Randomized, Controlled Trial of Darbepoetin Alfa for the Treatment of Anemia in Hemodialysis Patients

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● ***Background:*** **Darbepoetin alfa (Aranesp; Amgen, Thousand Oaks, CA) is a new erythropoiesis-stimulating protein with a threefold longer terminal half-life than recombinant human erythropoietin (epoetin) in patients with chronic kidney disease (CKD). The purpose of this randomized, double-blind, noninferiority study is to determine whether darbepoetin alfa is as effective as epoetin for the treatment of anemia in hemodialysis patients when administered at a reduced dosing frequency.** ***Methods:*** **Patients receiving epoetin therapy were randomized to continue epoetin administered intravenously (IV) three times weekly (n = 338) or change to darbepoetin alfa administered IV once weekly (n = 169). The dose of darbepoetin alfa or epoetin was individually titrated to maintain hemoglobin concentrations within −1.0 to +1.5 g/dL (−10 to +15 g/L) of patients' baseline values and within a range of 9.0 to 13.0 g/dL (90 to 130 g/L) for up to 28 weeks (20-week dose-titration period followed by an 8-week evaluation period). The primary end point was change in hemoglobin level between baseline and the evaluation period (weeks 21 to 28).** ***Results:*** **Mean changes in hemoglobin levels from baseline to the evaluation period were 0.24 ± 0.10 (SE) g/dL (2.4 ± 1.0 g/L) in the darbepoetin alfa group and 0.11 ± 0.07 g/dL (1.1 ± 0.7 g/L) in the epoetin group, a difference of 0.13 g/dL (95% confidence interval [CI], −0.08 ± 0.33 [1.3 g/L; 95% CI, −0.8 to 3.3]). This difference was not statistically significant or clinically relevant despite the reduced frequency of darbepoetin alfa administration. The safety profile of darbepoetin alfa was similar to that of epoetin, and no antibody formation to either treatment was detected.** ***Conclusion:*** **These results show that darbepoetin alfa maintains hemoglobin concentrations as effectively and safely as epoetin in patients with CKD, but with a reduced dosing frequency.**

INDEX WORDS: Darbepoetin alfa; new erythropoiesis-stimulating protein (NESP); anemia; chronic kidney disease (CKD).

ANEMIA IS COMMON in patients with chronic kidney disease (CKD) and can have a significant impact on patient morbidity and mortality. The anemia of CKD is predominantly caused by inadequate erythropoietin production by the kidneys, resulting in inappropriately low circulating erythropoietin levels for the degree of anemia present.[1] Replacement therapy with recombinant human erythropoietin (epoetin) has provided an effective treatment for patients with renal anemia and has been shown to increase red blood cell (RBC) mass, reduce the need for RBC transfusions, and alleviate symptoms of anemia in this population.[2,3] Because epoetin has a relatively short circulating half-life, administration two to three times weekly is recommended.[4,5]

Previous research has indicated that the sialic acid–containing carbohydrate of erythropoietin determines its serum half-life.[6] Darbepoetin alfa (Aranesp; Amgen, Thousand Oaks, CA) is a new erythropoiesis-stimulating protein (NESP) designed by introducing five amino acid changes into the primary sequence of erythropoietin to create two extra consensus N-linked carbohydrate addition sites. Consequently, darbepoetin alfa has five N-linked carbohydrate chains, whereas epoetin has only three. Because of its increased sialic acid–containing carbohydrate content, darbepoetin alfa has a threefold longer serum half-life (25.3 hours) compared with epoetin (8.5 hours) in patients with CKD after intravenous (IV) administration,[7] potentially allowing it to be administered at a reduced dosing frequency.

This multicenter, randomized, double-blind,

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The United States and Canadian Aranesp™ 980117 Study Group members and institutions are listed in the Appendix.

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noninferiority study was conducted to determine whether darbepoetin alfa, administered at a reduced dosing frequency relative to epoetin, is as effective and well tolerated as epoetin for the treatment of anemia in patients with CKD on hemodialysis therapy.

METHODS

Patients

Patients with CKD, recruited from 35 dialysis centers in the United States and 5 centers in Canada, were required to be 18 years or older, clinically stable, and on hemodialysis therapy for at least 12 weeks. They also were required to be administered stable IV epoetin alfa therapy three times weekly for a minimum of 8 weeks and have a mean baseline hemoglobin concentration of 9.5 to 12.5 g/dL (95 to 125 g/L). To ensure adequate iron stores to support erythropoiesis, transferrin saturation was required to be 20% or greater.[4] Patients were excluded from the study if they had hematologic, inflammatory, infectious, or other conditions that might interfere with the erythropoietic response or had been administered RBC transfusions within 8 weeks of enrollment. Although no specific laboratory criteria for inflammatory or infectious disease were defined in the study protocol, clinicians were requested to exercise clinical judgment regarding patient exclusion based on underlying disease.

The study was approved by each center's institutional review board, and all patients gave written informed consent before participation.

Study Design

This multicenter, randomized, double-blind, noninferiority study was conducted to determine whether darbepoetin alfa, administered at a reduced dosing frequency relative to epoetin, is as effective and well tolerated as epoetin for the treatment of anemia in patients with CKD on dialysis therapy.

After a 4-week screening and baseline period, patients were randomized in a 2:1 ratio to continue epoetin administered IV three times weekly or change to darbepoetin alfa administered IV once weekly (plus placebo two times weekly to maintain the study blind). A 2:1 patient allocation ratio was chosen to increase patient exposure and safety information for the darbepoetin alfa clinical development program. Randomization was performed by using a central computerized system and stratified by center. For patients randomized to administration of darbepoetin alfa, the initial dose was based on their total weekly dose of epoetin at the time of randomization, using a formula equating the protein mass of the two molecules (200 U of epoetin = 1 μg of NESP). A period of 20 weeks (weeks 1 to 20) after the first dose of study drug was used for dose titration and stabilization of hemoglobin level, followed by an 8-week evaluation period to determine the primary efficacy end point (weeks 21 to 28). Because of the circulating half-life of RBCs (~60 days in patients with CKD), it was anticipated that equilibrium of hemoglobin level after switching from epoetin to darbepoetin alfa therapy would occur within 20 to 24 weeks.[8]

Darbepoetin alfa or epoetin (epoetin alfa) was administered as an IV bolus through the venous access during dialysis sessions. In each treatment group, the dose of study drug was adjusted as necessary to maintain individual patients' hemoglobin concentrations within −1.0 to +1.5 g/dL (−10 to +15 g/L) of their baseline values and within a range of 9.0 to 13.0 g/dL (90 to 130 g/L) throughout the 28-week study period. If a patient's hemoglobin concentration decreased to less than the target range on two consecutive weekly assessments, the dose of study drug was increased by 25% of the starting dose. The dose could be increased further if the hemoglobin concentration remained below the target range for an additional 2 consecutive weeks. If a patient's hemoglobin concentration increased above the target range for two consecutive weekly assessments, the dose of study drug was reduced by 25% of the starting dose. The dose could be decreased further if the hemoglobin concentration remained above the target range for an additional 2 consecutive weeks.

Iron supplementation was administered according to individual unit policy to maintain a transferrin saturation of 20% or greater. Periodic reviews of safety data were conducted by an external safety monitoring committee.

Statistical Analysis

The primary efficacy analysis compared mean change in hemoglobin levels between the baseline and evaluation periods for patients administered darbepoetin alfa and epoetin. To show noninferiority (comparable), the lower limit of the two-sided 95% confidence interval (CI) for the difference in mean change in hemoglobin levels between treatment groups had to be greater than −1.0 g/dL (−10 g/L). A 1.0-g/dL (10-g/L) difference between the two groups was prospectively chosen because it was considered to be the greatest clinically acceptable difference. The 95% CI was calculated with and without adjustment for covariates that might influence hemoglobin response (ie, study center and baseline hemoglobin concentration). A sample size of 495 patients was selected to provide more than 90% power to show that darbepoetin alfa is as effective as epoetin.[9] After all patients had been randomized, it was discovered that there had been a reversal of randomization assignments. The statistical power to show noninferiority and other comparisons between darbepoetin alfa and epoetin were not affected by this reversal.

A per-protocol (pP) analysis set was used for the main analysis of efficacy. In superiority trials, in which an intent-to-treat population is the preferred analysis set, inclusion of all subjects tends to reduce treatment differences. For noninferiority (equivalence) trials, a pP analysis is a more conservative approach because it removes uninformative noise and maximizes the ability to detect treatment differences between groups.[9] The pP analysis compared patients according to the treatment they actually received and included only patients who satisfied protocol-specified criteria. A modified intent-to-treat (mITT) analysis set was used for the secondary analysis, with three methods for imputing missing values for patients who discontinued treatment. These included using the last value carried forward, substitution of worst-case values, and multiple imputation using the propensity score method. mITT and safety analysis sets included all randomized patients administered study drug.

Secondary efficacy analyses included the percentage of hemoglobin values within the target range (−1.0 to +1.5

g/dL of baseline and 9.0 to 13.0 g/dL; −10 to +15 g/L of baseline and 90 to 130 g/L) and therapeutic range (9.0 to 13.0 g/dL; 90 to 130 g/L), percentage of unstable hemoglobin values (hemoglobin concentrations necessitating a dose change), within-patient variance in hemoglobin levels, and dose of study drug. Within-patient variance in hemoglobin levels was calculated from residuals of the linear regression model (ie, mean squared error). All statistical analyses were performed using the SAS software package (version 6.12; SAS Inc, Cary, NC).

RESULTS

Patient Characteristics

Five hundred seven patients were randomized onto the study. Five hundred four patients were administered study drug and included in the mITT and safety analysis sets (169 patients, darbepoetin alfa; 335 patients, epoetin). Three hundred sixty-one patients (121 patients, darbepoetin alfa; 240 patients, epoetin) were included in the pP analysis set, with a similar proportion of assessable patients from each treatment group (72%, darbepoetin alfa; 71%, epoetin). Reasons for exclusion from the pP analysis set were well balanced between treatment groups. Additional details about the flow of study participants through this comparative trial are shown in Fig 1.

Demographic and baseline characteristics were similar between treatment groups (Table 1) and generally representative of the CKD patient population in the United States.[10] Fifty-six percent of study patients were men, and most were white (42%) or black (39%). Mean age was 57.9 years (range, 20 to 90 years). The most common causes of CKD in study patients were diabetes mellitus (35%) and hypertension (26%). At baseline, the mean weekly epoetin dose was 13,776 U/wk (range, 1,200 to 120,000 U/wk), and mean hemoglobin concentration was 11.2 g/dL (range, 9.6 to 12.6 g/dL; 112 g/L; range, 96 to 126 g/L). Demographics and baseline characteristics were similar for the pP, mITT, and safety analysis sets.

Eighty-five patients did not complete the 28-week study period. The rate of discontinuation was similar between treatment groups during the dose-titration (10.1%, darbepoetin alfa; 11.8%, epoetin) and evaluation periods (5.3%, darbepoetin alfa; 3.8%, epoetin) and at the end-of-study assessment (1.2%, darbepoetin alfa; 0.3%, epoetin). The most frequent reasons for discontinuation from the study were death, intolerable adverse events, and kidney transplantation and were generally similar between treatment groups.

Primary Efficacy Analysis

Mean weekly hemoglobin concentrations were similar in the darbepoetin alfa and epoetin groups throughout the 28-week study period (Fig 2). Mean changes in hemoglobin levels from baseline to the evaluation period, adjusted for effects of study center and baseline hemoglobin level, were 0.24 ± 0.10 (SE) g/dL (2.4 ± 1.0 g/L) for the darbepoetin alfa group and 0.11 ± 0.07 g/dL (1.1 ± 0.7 g/L) for the epoetin group, a difference of 0.13 g/dL (95% CI, −0.08 to 0.33; 1.3 g/L; 95% CI, −0.8 to 3.3).

In an analysis that was not adjusted for study center and baseline hemoglobin level, mean changes in hemoglobin levels from baseline to the evaluation period also were similar between the darbepoetin alfa (0.16 − 0.09 g/dL; 1.6 ± 0.9 g/L) and epoetin (−0.00 ± 0.06 g/dL; −0.0 ± 0.6 g/L) groups, resulting in an unadjusted difference of 0.16 g/dL (95% CI, −0.06 to 0.38; 1.6 g/L; 95% CI, −0.6 to 3.8). Thus, the lower limit of the two-sided 95% CI was well above the protocol-specified noninferiority margin of −1.0 g/dL (−10 g/L) whether adjusted (−0.08 g/dL; −0.8 g/L) or unadjusted (−0.06 g/dL; −0.6 g/L) for covariates, indicating that darbepoetin alfa was as effective as epoetin for maintaining hemoglobin concentrations (Fig 3).

The robustness of the pP analysis was confirmed in an analysis of the primary end point using the mITT data set. In this analysis, the difference between treatment groups in mean (95% CI) change in hemoglobin levels from baseline to the evaluation period also was well above the noninferiority margin of −1.0 g/dL (−10 g/L), whether adjusted (0.06 g/dL; 95% CI, −0.15 to 0.27; 0.6 g/L; 95% CI, −1.5 to 2.7) or unadjusted (0.07 g/dL; 95% CI, −0.14 to 0.29; 0.7 g/L; 95% CI, −1.4 to 2.9) for covariates (Fig 3).

Secondary Efficacy Analysis

Results of the analysis of secondary efficacy end points examining hemoglobin level variability are shown in Fig 4. For each of the secondary end points, the 95% CI of the ratio between darbepoetin alfa and epoetin included 1, indicating no statistically significant difference in hemo-

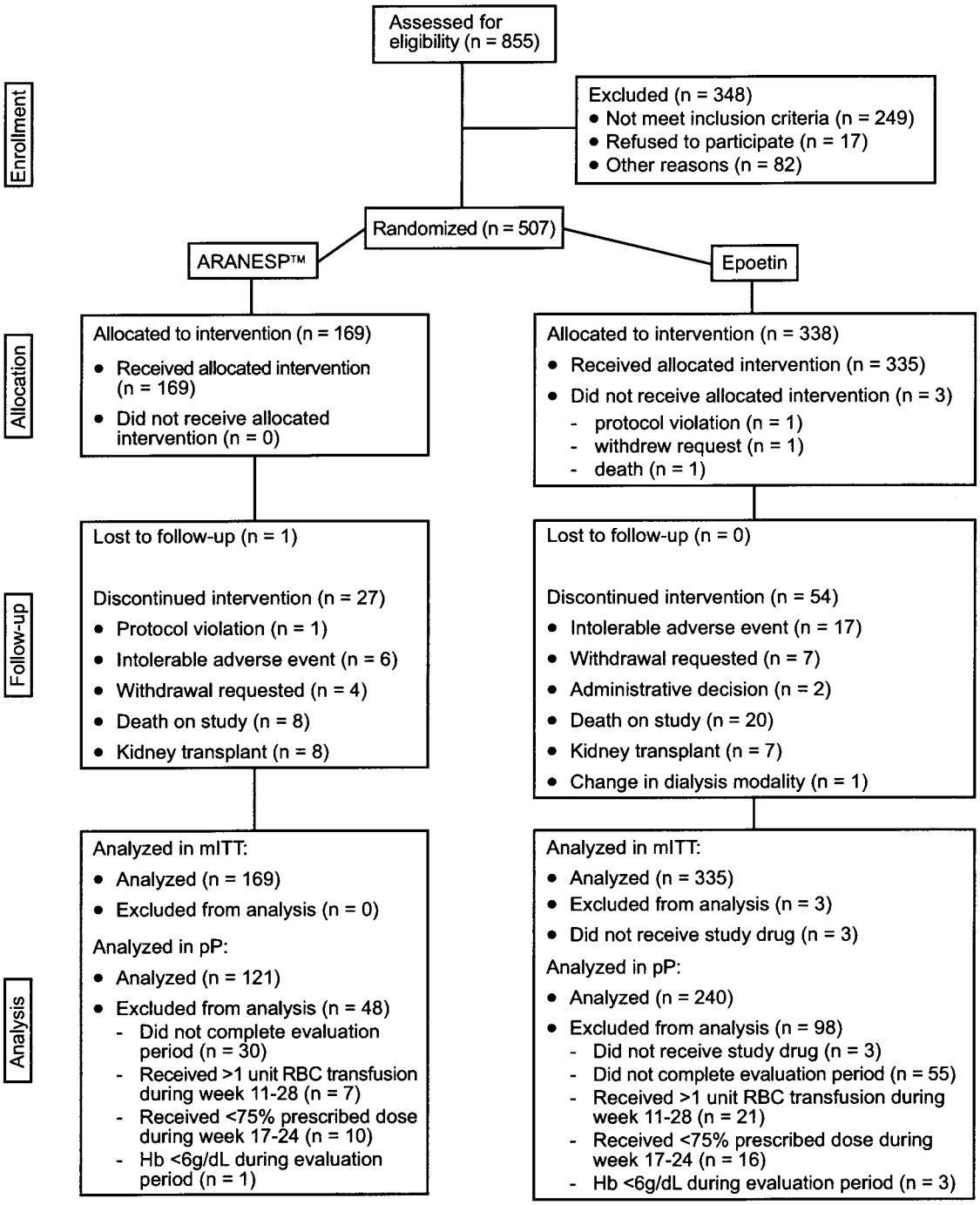

Fig 1. Flow diagram showing patient enrollment, allocation, and disposition. Abbreviation: Hb, hemoglobin

globin variability during the evaluation period between treatment groups.

For both the darbepoetin alfa and epoetin groups, the average dose during the evaluation period was similar to the average dose at baseline (Table 2). Percentages of patients with dose changes throughout the study also were similar in the two treatment groups (Fig 5). In the darbepoetin alfa group, 69% of patients had a dose change during the titration period, and 44%

Table 1. Demographics and Baseline Characteristics for All Randomized Patients

	Darbepoetin Alfa (n = 169)	Epoetin (n = 338)	Total (n = 507)
Sex			
Women	75 (44)	147 (43)	222 (44)
Men	94 (56)	191 (57)	285 (56)
Race			
Black	69 (41)	129 (38)	198 (39)
White	68 (40)	144 (43)	212 (42)
Other	32 (19)	65 (19)	97 (19)
Age (y)	58.0 (20-86)	57.8 (21-90)	57.9 (20-90)
Cause of renal failure			
Diabetes mellitus	62 (37)	116 (34)	178 (35)
Hypertension	44 (26)	88 (26)	132 (26)
Glomerulonephritis	18 (11)	36 (11)	54 (11)
Polycystic kidney disease	9 (5)	16 (5)	25 (5)
Urologic	2 (1)	5 (1)	7 (1)
Other	26 (15)	65 (19)	91 (18)
Unknown	8 (5)	12 (4)	20 (4)
Time since first dialysis (mon)	52.9 (4-325)	49.2 (4-267)	50.4 (4-325)
Epoetin dose (U/wk)	14,177 (1,500-120,000)	13,576 (1,200-60,000)	13,776 (1,200-120,000)
Hemoglobin (g/dL)	11.2 (9.7-12.5)	11.2 (9.6-12.6)	11.2 (9.6-12.6)
Serum ferritin (ng/mL)	411 (16-1,792)	425 (18-1,913)	420 (16-1,913)
Transferrin saturation (%)	33 (20-85)	32 (16-92)*	32 (16-92)

NOTE. Values expressed as number (percent) or mean (range). Hemoglobin conversion to SI units in grams per liter is ×10. Serum ferritin conversion to SI units in micrograms per liter is ×1.

*Data unavailable for one patient.

changed dose during the evaluation period. In epoetin-treated patients, 73% and 49% had dose changes during the titration and evaluation periods, respectively.

Safety

Adverse events occurring in at least 10% of patients in either treatment group are listed in Table 3. The overall incidence of adverse events was similar between treatment groups, with 93% of patients administered darbepoetin alfa and 99% of patients administered epoetin experiencing at least one adverse event. The most frequently reported adverse events included nausea (29%, darbepoetin alfa; 27%, epoetin), upper

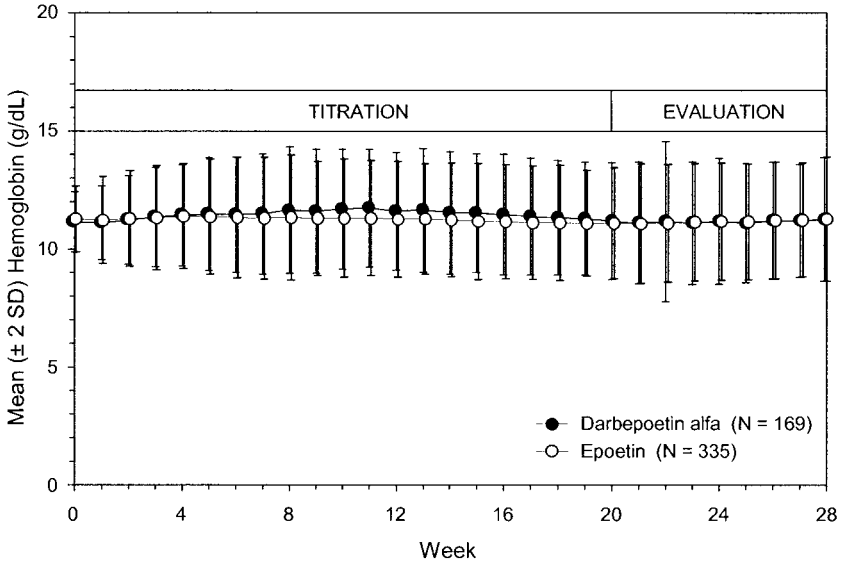

Fig 2. Mean ± 2 SD hemoglobin concentrations by study week and treatment group.

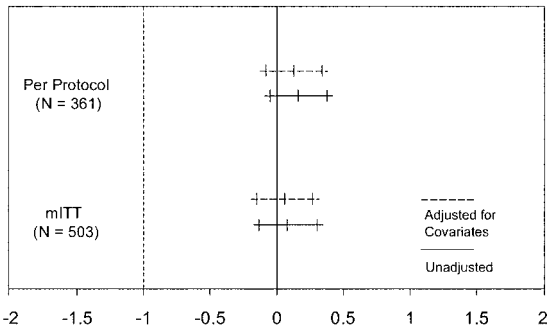

Fig 3. Ninety-five percent CIs for the difference between treatment groups (darbepoetin alfa – epoetin) in mean change in hemoglobin levels (grams per deciliter). Hemoglobin conversion to SI units in grams per liter is × 10. The mITT analysis excludes one patient who did not have hemoglobin assessments before discontinuation from the study.

respiratory infection (27%, both groups), and hypertension (28%, darbepoetin alfa; 24%, epoetin). Adverse events were consistent with those typically observed in patients with CKD on dialysis therapy and were not necessarily attributable to treatment with darbepoetin alfa or epoetin.

Nine patients (5%) in the darbepoetin alfa group and 23 patients (7%) in the epoetin group died during the study or within 30 days of the last dose of study drug. All deaths were attributed to comorbid conditions and were reported by the study investigators as unrelated to study drug.

During the 28-week study period, no significant changes were observed for mean systolic and diastolic blood pressures in either treatment group. Use of antihypertensive medications was similar in both groups. Mean changes in hematologic and biochemistry variables were similar between treatment groups throughout the study and were not considered clinically significant. No difference in the patient incidence of RBC transfusions was observed between the darbepoetin alfa (10%) and epoetin (11%) groups. The incidence of patients with iron deficiency and the implementation of IV and/or oral iron supplementation also were similar between treatment groups. No antibodies to darbepoetin alfa or epoetin were detected for any patient.

DISCUSSION

Results of this randomized double-blind study show that darbepoetin alfa maintains hemoglobin concentrations as safely and effectively as epoetin in patients with CKD on hemodialysis therapy, but with a reduced dosing frequency. Results were consistent regardless of which data set was analyzed or whether adjustments were made for covariates. In addition, changing from epoetin to darbepoetin alfa was not associated with an increased risk for unstable hemoglobin

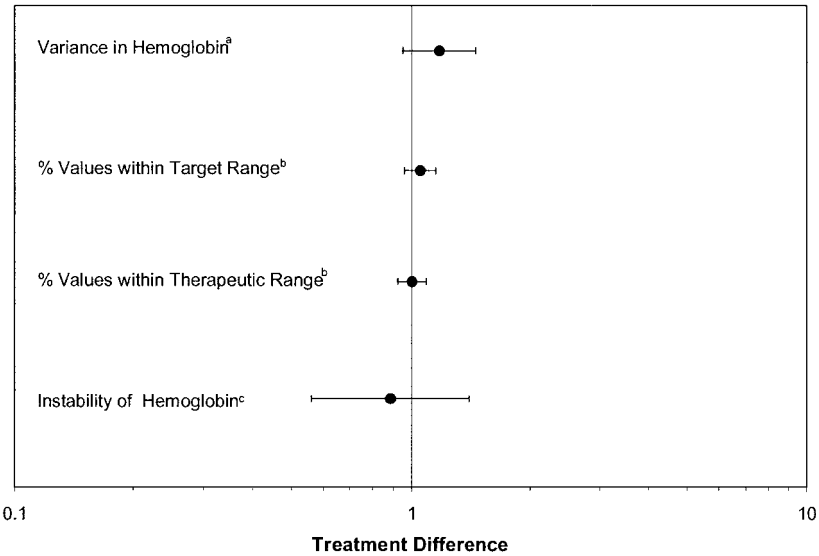

Fig 4. Assessments of hemoglobin level variability during the evaluation period.

[a] Ratio of hemoglobin variance between darbepoetin alfa and epoetin
[b] Ratio of mean percentage of hemoglobin values within range between darbepoetin alfa and epoetin
[c] Odds ratio for instability of hemoglobin between darbepoetin alfa and epoetin

Table 2. Weekly Doses of Darbepoetin Alfa and Epoetin at Baseline and During the Evaluation Period

	Baseline	Evaluation Period	Change
Darbepoetin alfa dose (μg/wk)			
No.	118	118	118
Mean	63.18	54.18	−9.00
Median	45.75	38.00	0.00
SD	49.27	47.56	34.79
Range	7.5-270.0	0.0-309.0	−157.0-75.0
Epoetin dose (U/wk)			
No.	240	240	240
Mean	12,706	13,639	934
Median	9,950	9,900	0
SD	10,349	12,805	7,886
Range	1,200-60,000	0-78,750	−37,550-37,500

concentrations. The percentage of hemoglobin values within the target and therapeutic ranges and within-patient variance in hemoglobin levels were similar between treatment groups. These results confirm the outcome of an open-label phase 3 trial conducted in Europe and Australia of 522 patients with CKD on hemodialysis or peritoneal dialysis therapy in which darbepoetin alfa was administered IV and subcutaneously.[11] Results in patients with CKD not yet on dialysis therapy also indicate that darbepoetin alfa can be administered at a reduced dosing frequency for the correction of anemia in this population.[12]

Mean doses of study drug were similar between baseline and the evaluation period in this study, suggesting that the initial protein mass formula was appropriate to identify a therapeutic starting dose for patients switching to darbepoetin alfa therapy. Forty-four percent of patients in the darbepoetin group and 49% of patients in the epoetin group experienced at least one dose change during the evaluation period. Intrapatient variability in dose is typical for patients with CKD on epoetin therapy, and dose changes usually are required to maintain patients' hemoglobin concentrations within a therapeutic range.[8] Thus, the percentage of patients on this study who had dose changes during the evaluation period is not unexpected. It previously was reported for epoetin that the dose required to maintain a given hemoglobin target range varied among patients as much as 40-fold.[3] Dose requirements for darbepoetin alfa and epoetin also varied substantially between patients on this study, indicating that titration to optimal therapeutic doses may be required for individual patients.

Treatment guidelines recommend that epoetin should be administered two or three times weekly

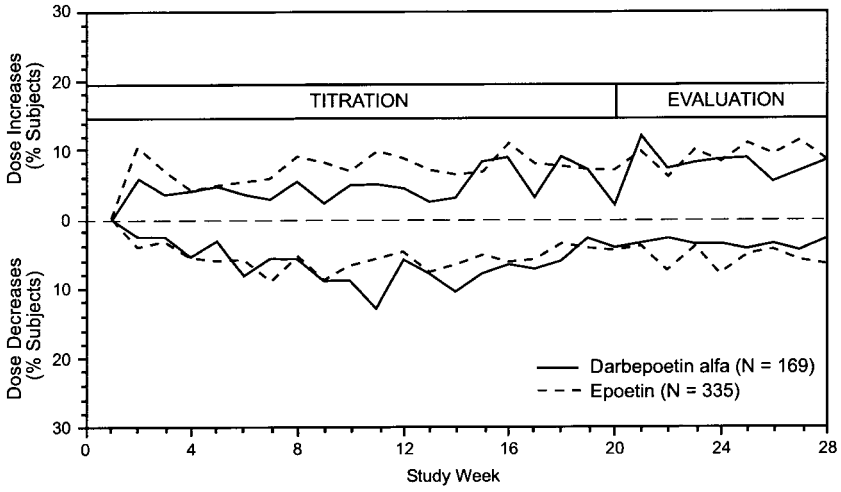

Fig 5. Dose changes over study duration by treatment group (mITT analysis set).

Table 3. Adverse Events Occurring in at Least 10% of Patients Administered Darbepoetin Alfa or Epoetin

	Darbepoetin Alfa (n = 169)	Epoetin (n = 335)
No. of patients reporting adverse events	158 (93)	332 (99)
Nausea	49 (29)	92 (27)
Hypertension	48 (28)	80 (24)
Infection, upper respiratory	45 (27)	90 (27)
Dyspnea	44 (26)	67 (20)
Hypotension	41 (24)	61 (18)
Diarrhea	36 (21)	76 (23)
Myalgia	36 (21)	73 (22)
Pain, chest	35 (21)	50 (15)
Vomiting	34 (20)	70 (21)
Edema, peripheral	32 (19)	62 (19)
Headache	32 (19)	59 (18)
Pain, limb	30 (18)	53 (16)
Dizziness	28 (17)	57 (17)
Pain, abdominal	28 (17)	56 (17)
Thrombosis, vascular access	27 (16)	59 (18)
Fatigue	23 (14)	45 (13)
Arthralgia	22 (13)	40 (12)
Cough	20 (12)	42 (13)
Access complication	18 (11)	48 (14)
Fever	16 (9)	39 (12)
Pain, back	15 (9)	37 (11)
Asthenia	10 (6)	34 (10)

NOTE. Values expressed as number (percent).

for the treatment of anemia in CKD.[4,5] However, epoetin also has been evaluated using a once-weekly schedule.[13] As a result of the extended half-life of darbepoetin alfa relative to epoetin,[7] even longer dosing intervals are possible with darbepoetin alfa therapy. In a randomized comparative study of darbepoetin alfa and epoetin in dialysis patients, 95% of patients administered epoetin once weekly at baseline successfully maintained stable hemoglobin concentrations when switched to darbepoetin alfa administered once every 2 weeks.[10] Further clinical studies to evaluate the efficacy and safety of darbepoetin alfa at extended dosing intervals currently are underway.

The safety profile of darbepoetin alfa in this study is similar to that of epoetin with respect to type and frequency of adverse events, changes in laboratory parameters and vital signs, and RBC transfusions. Adverse events reported were consistent with those expected for a population of patients with CKD on dialysis therapy. No antibody formation to either darbepoetin alfa or epoetin was detected for any patient.

In conclusion, this study shows that darbepoetin alfa administered once weekly is as effective and well tolerated as epoetin administered three times weekly for the treatment of anemia in patients with CKD on dialysis therapy, providing the benefits of less frequent administration.

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APPENDIX

The United States and Canadian Aranesp™ 980117 Study Group included the following members and institutions: Sharon Adler, Harbor-University of California at Los Angeles Medical Foundation, Torrance, CA; Michael Allon, Gambro Healthcare-Birmingham Central; Birmingham Acutes, Birmingham, AL; Paul Barre, Royal Victoria Hospital, Montreal, Quebec, Canada; William H. Bay, The Ohio State University Medical Center; Central Ohio Dialysis Center, Columbus, OH; Robert L. Benz, Lankenau Hospital/Research Center, Wynnewood; Bryn Mawr Hospital, Bryn Mawr, PA; Anatole Besarab, Henry Ford Hospital, Detroit, MI; W. Kline Bolton, University of Virginia Health Sciences Center, Charlottesville, VA; Borut Cizman, Lankenau Hospital/Research Center, Wynnewood; Bryn Mawr Hospital, Bryn Mawr, PA; Daniel W. Coyne, Washington University Medical Center; Barnes-Jewish Hospital, St Louis, MO; Mario Curzi, Diablo Renal Services, Walnut Creek and Antioch, CA; Joseph W. Eschbach, Northwest Kidney Centers, Seattle, WA; Adrian Fine, St Boniface General Hospital, Winnipeg, Manitoba, Canada; Steven Fishbane, The Dialysis Center, Mineola; The Dialysis Center at Bethpage, Bethpage, NY; Robert J. Goldstein, Florida West Coast Clinical Research; Gambro Central Dialysis, Tampa, FL; Gerald A. Hladik, Carolina Dialysis, Carrboro and Sanford, NC; David S.

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