up to 22 sialic acid residues. Darbepoetin alfa can be administered less frequently than r-HuEPO because of an approximately three-fold longer serum half-life and greater biological activity.[6]

The efficacy and safety of darbepoetin alfa have been well studied, especially in pre-dialysis[7,8] and hemodialysis patients.[9,10] Darbepoetin is also effective and safe for the treatment of anemia in peritoneal dialysis (PD) patients.[11] The purpose of this open-label, single-center, randomized, comparative study is to confirm that darbepoetin alfa at a reduced dosing schedule can safely maintain a target hemoglobin (Hb) level in end-stage renal failure (ESRD) patients undergoing PD. Therapy with r-HuEPO was used as reference.

Methods

Patients

Patients with ESRD undergoing PD for at least 3 months prior to enrolment in the study were included. Patients were 18 years or older and clinically stable with no planned change in dialysis mode. Eligibility criteria were administration of stable subcutaneous r-HuEPO therapy for 3 months prior to enrolment into the study and an Hb of 8.0–12.0 g/dL during the screening/baseline period. There were no signs of iron deficiency (serum ferritin > 100 ng/mL and transferrin saturation no less than 20%). Patients were excluded from the study if they were receiving treatment for grand mal epilepsy or had uncontrolled hypertension (diastolic blood pressure > 100 mmHg), congestive heart failure (New York Heart Association class III or IV), clinical evidence of severe hyperparathyroidism (intact parathyroid hormone [PTH] ≥ 800 pg/mL), hematologic or systemic infection or inflammatory disease, current active liver disease, current active peritonitis, or current malignancy that might interfere with the erythropoietic response. Patients with psychiatric, addictive, or any disorder that compromised the ability to give informed consent for participation in this study were also excluded. Pregnant or breast-feeding women were excluded. Patients who had had red blood cell transfusion to treat anemia within 1 month prior to enrolment, or major surgery or androgen therapy within 3 months prior to enrolment in the study, were not included.

The study was approved by the institutional review board and all patients gave written informed consent before participation.

Study design

This open-label, single-center, randomized, comparative study was conducted to assess the safety and efficacy of darbepoetin alfa in ESRD patients receiving PD. After an initial screening/baseline period, patients currently undergoing r-HuEPO therapy were randomized in a 1:1 ratio to either continue r-HuEPO at their current dose, schedule and route of administration or to convert to darbepoetin alfa. Patients receiving r-HuEPO 10 times per month changed to receive darbepoetin alfa four times per month. The monthly dose of darbepoetin alfa for each patient was based on the monthly r-HuEPO dose at the time of randomization by dividing it by 200 (Aranesp®, *Product Information Sheet*). Patients receiving r-HuEPO five times per month changed to receive darbepoetin alfa twice per month.

Patients were maintained within a target range of −1.0 to +1.0 g/dL of their baseline Hb level and between Hb levels of 9.5 and 12.5 g/dL for up to 5.5 months, by adjusting the dose and frequency of r-HuEPO and darbepoetin alfa therapy if necessary. A period of 4 months was allowed after randomization in both study arms for dose titration and stabilization of Hb level. The evaluation period for Hb level was 1.5 months immediately following this dose-titration period.

After completion of the study, we retrospectively divided the darbepoetin alfa group into two subgroups according to dosage. The dosages, basic

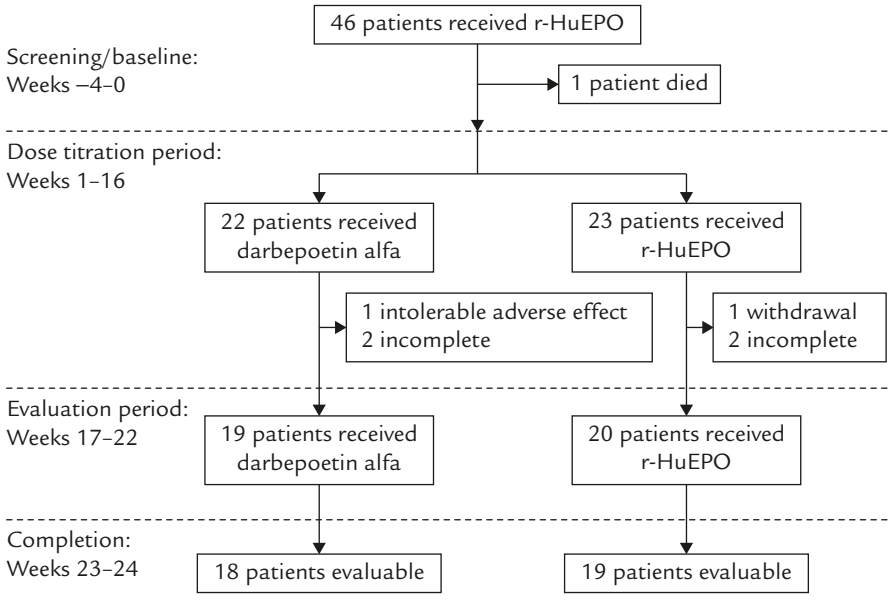

Figure 1. Patient characteristics and evaluability.

characteristics and biochemical changes of the two subgroups were compared.

Study endpoints

The primary endpoint of this study was to evaluate the mean change in Hb level between the screening/baseline and evaluation period. Secondary endpoints included the dose and frequency of darbepoetin alfa administration during the evaluation period, and the assessment of safety variables.

Statistical procedures

All statistical analyses were based on two-sided hypothesis tests with a significance level of $p < 0.05$. For continuous data, the mean and 95% confidence interval (CI) of change from baseline in each treatment group were calculated. The difference between the two treatment groups was analyzed by analysis of covariance (ANCOVA) with the baseline value as the covariate. The difference of the mean and 95% CI of change from baseline between the two treatment groups was also calculated. Discrete variables are presented as percentages and analyzed using Fisher's exact test. The number and percent of patients attaining a response and the corresponding 95% CIs are also presented. For the safety assessment, the incidence of adverse events was compared by Fisher's exact test.

Results

Patient characteristics

A total of 46 patients were randomized to the trial with 22 in the darbepoetin alfa arm and 24 in the r-HuEPO arm. Among the 46 randomized patients, a total of seven patients did not complete the study (3 in the darbepoetin alfa arm, 4 in the r-HuEPO arm). One patient in the r-HuEPO arm died during the screening period. Two other patients were excluded because of intact PTH > 800 pg/mL (in the darbepoetin alfa arm) or diastolic blood pressure > 100 mmHg (in the r-HuEPO arm). Thirty-seven patients (18 in the darbepoetin alfa arm, 19 in the r-HuEPO arm) were valuable for efficacy as demonstrated in Figure 1.

Demographic and baseline characteristics were similar between the two groups (Table 1). The r-HuEPO therapy was Recormon® and formulated in a pre-filled syringe. The overall mean age of patients was 48.7 years and the mean body weight was 58.8 kg. The most commonly reported primary causes of renal failure in the darbepoetin alfa arm were glomerulonephritis (GN) (6 patients, 27.3%) and other causes (5 patients, 22.7%), compared with GN (13 patients, 56.5%) and other causes (7 patients, 30.4%) in the r-HuEPO arm. No statistically significant difference was noted

Table 1. Patient demographics and characteristics at baseline

	Darbepoetin alfa ($n=22$)	r-HuEPO ($n=23$)	Total ($n=45$)
Sex			
Women	10 (45.5)	15 (65.2)	25 (55.6)
Men	12 (54.5)	8 (34.8)	20 (44.4)
Age (yr)	49.5 (9.75)	48 (11.15)	48.7 (10.4)
Weight (kg)	60.5 (11.56)	57.3 (9.46)	58.8 (10.51)
Intact PTH (pg/mL)	391.4 (309.99)	231.6 (156.62)	309.7 (254.08)
Primary cause of renal failure			
Diabetes	1 (4.5)	1 (4.3)	2 (4.4)
Hypertension	3 (13.6)	1 (4.3)	4 (8.9)
Glomerulonephritis	6 (27.3)	13 (56.5)	19 (42.2)
Polycystic kidney disease	2 (9.1)	1 (4.3)	3 (6.7)
Other urologic cause	1 (4.5)	0 (0)	1 (2.2)
Other	5 (22.7)	7 (30.4)	12 (26.7)
Unknown	4 (18.2)	0 (0)	4 (8.9)
Duration of PD (yr)	1.7 (1.93)	2.3 (2.49)	2.0 (2.23)
Type of dialysis			
CAPD	17 (77.3)	17 (73.9)	34 (75.6)
APD	5 (22.7)	6 (26.1)	11 (24.4)

r-HuEPO = recombinant human erythropoietin; PTH = parathyroid hormone; PD = peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; APD = automated peritoneal dialysis.

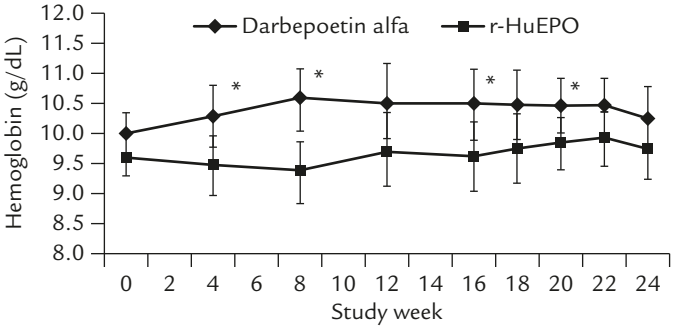

Figure 2. Mean hemoglobin concentrations over time. *Significant difference in hemoglobin levels between the darbepoetin alfa group and r-HuEPO group ($p<0.05$). Bars represent 95% confidence intervals.

between the two groups in any baseline characteristic except for intact PTH ($p=0.0376$), due to an intact PTH level of 1295 pg/mL for one patient. The mean ± standard deviation of intact PTH was 391.4 ± 309.99 pg/mL for the darbepoetin alfa arm, while it was 231.6 ± 156.62 pg/mL for the r-HuEPO arm.

Efficacy of darbepoetin alfa

The mean baseline Hb level was 9.98 g/dL for darbepoetin alfa treated patients and 9.66 g/dL for r-HuEPO treated patients. During the evaluation period, the mean Hb level was 10.46 g/dL (95% CI, 10.02–10.91) for the darbepoetin alfa group, and 9.78 g/dL (95% CI, 9.35–10.22) for the r-HuEPO group (Figure 2). Both treatments maintained the Hb concentration within our target level. Overall, the mean change in Hb from baseline to the evaluation period was 0.53 g/dL for the darbepoetin alfa group, compared with 0.08 g/dL for the r-HuEPO group. The difference in the mean change from baseline between the two groups was 0.45 g/dL (95% CI, −0.06–0.95), which was not statistically significant ($p=0.083$) (Table 2).

The total dose of study drug per month is presented in Table 3. For darbepoetin alfa treated patients, the mean monthly dose was 80.9 μg in the titration period and 93.0 μg in the evaluation

Table 2. Mean change in hemoglobin values from baseline to evaluation period

	Darbepoetin alfa ($n=18$)	r-HuEPO ($n=19$)	Treatment difference	Treatment effect p
Mean hemoglobin (g/dL)				
Baseline (SE)	9.98 (0.18)	9.66 (0.18)	0.32	0.2243
Average during evaluation (SE)	10.46 (0.22)	9.78 (0.21)	0.68	0.033
Change from baseline (95% CI)	0.53 (0.17, 0.89)	0.08 (–0.27, 0.43)	0.45 (–0.06, 0.95)	0.083

r-HuEPO = recombinant human erythropoietin; SE = standard error; CI = confidence interval.

Table 3. Monthly total dose of study drug

	Darbepoetin alfa (μg) ($n=18$)	r-HuEPO (unit) ($n=19$)	r-HuEPO/darbepoetin alfa (95% CI)
Titration period			
Mean (SD)	80.9 (43.61)	16,089.5 (4690.58)	198.92 (150.07, 278.31)
Evaluation period			
Mean (SD)	93.0 (61.80)	18,339.9 (5800.75)	197.13 (141.68, 300.41)

r-HuEPO = recombinant human erythropoietin; CI = confidence interval; SD = standard deviation.

Table 4. Frequency of administration

Evaluation period	Darbepoetin alfa ($n=18$)	r-HuEPO ($n=19$)	All groups ($n=37$)
1–4/mo (%)	17 (94.4)	0 (0)	17 (45.9)
5–8/mo (%)	1 (5.6)	6 (31.6)	7 (18.9)
9–12/mo (%)	0 (0)	9 (47.4)	9 (24.3)
13–16/mo (%)	0 (0)	4 (21.1)	4 (10.8)
Mean (SD)	3.9 (0.96)	9.2 (3.02)	6.59 (3.48)

r-HuEPO = recombinant human erythropoietin; SD = standard deviation.

period. The mean monthly doses for the r-HuEPO group were 16,089.5 units in the titration period and 18,339.9 units in the evaluation period. The mean monthly doses increased slightly from the titration period to the evaluation period for both treatment groups. In addition, the ratio of average monthly doses (r-HuEPO/darbepoetin alfa) was 198.92 (95% CI, 150.07–278.31) during the titration period and decreased to 197.13 (95% CI, 141.68–300.41) during the evaluation period.

The most often observed dosing frequency was less than four times a month for the darbepoetin alfa group (17 patients, 94.4%) and nine to 12 times a month for the r-HuEPO group (9 patients, 47.4%) (Table 4). Therefore, the dosing frequency of darbepoetin alfa (mean = 3.9) was less than that of r-HuEPO (mean = 9.2).

Safety

A total of 436 treatment-emergent adverse events were reported by 45 patients after randomization; 203 events were reported by 22 patients in the darbepoetin alfa group and 233 events were reported by 23 patients in the r-HuEPO group. The most commonly reported adverse events for both treatment groups were iron deficiency (31.32% in darbepoetin alfa group, 45.83% in r-HuEPO group) and edema (36.36% in darbepoetin alfa group, 37.50% in r-HuEPO group). Except for three adverse events reported by two patients in

Table 5. Darbepoetin alfa dose and patient body weight

	Dose ≥ 70 μg ($n = 9$)	Dose < 70 μg ($n = 9$)	p
Monthly dose at titration period, μg (SD)	113.4 (39.53)	48.4 (10.23)	0.0002
Monthly dose at evaluation period, μg (SD)	132.1 (65.32)	54.0 (20.56)	0.0035
Body weight, kg (SD)	66.4 (11.49)	52.5 (4.40)	0.0058
Average dose, μg/kg/wk	0.43	0.24	

SD = standard deviation.

Table 6. Summary of mean changes in serum ferritin in the darbepoetin alfa group

	Dose ≥ 70 μg ($n = 9$)	Dose < 70 μg ($n = 9$)	Treatment difference	p
Baseline, ng/mL (SE)	487.56 (133.1)	381.42 (133.1)	106.13	0.5807
Week 12, ng/mL (SE)	287.8 (93.3)	380.44 (93.3)	−92.64	0.4927
Change from baseline (SE)	−181.3 (35.28)	−19.4 (35.28)	−161.9	0.0056
Week 24, ng/mL (SE)	347.44 (118.1)	355.24 (118.1)	−7.80	0.9633
Change from baseline (SE)	−125.8 (69.43)	−40.45 (69.43)	−85.39	0.4004

SE = standard error.

the darbepoetin alfa arm, no other adverse events were considered to be study-drug related. In the darbepoetin alfa arm, two patients experienced pruritus and one patient experienced myalgia. No statistically significant difference in the incidence of adverse events was found between the two treatment groups.

A total of two serious adverse events were reported by one patient in the r-HuEPO group and the patient subsequently died. None of these two serious adverse events were considered to be study-drug related. One patient in the darbepoetin alfa arm discontinued the study due to an adverse drug reaction (general soreness).

Systolic and diastolic blood pressures were stable throughout the study for both treatment groups. In addition, the proportions of patients with at least one dose of antihypertensive medication decreased from the titration period to the evaluation period. Serum ferritin levels showed a decreasing trend and transferrin saturation levels stabilized for both treatment groups in this trial.

Dose and patient weight

We divided the darbepoetin alfa group into low-dose (< 70 μg/month) and high-dose (≥ 70 μg/month) subgroups. Each subgroup included nine patients. The high-dose group required 132.1 μg of darbepoetin alfa per month, while the low-dose group needed only 54 μg. The body weight of patients in the high-dose group was greater than that in the low-dose group (66.4 ± 11.49 kg *vs.* 52.5 ± 4.4 kg, $p < 0.01$) (Table 5). The dosage of darbepoetin alfa was not related to sex, age, peritoneal equilibrium test, Kt/V, baseline Hb, serum calcium, phosphate or intact PTH levels.

Nearly 40% of patients received at least one intravenous iron supplement during the titration period. Serum ferritin level in the high-dose group at week 12 was less than that at baseline (287.8 ± 93.3 ng/mL *vs.* 487.56 ± 133.1 ng/mL, $p < 0.05$) (Table 6).

Discussion

The results of this open-label, single-center, randomized, parallel trial demonstrate that darbepoetin alfa is as effective as r-HuEPO for treating renal anemia in patients on PD, but with a reduced dosing frequency. For both treatment groups, the mean monthly dosage increased slightly from the titration period to the evaluation period. Changing from r-HuEPO to darbepoetin alfa was not

associated with an increased risk of unstable Hb levels.

Clinical studies have shown that darbepoetin alfa safely and effectively corrects anemia in patients on PD using once weekly,[12] once every 2 weeks[13,14] or once monthly[15] dosing schedules. These studies have also shown that darbepoetin alfa may be administered both subcutaneously and intravenously with similar dosing requirements. We usually use the protein mass substitution formula to provide patients with a therapeutic starting dose of darbepoetin alfa. The original conversion rate was extended from biochemical data where 200 units of epoetin alfa have the peptide mass of 1 μg of darbepoetin alfa.[13] The usual dosage of darbepoetin alfa is 25 μg per week. Analysis of data from studies performed in the United States, Europe and Australia would suggest that at higher initial epoetin alfa dosages, a greater than 200 units to 1 μg conversion may be applicable. In addition, at longer dosing intervals, less darbepoetin alfa was required to maintain Hb levels relative to r-HuEPO.[16,17] The dose conversion ratio between epoetin alfa and darbepoetin alfa for Canada is 169:1.[18] Geographic and ethnic differences may play an important role. In our study, the ratio of average monthly doses was 198.92:1 during the titration period and decreased to 197.13:1 during the evaluation period. This may be an index to predict dose conversion for the Asian population.

The dose of darbepoetin alfa was associated with patients' body weight, but not baseline Hb levels. The largest dose of darbepoetin alfa provided by the health care insurance in Taiwan is 100 μg per month, which is less than the requirement of our high-dose group. Iron deficiency can inhibit the response to darbepoetin alfa or r-HuEPO. The National Kidney Foundation–Dialysis Outcomes Quality Initiative (NKF–DOQI) guidelines advocate consistent detection and management of iron deficiency, and recommend a ferritin level > 100 ng/mL and transferrin saturation > 20%.[19] Although the serum ferritin level in the high-dose group was maintained above 100 ng/mL during the titration and evaluation periods, there was a statistically significant decline in serum ferritin at week 12. Therefore, intravenous or oral iron should be supplied if darbepoetin responsiveness is poor, unless serum ferritin is more than 500 ng/mL. When patients are switched from r-HuEPO to darbepoetin alfa, dose adjustments should be made as needed, based on the individual's Hb response, body weight and iron status.

The safety profile of darbepoetin alfa in this study was similar to that of r-HuEPO with respect to type and frequency of adverse events. The majority of adverse events were related to the underlying disease and its treatment, and only a small number were associated with the study drug. We did not find any patient with pure red cell aplasia, as recently reported,[20] during our trial. Long-term observational studies should be conducted to establish the safety and efficacy of darbepoetin.

Several limitations in our study should be noted. Firstly, our PD patients had a relatively low Hb level at the screening/baseline period because of restraints in health care insurance reimbursement. According to the latest NKF–DOQI guidelines,[19] a target Hb level of 11–12 g/dL is recommended. This indicated that our PD patients had an inadequate dose frequency profile of r-HuEPO, which would probably lead to under- or over-estimation of dose-conversion ratios. Secondly, the observational period for safety of darbepoetin therapy was only 1.5 months. We might need to evaluate the efficacy and adverse effects of darbepoetin long term.

To summarize, the efficacy profiles show that both darbepoetin alfa and r-HuEPO safely maintained Hb concentrations within the target range during the study period in CRF patients undergoing PD. Compared with the r-HuEPO group, patients in the darbepoetin alfa group had similar Hb levels during the evaluation period and a comparative incidence of adverse events with less frequent dosing. Conversion from r-HuEPO to darbepoetin alfa must be based on clinical patient data rather than on a fixed dose conversion factor derived from a protein mass relationship.[16] The dose of darbepoetin alfa was better adjusted

by body weight. It is important to give adequate iron when darbepoetin alfa is administered.

Acknowledgments

The study was supported by Kirin Pharmaceuticals Co.

References

1. Caro J, Brown S, Miller O, et al. Erythropoietin levels in uremic nephric and anephric patients. *J Lab Clin Med* 1979;93:449–58.
2. Eschbach JW, Kelly MR, Haley NR, et al. Treatment of the anemia of progressive renal failure with recombinant human erythropoietin. *N Engl J Med* 1989;321:158–63.
3. Eschbach JW, Egrie JC, Downing MR, et al. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin: results of a combined phase I and II clinical trial. *N Engl J Med* 1987;316:73–8.
4. Cameron JS. European best practice guidelines for the management of anaemia in patients with chronic renal failure. *Nephrol Dial Transplant* 1999;14(Suppl 2):61–5.
5. Egrie JC, Browne JK. Development and characterization of novel erythropoiesis stimulating protein (NESP). *Nephrol Dial Transplant* 2001;16(Suppl 3):3–13.
6. Macdougal IC, Gray SJ, Elston O. Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients. *J Am Soc Nephrol* 1999; 10:2392–5.
7. Locatelli F, Olivares J, Walker R, et al. Novel erythropoiesis-stimulating protein for treatment of anemia in chronic renal insufficiency. *Kidney Int* 2001;60:741–7.
8. Toto RD, Pichette V, Navarro J, et al. Darbepoetin alfa effectively treats anemia in patients with chronic kidney disease with *de novo* every-other-week administration. *Am J Nephrol* 2004;24:453–60.
9. Macdougal IC. Novel erythropoiesis stimulating protein. *Semin Nephrol* 2000;20:375–81.
10. Nissenson AR, Swan SK, Lindberg JS, et al. Randomized, controlled trial of darbepoetin alfa for the treatment of anemia in hemodialysis patients. *Am J Kidney Dis* 2002; 40:110–8.
11. Theodoridis M, Passadakis P, Kriki P, et al. Efficient monthly subcutaneous administration of darbepoetin in stable CAPD patients. *Perit Dial Int* 2005;25:564–9.
12. Macdougall IC, Matcham J, Gray SJ. Correction of anaemia with darbepoetin alfa in patients with chronic kidney disease receiving dialysis. *Nephrol Dial Transplant* 2003;18: 576–81.
13. Vanrenterghem Y, Barany P, Mann JF, et al. Randomized trial of darbepoetin alfa for treatment of renal anemia at a reduced dose frequency compared with rHuEPO in dialysis patients. *Kidney Int* 2002;62:2167–75.
14. Mahajan S, Boulton H, Gokal R. A trial of subcutaneous administration of darbepoetin alfa once every other week for the treatment of anemia in peritoneal dialysis patients. *J Nephrol* 2004;17:687–92.
15. Jadoul M, Vanrenterghem Y, Foret M, et al. Darbepoetin alfa administered once monthly maintains haemoglobin levels in stable dialysis patients. *Nephrol Dial Transplant* 2004;19:898–903.
16. Scott S. Dose conversion from recombinant human erythropoietin to darbepoetin alfa: recommendations from clinical studies. *Pharmacotherapy* 2002;22:S160–5.
17. Roger SD, Cooper B. What is the practical conversion dose when changing from epoetin alfa to darbepoetin outside of clinical trials? *Nephrology* 2004;9:223–8.
18. Cremieux PY, Van Audenrode M, Lefebvre P. The relative dosing of epoetin alfa and darbepoetin alfa in chronic kidney disease. *Curr Med Res Opin* 2006;22:2329–36.
19. National Kidney Foundation. K/DOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis* 2006;47: S58–70.
20. Jacob A, Sandhu K, Nicholas J, et al. Antibody-mediated pure red cell aplasia in a dialysis patient receiving darbepoetin alfa as the sole erythropoietic agent. *Nephrol Dial Transplant* 2006;21:2963–5.