Kidney International, Vol. 62 (2002), pp. 2167–2175

Randomized trial of darbepoetin alfa for treatment of renal anemia at a reduced dose frequency compared with rHuEPO in dialysis patients

YVES VANRENTERGHEM, PETER BÁRÁNY, JOHANNES F.E. MANN, PETER G. KERR, JANET WILSON, NIGEL F. BAKER, and STEPHEN J. GRAY, on behalf of the EUROPEAN/AUSTRALIAN NESP 970200 STUDY GROUP[1]

Department of Nephrology, University Hospital Leuven, Leuven, Belgium; Division of Renal Medicine, Huddinge University Hospital, Stockholm, Sweden; Schwabing General Hospital, LMU, Munich, Germany; Department of Nephrology, Monash Medical Centre, Melbourne, Australia; and Amgen Limited, Cambridge, England, United Kingdom

Randomized trial of darbepoetin alfa for treatment of renal anemia at a reduced dose frequency compared with rHuEPO in dialysis patients.

Background. Darbepoetin alfa is a glycoprotein with a threefold longer terminal half-life than recombinant human erythropoietin (rHuEPO). We aimed to determine whether darbepoetin alfa is as effective and well tolerated as rHuEPO for treating renal anemia in dialysis patients when administered at a reduced dose frequency.

Methods. A total of 522 European and Australian hemodialysis and peritoneal dialysis patients receiving stable rHuEPO therapy by either the intravenous (IV) or subcutaneous (SC) route were randomized, open-label in a 1:2 ratio to continue rHuEPO or to receive an equivalent dose of darbepoetin alfa at a reduced dose frequency. Patients receiving rHuEPO once weekly changed to once every other week darbepoetin alfa, and those receiving rHuEPO two or three times weekly changed to once-weekly darbepoetin alfa. The doses of rHuEPO and darbepoetin alfa were titrated to maintain hemoglobin close to the patient's baseline level for up to 52 weeks. The primary endpoint was the change in hemoglobin between baseline and the evaluation period at weeks 25 to 32 of treatment.

Results. The mean change in hemoglobin from baseline to the evaluation period was similar in the darbepoetin alfa (−0.03 g/dL; SE 0.11) and rHuEPO (−0.06 g/dL; SE 0.13) groups, and the difference between the two treatments was 0.03 g/dL (95% CI −0.16, 0.21). This was not a statistically significant or clinically relevant difference, despite the reduced frequency of darbepoetin alfa administration. At the end of the evaluation period, ≥95% of patients had their hemoglobin successfully maintained on their assigned dose frequency for darbepoetin alfa (once weekly and once every other week) and rHuEPO (once, twice and three times weekly). The safety profiles of darbepoetin alfa and rHuEPO were similar, and no antibodies to either treatment were detected.

Conclusions. Darbepoetin alfa maintains hemoglobin as effectively as rHuEPO, but with a reduced dose frequency.

Anemia is a frequent complication of chronic renal failure (CRF), caused predominantly by inadequate production of erythropoietin from the failing kidneys and inappropriately low circulating levels of erythropoietin [1]. Replacement therapy with recombinant human erythropoietin (rHuEPO) has been used for the treatment of renal and other anemias since its introduction into clinical practice over 10 years ago [2–5]. During this time, rHuEPO has become widely accepted as an effective and well-tolerated treatment, and its clinical benefits to patients with CRF are well documented [6]. rHuEPO is administered by subcutaneous (SC) or intravenous (IV) injection and, because of its relatively short circulating half-life, is recommended to be given two or three times per week [4, 6–8].

Erythropoietin is a glycoprotein hormone comprised of approximately 60% protein and 40% carbohydrate. The sialic acid-containing carbohydrate has been shown to determine the serum half-life and in vivo activity of erythropoietin [9]. Darbepoetin alfa (novel erythropoiesis stimulating protein; NESP) was designed by introducing five amino acid changes into the primary sequence of rHuEPO to create two additional consensus N-linked carbohydrate addition sites. Darbepoetin alfa has five N-linked carbohydrate chains, whereas rHuEPO has only three [9]. Because of its increased sialic acid-containing carbohydrate content, darbepoetin alfa has a threefold

[1] A complete list of study group members is in the **Acknowledgments** section.

Key words: darbepoetin alfa, novel erythropoiesis stimulating protein (NESP), chronic renal failure, hemodialysis, peritoneal dialysis, anemia, recombinant human erythropoietin.

Received for publication September 19, 2001
and in revised form June 10, 2002
Accepted for publication July 8, 2002

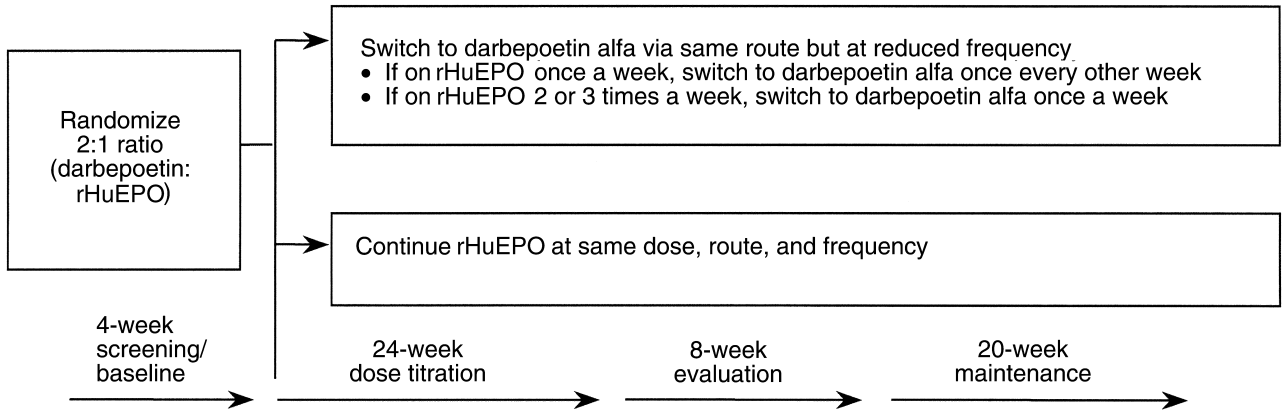

Fig. 1. Study design.

longer terminal half-life in animal models [9] and in humans [10] when compared with rHuEPO. This allows once weekly or once every other week dosing to treat anemia in CRF patients on dialysis [11]. We aimed to determine whether darbepoetin alfa is as effective and well tolerated as rHuEPO for treating renal anemia in dialysis patients, but at a reduced dose frequency.

METHODS

Patients

Patients were recruited from European and Australian dialysis units, and were required to be ≥18 years of age with CRF, clinically stable and on hemodialysis (HD) or peritoneal dialysis (PD) for at least six months. They also had to be on stable rHuEPO (alfa or beta) therapy given one, two, or three times weekly by the IV or SC route for at least three months, and to have a mean baseline hemoglobin of 9.5 to 12.5 g/dL. To ensure adequate iron stores for supporting erythropoiesis, serum ferritin had to be >100 μg/L [6]. Patients were excluded from the study if they had hematological, inflammatory, infectious or other conditions that might interfere with the erythropoietic response, or had red blood cell (RBC) transfusions within one month before enrollment.

The study was conducted in accordance with the Declaration of Helsinki and was approved by each institution's independent Research Ethics Committee. All patients gave written informed consent before participation.

Study design

This was a multicenter, randomized, open-label comparative study designed to determine whether darbepoetin alfa is as effective and well tolerated as rHuEPO when administered IV or SC for treatment of anemia in dialysis patients.

After an initial four-week screening/baseline period, patients receiving rHuEPO therapy were randomized in a 1:2 ratio to continue rHuEPO at their current dose, schedule and route of administration, or to change to darbepoetin alfa using the same route but at a reduced dose frequency (Fig. 1). The randomization was conducted via a central computerized system, with unequal block sizes and stratification by center and frequency of rHuEPO dosing at study entry. Patients receiving rHuEPO once weekly changed to darbepoetin alfa once every other week, and patients receiving rHuEPO two or three times weekly changed to darbepoetin alfa once weekly. The initial dose of darbepoetin alfa for all patients was based on their rHuEPO dose at the time of randomization, using a formula equating the protein mass of the two molecules (200 IU rHuEPO = 1 μg darbepoetin alfa). A period of 24 weeks (weeks 1 to 24) after the first dose of study drug was then used for dose-titration and stabilization of hemoglobin. This was followed by an eight-week evaluation period (weeks 25 to 32) for determining the primary efficacy endpoint, and a further 20 weeks (weeks 33 to 52) for additional safety information.

In each treatment group, the dose of study drug was adjusted to maintain individual patients' hemoglobin within a target range of −1.0 to +1.5 g/dL of their baseline hemoglobin and between 9 to 13 g/dL throughout the 52-week study period. If a patient's hemoglobin fell below the target range on two consecutive weekly assessments, the dose of study drug was increased by 25% of the starting dose to a maximum of +100%. If the hemoglobin was still out of range, then the dose frequency was increased. If a patient's hemoglobin increased above the target range on two consecutive weekly assessments, the dose of study drug was decreased by 25% of the starting dose to a maximum of −75%. If the hemoglobin was still out of range, then the dose frequency was decreased. Dose frequency was adjusted incrementally as follows: 3 times weekly ⇔ 2 times weekly ⇔ once weekly ⇔ once every other week.

Study medications

Darbepoetin alfa was supplied by Amgen Inc. (Thousand Oaks, CA, USA). rHuEPO (alfa or beta) was obtained from commercial sources and provided by the pharmacy at each study center. To ensure adequate support of the erythropoietic response to study drug, IV iron therapy was required to be administered to patients with serum ferritin values <100 μg/L. The IV iron dosing regimen used for patients with serum ferritin values <100 μg/L or ≥ 100 μg/L was determined by the individual center's treatment policy.

Statistical analysis

The primary efficacy analysis compared the mean change in hemoglobin between the screening/baseline and evaluation periods for patients receiving darbepoetin alfa and rHuEPO. To demonstrate non-inferiority, the lower limit of the two-sided 95% confidence interval (CI) for the difference in mean change in hemoglobin on darbepoetin alfa and rHuEPO had to be above -0.5 g/dL. This was prospectively determined by the Study Group to be the greatest clinically acceptable difference. The 95% CI was calculated with and without adjustment for covariates which might influence hemoglobin response (study center, baseline rHuEPO dose, route and frequency, dialysis modality, baseline hemoglobin). The sample size of the study (495 patients) was selected using a power of 90% (assessed at zero difference) and an allocation ratio of 2:1 for darbepoetin alfa:rHuEPO, assuming a standard deviation for change in hemoglobin of 1.44 and a drop-out rate of 30% over 12 months. Using these criteria, the sample size was calculated to be 330 darbepoetin alfa patients and 165 rHuEPO patients [12].

A per-protocol (pP) analysis set was chosen for the main analysis of the efficacy endpoints. A modified intent-to-treat (mITT) analysis set was chosen for secondary analysis, using several methods for imputing missing values. Per-protocol analysis compares patients according to the treatment actually received and includes only those patients who satisfy the protocol-specified criteria (Fig. 2). This type of analysis is expected to increase any treatment difference, as it tends to remove uninformative data and is generally more conservative for non-inferiority studies [12]. The mITT analysis set and the safety analysis set included all randomized patients who received the study drug. However, for the safety analysis set, rHuEPO patients who inadvertently received at least one dose of darbepoetin alfa were included in the darbepoetin alfa group. Adverse event data are presented as the proportion of patients experiencing an event one or more times (subject incidence), and comparison between treatment groups was performed by calculating the odds ratio (95% CI) for these proportions.

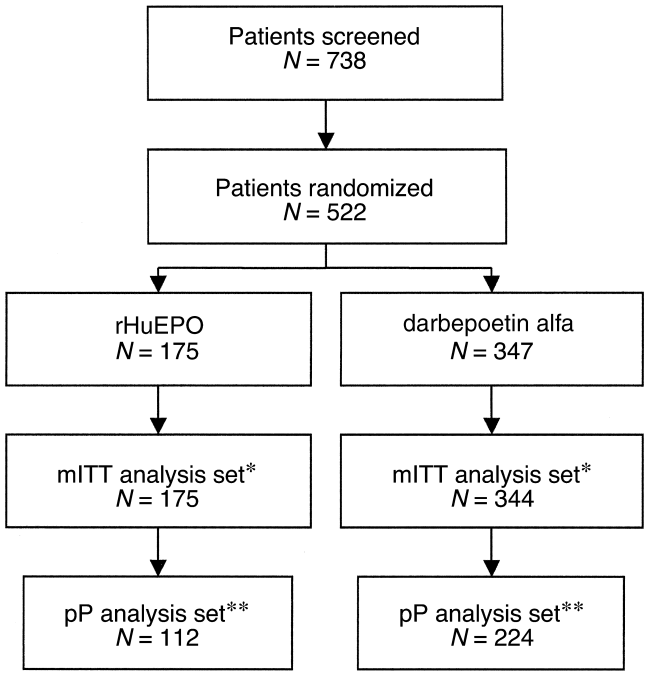

Fig. 2. Patients included in the analysis. * Includes all randomized patients who received at least one dose of the study drug. ** Includes only patients who completed and had 6/8 hemoglobin assessments during the evaluation period; received the allocated study drug according to protocol; had no change to dialysis modality or route of study drug administration; and received no red blood cell transfusions during weeks 15–32 of study.

Within-subject variance in hemoglobin was calculated from the residuals of the linear regression model (that is, mean squared error). All statistical analyses were performed with the SAS software package (version 6.12; SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

A total of 522 patients were randomized into the study, of whom 347 were allocated to darbepoetin alfa and 175 remained on rHuEPO (Fig. 2). Patients were recruited from 27 study sites in Europe and 4 in Australia between November 1997 and July 1998. A total of 519 patients received study drug and were included in the mITT analysis set (344 darbepoetin alfa, 175 rHuEPO) and the safety analysis set (346 darbepoetin alfa, 173 rHuEPO). Three hundred and thirty-six patients were included in the pP analysis set (224 darbepoetin alfa, 112 rHuEPO). The proportion of patients in the pP analysis set was the same for each treatment group (65% darbepoetin alfa, 64% rHuEPO). Reasons for exclusion from the pP set were well balanced between treatment groups, suggesting that there was no selection bias.

Overall, 55% of the patients were male and 92% were white. The mean age was 60.3 years (range 18 to 88) and

Table 1. Patient demographics

	Darbepoetin alfa (N = 347)	rHuEPO (N = 175)
Sex		
Male	188 (54%)	100 (57%)
Female	159 (46%)	75 (43%)
Race		
White	316 (91%)	165 (94%)
Asian	18 (5%)	5 (3%)
Black	11 (3%)	5 (3%)
Other	2 (1%)	0 (0%)
Age[a] *years*	60.1 (18–88)	60.9 (22–87)
Weight[a] *kg*	68.4 (31.5–123.0)	69.0 (38.0–184.0)

[a] Mean (range)

Table 2. Patient baseline characteristics

	Darbepoetin alfa (N = 347)	rHuEPO (N = 175)
Cause of renal failure		
Diabetes	58 (17%)	18 (10%)
Hypertension	27 (8%)	13 (7%)
Glomerulonephritis	66 (19%)	36 (21%)
Polycystic kidney disease	30 (9%)	14 (8%)
Other/unknown[a]	166 (48%)	94 (54%)
Dialysis modality		
HD	318 (92%)	163 (93%)
PD	29 (8%)	12 (7%)
Time since first dialysis[a] *months*	32.0 (18.5–55.5)	36.7 (19.3–63.6)
rHuEPO dose[a] *IU/week*	6000 (4000–9000)	6000 (4000–9000)
Route of rHuEPO administration		
IV	134 (39%)	73 (42%)
SC	213 (61%)	102 (58%)
Frequency of rHuEPO		
Once per week	66 (19%)	35 (20%)
Twice per week	118 (34%)	59 (34%)
Three times per week	163 (47%)	81 (46%)
Baseline hemoglobin level[b] *g/dL*	11.0 (9.5–12.5)	11.0 (9.5–12.5)
Serum ferritin[a] *μg/L*	305.8 (199.3–517.4)	288.7 (184.6–487.9)

[a] Unknown category includes 'suspected' unconfirmed causes
[b] Median (quartiles)
[c] Mean (range)

the mean weight was 69 kg (range 32 to 184). The most common single causes of CRF were glomerulonephritis and diabetes mellitus. The median time since initiation of dialysis was 34 months (quartiles 18.8 to 59.6), with 92% of patients receiving hemodialysis (HD) and 8% peritoneal dialysis (PD). The median weekly rHuEPO dose at baseline was 6000 IU/week (quartiles 4000 to 6000) and 82% of patients were receiving rHuEPO alpha. rHuEPO injection frequencies were once (19%), twice (34%) and thrice weekly (47%), and mostly by the SC route (60%). The mean baseline hemoglobin was 11.0 g/dL (range 9.5 to 12.5). Demographic and baseline characteristics of the two treatment groups were well balanced (Tables 1 and 2), and were representative of the CRF population from which they were derived. Transferrin saturation, C-reactive protein and dialysis membrane data were not collected in the study. Characteristics of the pP, mITT, and safety analysis sets were similar and also were well balanced between treatment groups.

The overall exposure to study drug in weeks (mean; range) was similar in the darbepoetin alfa (44; 0 to 52) and rHuEPO (46; 2 to 52) treatment groups. One hundred and thirty-three patients (25%) did not complete the 52 weeks of study. The most common reasons were death, kidney transplant and withdrawal requested. The rates of discontinuation were similar between the treatment groups during the dose-titration (12% darbepoetin alfa, 10% rHuEPO) and evaluation (4% darbepoetin alfa, 3% rHuEPO) periods. However, in the maintenance period the difference was 6% (12% darbepoetin alfa, 6% rHuEPO), and this is discussed further in the analysis of safety.

Efficacy evaluation

Primary analysis. The mean weekly hemoglobin values for the darbepoetin alfa and rHuEPO groups were very similar throughout the study (Fig. 3). The mean change in hemoglobin from baseline to the evaluation period was similar in the darbepoetin alfa (0.05 g/dL; SD 0.80) and rHuEPO (0.00 g/dL; SD 0.87) groups before the adjustment for covariates. The difference in the mean change in hemoglobin between these two groups was 0.05 g/dL (95% CI −0.14, 0.24). After adjusting for covariates, the mean change in hemoglobin from baseline to the evaluation period also was similar in the darbepoetin alfa (−0.03 g/dL; SE = 0.11) and rHuEPO (−0.06 g/dL; SE = 0.13) groups. The difference in the mean change in hemoglobin between these two groups was 0.03 g/dL (95% CI −0.16, 0.21). The lower limit of the two-sided 95% CI was therefore above the pre-specified non-inferiority margin of –0.5 g/dL whether adjusted (−0.16) or unadjusted (−0.14) for covariates, demonstrating that darbepoetin alfa was as effective as rHuEPO in maintaining the mean hemoglobin in this group of patients. The robustness of the pP analysis was confirmed by analyzing the primary endpoint using the mITT analysis set. The lower limit of the 95% CI was similar to the pP analysis set whether adjusted (−0.14) or unadjusted (−0.13) for covariates, and was well above the pre-specified non-inferiority margin of –0.5 g/dL.

Since the study enrolled dialysis patients receiving differing treatment practices, the primary efficacy endpoint was analyzed by sub-groups. The most important of these were route of study drug administration (SC/IV) and dialysis modality (HD/PD). Since PD patients receive rHuEPO (or darbepoetin alfa) solely by the SC route, three sub-groups were evaluated: the IV and SC routes in HD patients and the SC route in PD patients. The lower limit of the 95% confidence interval was above

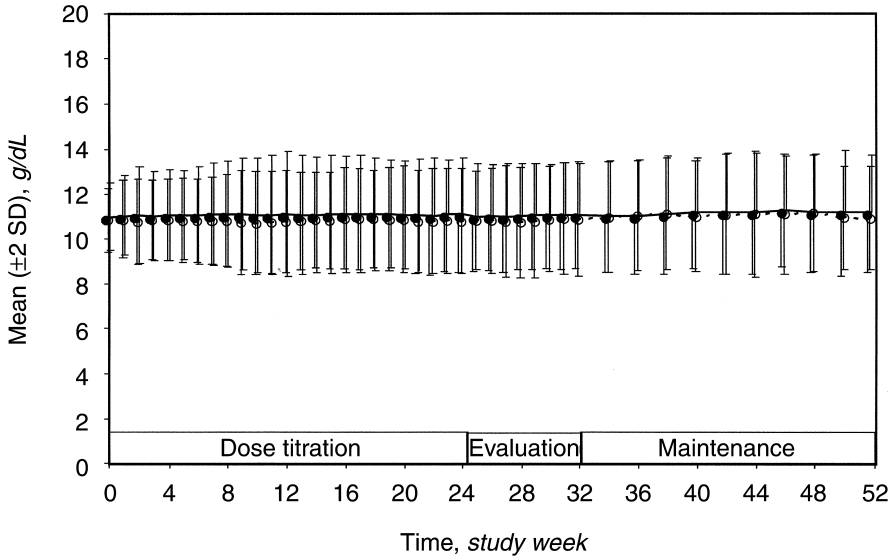

Fig. 3. Mean (± 2 SD) hemoglobin over time. Symbols are: (●) darbepoetin alfa ($N = 347$); (○) recombinant human erythropoietin (rHuEPO; $N = 175$). Whiskers denote standard deviation.

the protocol specified non-inferiority margin in each of these sub-groups (−0.05, −0.42, −0.31, respectively), demonstrating that darbepoetin alfa is as effective as rHuEPO. Additionally, when the primary endpoint was analyzed for other sub-groups (study center, baseline rHuEPO dose and frequency, baseline hemoglobin, age, sex and race), the results also were consistent with the main analyses.

Secondary analyses. A number of endpoints explored whether less frequent dosing with darbepoetin alfa could result in more unstable or more variable hemoglobin concentrations. These were: the proportion of patients with "unstable hemoglobin" (defined as hemoglobin values necessitating a dose change), within-subject variance of hemoglobin, and the proportion of patients with hemoglobin in the target (–1.0 to +1.5 g/dL of baseline and between 9 to 13 g/dL) and therapeutic (9 to 13 g/dL) ranges during the evaluation period. The ratios (95% CI) between the darbepoetin alfa and rHuEPO groups for each of these endpoints were calculated as 0.794 (0.476, 1.325), 1.030 (0.855, 1.242), 1.036 (0993, 1.081), and 1.018 (0.929, 1.116), respectively. In all cases the 95% CI included 1.0, indicating no significant difference between the two treatment groups. These results demonstrate that darbepoetin alfa does not increase hemoglobin variability compared with rHuEPO, despite the reduced frequency of dosing.

Dosing during the evaluation period was similar to baseline and was also similar between treatment groups. The mean (95% CI) treatment difference, when the dosing units of rHuEPO were converted to the dosing units of darbepoetin alfa, was −0.40 μg/week (−5.9, 5.2). Additionally, the proportion of patients requiring dose changes

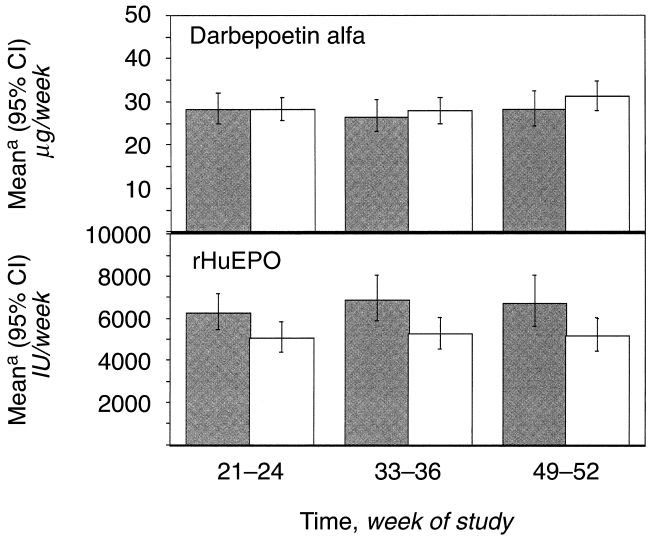

Fig. 4. Mean (95% CI) dose of study drug by route of administration. Symbols are: (■) IV dosing; (□) SC dosing.

was similar in the two treatment groups during each week of the study. Dosing was further evaluated by route of administration in patients who received darbepoetin alfa and rHuEPO during weeks 21 to 24, 33 to 36 and 49 to 52 of the study, when patients had been titrated to a stable hemoglobin level (Fig. 4). The ratio (95% CI) of SC to IV doses during these three periods of the study was 1.00 (0.84, 1.18), 1.05 (0.87, 1.28) and 1.11 (0.88, 1.39) for darbepoetin alfa. These ratios were not significantly different from 1.0, suggesting similar dose requirements for the SC and IV route. In contrast, the ratio (95% CI) of SC to IV doses was 0.81 (0.65, 1.02), 0.76 (0.61, 0.96) and 0.77 (0.60, 0.99) for rHuEPO, and the second and third of these ratios were significantly different from 1.0

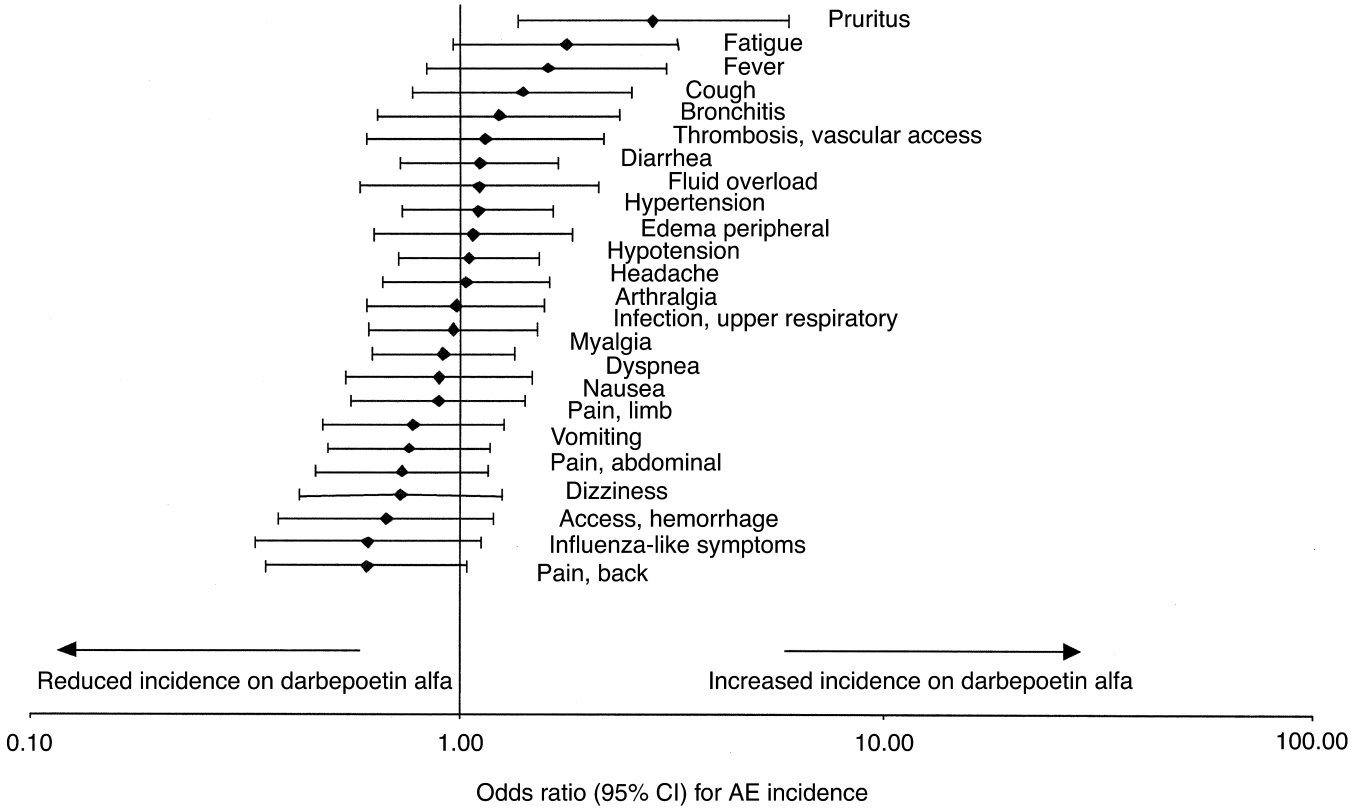

Fig. 5. Odds ratio (95% CI) between darbepoetin alfa and rHuEPO for adverse events occurring with a frequency of ≥10% in either treatment group.

($P < 0.05$). The average ratio for the three periods was 0.78, suggesting that the rHuEPO dose requirements were 22% lower by the SC route compared with the IV route.

The frequency of study drug administration during the evaluation period was evaluated for each treatment group. Ninety-seven percent (178/183) of patients whose baseline rHuEPO dose frequency was two or three times weekly were successfully maintained on darbepoetin alfa given once weekly or less. Ninety-five percent (39/41) of patients whose baseline rHuEPO dose frequency was once-weekly were successfully maintained on darbepoetin alfa given once every other week. Ninety-five percent (20/21), 98% (39/40) and 98% (50/51) of the rHuEPO treated patients were successfully maintained on the same dose frequency as at baseline (1, 2 or 3 times weekly, respectively). Dosing frequency during evaluation also was analyzed by sub-group, and the results of these analyses were consistent with the main analysis. Weekly serum trough concentrations of darbepoetin alfa and rHuEPO were determined by enzyme-linked immunosorbent assay (ELISA) over the 52 weeks of the study. There was minimal accumulation of either drug when analyzed overall and within patient sub-groups. At weeks 12, 24, 36 and 52, the mean serum concentration was 0.43, 0.48, 0.54 and 0.49 ng/mL for darbepoetin alfa and 17.9, 19.9, 18.5 and 19.8 mU/mL for rHuEPO.

Safety

A similar proportion of patients on darbepoetin alfa (96%) and rHuEPO (95%) experienced at least one adverse event. The odds ratio (95% CI) between darbepoetin alfa and rHuEPO for those events occurring with a frequency of ≥10% in either treatment group are presented in Figure 5. There was no difference in adverse event reporting between darbepoetin alfa and rHuEPO, with the exception of pruritus. The three most commonly reported events were hypotension (39% darbepoetin alfa, 38% rHuEPO), myalgia (34% darbepoetin alfa, 36% rHuEPO) and hypertension (30% darbepoetin alfa, 28% rHuEPO), and the largest between group differences were for pruritus (14% darbepoetin alfa, 5% rHuEPO) and back pain (10% darbepoetin alfa, 16% rHuEPO). Most of these events were attributed to concurrent medical conditions and were consistent with events expected in this patient population.

Six adverse events were prospectively defined to be of particular interest because of previous concerns with increasing hemoglobin in dialysis patients. Analysis of these six events showed no significant difference ($P \geq 0.682$) in incidence between treatment groups: hypertension (30% darbepoetin alfa, 28% rHuEPO), cerebrovascular disorder (2% darbepoetin alfa, 1% rHuEPO),

myocardial infarction (1% darbepoetin alfa, 2% rHuEPO), convulsions (2% darbepoetin alfa, 2% rHuEPO), vascular access thrombosis (10% darbepoetin alfa, 9% rHuEPO), and transient ischemic attack (0% darbepoetin alfa, 1% rHuEPO).

Adverse events that were commonly (>1%, ≤10%) reported by the investigators to be at least possibly related to study drug were hypertension, injection site pain, headache, vascular access thrombosis, anemia and fatigue. Injection site pain following subcutaneous administration of darbepoetin alfa was reported more frequently than with rHuEPO. This discomfort was generally mild and transient in nature and occurred predominantly after the first injection. All other treatment related adverse events were reported at a level of ≤1% in both treatment groups, including pruritus (1% darbepoetin alfa, 0% rHuEPO). The majority were mild to moderate in severity and were consistent with the comorbidities expected in this patient population.

There were 52 deaths during the study and within 28 days after the last dose of study drug or last assessment, whichever was latest. A higher proportion of patients died in the darbepoetin alfa treatment group (41/346; 12%) compared with the rHuEPO group (11/173; 6%), although this difference was not statistically significant ($P = 0.062$). Deaths resulted from co-morbid conditions and no apparent relationship to study drug could be determined. All deaths were reported by the study investigators as unrelated to study drug. As the majority of patients who received darbepoetin alfa carried on treatment in a long-term protocol after this study, a further survival follow-up was performed on all randomized patients who received study drug (darbepoetin alfa and rHuEPO). After a mean follow-up of two years, the mortality rate was similar in both treatment groups (25% darbepoetin alfa vs. 21% rHuEPO). When the mortality rates for the total follow-up period were annualized, the rate was 13% for darbepoetin alfa and 11% for rHuEPO. There was no statistically significant difference between the survival in the two treatment groups ($P = 0.212$).

Serum ferritin concentrations were similar in the darbepoetin alfa and rHuEPO treatment groups throughout the study. At weeks 12, 24, 36 and 52, mean serum ferritin was 394, 382, 353 and 391 μg/L for darbepoetin alfa and 367, 385, 362 and 375 μg/L for rHuEPO. Most patients had serum ferritin concentration >100 μg/L at baseline (99%) and at the end of study (95%). The proportion of patients receiving intravenous iron supplementation was the same in both treatment groups (87%), and the mean weekly patient-dose of intravenous iron was similar in the darbepoetin alfa (136 mg) and rHuEPO (145 mg) treatment groups.

Clinical laboratory evaluation of hematology, biochemistry and coagulation throughout the study showed no unexpected changes that could be attributable to the study drug. There was no difference in the proportion of patients requiring transfusions in the darbepoetin alfa group (4%) compared with the rHuEPO group (5%). Vital signs were monitored throughout the study, and no changes in mean blood pressure or heart rate were observed in either treatment group. The use of antihypertensive medications also was similar in each treatment group. Screening for darbepoetin alfa and rHuEPO antibodies was performed by radioimmune precipitation assay before the first dose of study drug and at three-month intervals thereafter, and all were negative.

DISCUSSION

The results of this randomized, comparative study demonstrate that darbepoetin alfa is as effective as rHuEPO for treating renal anemia in dialysis patients, but at a reduced dose frequency. When analyzed by route of study drug administration (IV/SC) and dialysis modality (HD/PD), darbepoetin alfa was similarly demonstrated to be as effective as rHuEPO. Switching from rHuEPO to darbepoetin alfa was accomplished without an increased risk of unstable hemoglobin concentrations. Darbepoetin alfa-treated patients successfully maintained hemoglobin within the target and therapeutic ranges during the study, with a similar number of dose adjustments as the rHuEPO-treated patients. The results were consistent within patient sub-groups, and were robust to the type of analysis methods.

The mean dose of study drug during the evaluation period was similar in both treatment groups and also was similar to baseline, indicating that the initial protein mass substitution formula was appropriate for providing patients with a therapeutic starting dose of darbepoetin alfa. However, as with rHuEPO therapy [13–14], there was a large inter-patient variability in dose requirements, and dose titration may be required to maintain the recommended hemoglobin target range. When dosing of darbepoetin alfa and rHuEPO were analyzed by route of administration there was no difference in IV and SC dose requirements for darbepoetin alfa, but an average 22% lower dose requirement for SC rHuEPO compared with the IV route. The fact that no such dosing difference was observed with darbepoetin alfa might be explained by the longer terminal half-life of the molecule compared with rHuEPO, particularly when administered by the IV route. Results of a double-blind, randomized pharmacokinetic study indicated that the terminal half-life of darbepoetin alfa was 25.3 hours by the IV route and 48.8 hours by the SC route. In contrast, the terminal half-life of rHuEPO was 8.5 hours by the IV route and from historical data was 16 to 24 hours by the SC route [10]. Therefore, the ratio of the IV:SC half-life is higher for darbepoetin alfa than for rHuEPO, resulting in serum

concentrations above the threshold for stimulation of erythropoiesis for proportionately longer by the IV route.

The optimum frequency of rHuEPO dosing in CRF patients has been addressed in a number of clinical studies, and controversial results exist regarding the efficacy of once weekly rHuEPO dosing compared with two and three times weekly dosing. While a recent randomized study found no difference in the weekly SC dose of rHuEPO beta when administration frequency was reduced to once weekly [15], the European Anemia Best Practice Guidelines recommend that patients start with two or three injections per week and then subsequently reduce the dose frequency in patients with low rHuEPO dose requirements [6].

An important consideration when treating anemia in CRF patients is iron availability for erythropoiesis. In view of the potential for iron deficiency to inhibit the response to rHuEPO and darbepoetin alfa and influence the measurements of efficacy, the study included a requirement for iron replacement therapy in accordance with the European and Australian Anemia Best Practice Guidelines [6, 16]. Consequently, most patients received IV iron supplementation and maintained serum ferritin concentrations above the recommended level, and there was no difference between treatment groups with respect to either parameter.

Chronic renal failure is associated with high co-morbidity and mortality relative to the general population [6, 17, 18]. There is a high prevalence of hypertension, diabetes mellitus and cardiovascular disease. This results in an overall annualized mortality rate of 10 to 25%, depending on geographical region. In addition, patients suffer from symptoms associated with their renal failure and, in patients who require dialysis, there are additional complications associated with the dialysis process [19]. Thus, there is a high background level of adverse events, which are often serious in nature.

The safety profile of darbepoetin alfa was similar to that observed in the rHuEPO treatment group. The majority of adverse events were related to the underlying disease and its treatment, and only a small number were reported as being related to the study drug. The annualized proportion of deaths on study was consistent with the population at risk [15, 20], and did not differ between the two treatment groups. The causes of death were typical of patients with CRF receiving dialysis and all of the reasons were considered to be unrelated to the study drug. Results from a recently reported double-blind, randomized, comparative trial of darbepoetin alfa and rHuEPO have confirmed the similar safety profile of the two products in CRF patients receiving dialysis [21].

In conclusion, this study demonstrates that darbepoetin alfa given at a reduced dose frequency is as effective and well tolerated as rHuEPO for treating renal anemia in dialysis patients. The similar IV and SC dose requirements for darbepoetin alfa may allow European and Australian hemodialysis patients currently receiving SC injections to switch to IV dosing. Further studies will be needed to confirm this finding in patients in other geographic regions. There also is evidence that a reduced frequency of administration is possible in patients with chronic renal insufficiency (who are not yet receiving dialysis) [22].

ACKNOWLEDGMENTS

The European/Australian NESP 970200 Study Group comprised the following members and institutions (in alphabetical order): P. Attman (*Sahlgrenska Hospital, Gothenburg, Sweden*), U. Bahner (*Kuratorium für Dialyse und Nierentransplantation, Würzburg, Germany*), P. Bárány (*Huddinge University Hospital, Stockholm, Sweden*), J. Bommer (*University of Heidelberg, Heidelberg, Germany*), J. Bouchet (*CTMR Saint-Augustin, Bordeaux, France*), R.M.L. Brouwer (*Medisch Spectrum Twente, Enschede, Netherlands*), C. Buisson (*Centre Hospitalier Pasteur Vallery-Radot, Paris, France*), B. Canaud (*Hópital Lapeyronie, Montpellier, France*), N. Clyne (*Karolinska Hospital, Stockholm, Sweden*), G.A. Coles (*Cardiff Royal Infirmary, Cardiff, UK*), A.M. Davison (*St. James' University Hospital, Leeds, UK*), R. Gokal (*Manchester Royal Infirmary, Manchester, UK*), D. Harris (*Westmead Hospital, Sydney, Australia*), C. Hawley (*Princess Alexandra Hospital, Brisbane, Australia*), H. Holzer (*Medizinische Universitatsklinik Graz, Graz, Austria*), W.H. Hörl (*University Klinik für Innere Medizin III, Vienna, Austria*), P.G. Kerr (*Monash Medical Centre, Melbourne, Australia*), I.C. Macdougall (*King's College Hospital, London, UK*), J.F.E. Mann (*Schwabing General Hospital, LMU, Munich, Germany*), A. Martín-Malo (*Hospital Universitario Reina Sofia, Córdoba, Spain*), R.M. Schäfer (*Medizinische Poliklinik, Münster, Germany*), G. Stein (*Klinikum der Friedrich Schiller Universität, Jena, Germany*), C. Tielemans (*Hopital Erasme, Brussels, Belgium*), C. Tomson (*Southmead Hospital, Bristol, UK*), F. Valderrábano† (*Hospital Gregorio Maranón, Madrid, Spain*), M.A. van den Dorpel (*St. Clara Hospital, Rotterdam, The Netherlands*), Y. Vanrenterghem (*University Hospital Leuven, Leuven, Belgium*), R. Walker (*Royal Melbourne Hospital, Melbourne, Australia*), J. Walls (*Leicester General Hospital, Leicester, UK*), M. Wilkie (*Northern General Hospital, Sheffield, UK*), C. Winearls (*The Churchill, Oxford, UK*). N. Baker, M. Daley, S. Gray, B. Jenkins, J. Matcham, A. Robinson-Smith, and J. Wilson (*Amgen Ltd, Cambridge, UK*).

This study was supported by Amgen, Inc. (Thousand Oaks, CA, USA). We thank the co-investigators and study nurses at each of the Study Group institutions for their dedication and expertise in clinical management of patients involved in this study. Results from this study were presented in abstract form at the annual meeting of the American Society of Nephrology in Miami Beach, FL, November 1999.

Reprint requests to Prof. Yves Vanrenterghem, Department of Nephrology, University Hospital Leuven, UZ Gasthuisberg Herestraat 49, B-3000 Leuven, Belgium.
E-mail: Yves.Vanrenterghem@uz.kuleuven.ac.be

REFERENCES

1. Caro J, Brown S, Miller O, *et al*: Erythropoietin levels in uremic nephric and anephric patients. *J Lab Clin Med* 93:449–458, 1979
2. Winearls CG, Oliver DO, Pippard MJ, *et al*: Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. *Lancet* I:1175–1178, 1986
3. Eschbach JW, Egrie JC, Downing MR, *et al*: Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. *N Engl J Med* 316:73–78, 1987
4. Faulds D, Sorkin EM: Epoetin (recombinant human erythropoietin). A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in anaemia and the stimulation of erythropoiesis. *Drugs* 38:863–899, 1989
5. Cazzola M, Mercuriali F, Brugnara C: Use of recombinant

human erythropoietin outside the setting of uremia. *Blood* 89: 4248–4267, 1997
6. Working Party for European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure: European best practice guidelines for the management of anaemia in patients with chronic renal failure. *Nephrol Dial Transplant* 14(Suppl 5):1–50, 1999
7. Besarab A, Flaharty KK, Erslev AJ, *et al*: Clinical pharmacology and economics of recombinant human erythropoietin in end-stage renal disease: The case for subcutaneous administration. *J Am Soc Nephrol* 2:1405–1416, 1992
8. Macdougall IC, Roberts DE, Neubert P, *et al*: Pharmacokinetics of intravenous, intraperitoneal and subcutaneous recombinant erythropoietin in patients on CAPD. *Contrib Nephrol* 76:112–121, 1989
9. Egrie JC, Browne JK: Development and characterisation of novel erythropoiesis stimulating protein (NESP). *Br J Cancer* 84(Suppl 1):3–10, 2001
10. Macdougall IC, Gray SJ, Elston O, *et al*: Pharmacokinetics of novel erythropoiesis stimulating protein compared with Epoetin alfa in dialysis patients. *J Am Soc Nephrol* 10:2392–2395, 1999
11. Macdougall IC: Novel erythropoiesis stimulating protein. *Semin Nephrol* 20:375–381, 2000
12. Jones B, Jarvis P, Lewis JA, Ebbutt AF: Trials to assess equivalence: The importance of rigorous methods. *BMJ* 313:36–39, 1996
13. Uehlinger DE, Gotch FA, Sheiner LB: A pharmacodynamic model of erythropoietin therapy for uremic anemia. *Clin Pharmacol Ther* 51:76–89, 1992
14. Eschbach JW, Abdulhadi MH, Browne JK, *et al*: Recombinant human erythropoietin in anemic patients with end-stage renal disease: Results of a phase III multicenter clinical trial. *Ann Int Med* 111:992–1000, 1989
15. Weiss LG, Clyne N, Divino Fihlho J, *et al*: The efficiency of once weekly compared with two and three times weekly subcutaneous Epoetin beta: Results from a randomized controlled multicentre trial. Swedish Study Group. *Nephrol Dial Transplant* 15:2014–2019, 2000
16. *The CARI Guidelines (Caring for Australians with Renal Impairment).* Australian Kidney Foundation and Australia New Zealand Society of Nephrology, 2001, Web site: *http://www.cari.kidney.org.au*
17. Churchill DN, Taylor DW, Cook RJ, *et al*: Canadian hemodialysis morbidity study. *Am J Kidney Dis* 19:214–234, 1992
18. Locatelli F, Bommer J, London GM, *et al*: Cardiovascular disease determinants in chronic renal failure: Clinical approach and treatment. *Nephrol Dial Transplant* 16:459–468, 2001
19. Pastan S, Bailey J: Medical progress: Dialysis therapy. *N Engl J Med* 338:1428–1437, 1998
20. Berthoux F, Jones E, Gellert R, *et al*: Epidemiological data of treated end-stage renal failure in the European Union (EU) during the year 1995: Report of the European renal association registry and the national registries. *Nephrol Dial Transplant* 14:2332–2342, 1999
21. 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* 40:110–118, 2002
22. Locatelli F, Olivares J, Walker R, *et al*: Novel erythropoiesis stimulating protein for treatment of anemia in chronic renal insufficiency. European/Australian NESP 980202 Study Group. *Kidney Int* 60:741–747, 2001