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Darbepoetin Alfa Effectively Treats Anemia in Patients with Chronic Kidney Disease with de novo Every-Other-Week Administration

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Key Words
Cardiovascular mortality · Clinical nephrology · Erythropoietin

Abstract
Aim: This multicenter, open-label study determined safety and efficacy of once-every-other-week administration of darbepoetin alfa for anemia of chronic kidney disease in erythropoietin-naive patients not on dialysis. ***Methods:*** Participants with hemoglobin levels <11.0 g/dl at baseline were administered darbepoetin alfa at an initial dosage of 0.75 μg/kg once every other week. The dose was titrated to achieve and maintain a hemoglobin response, defined as a hemoglobin range of between 11.0 and 13.0 g/dl for up to 24 weeks. The primary end point was the dose of darbepoetin alfa at initial hemoglobin response. ***Results:*** Six hundred and eight patients were enrolled, and 463 completed the study; 95% (95% confidence interval: 0.93, 0.97) of the patients who completed treatment achieved a hemoglobin response. The mean darbepoetin alfa dose at the time of response was 63.5 ± (SD) 16.9 μg, and the mean time to hemoglobin response was 5.7 ± (SD) 4.5 weeks. Oral iron therapy was administered to 60% and intravenous iron to 16% of the participants. Darbepoetin alfa was well tolerated, and adverse events were consistent with those expected in patients with chronic kidney disease. ***Conclusion:*** Darbepoetin alfa administered once every other week is effective and safe for achieving and maintaining target hemoglobin levels in anemic patients with chronic kidney disease.

Introduction

Anemia usually begins during the early stages of chronic kidney disease and generally becomes progressively more severe, as the renal function deteriorates [1, 2]. Anemia is highly prevalent among patients who have chronic kidney disease with moderate to severe loss of kidney function not requiring dialysis [3]. The anemia associated with chronic kidney disease increases the need for red blood cell transfusions and impairs the patient's quality of life. In addition, many observational studies have suggested that anemia is a risk factor for cardiovascular disease and contributes to the increased morbidity and mortality associated with chronic kidney disease [4–10].

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Recombinant human erythropoietin (rHuEPO) increases red blood cell mass, reduces the need for transfusions, and alleviates symptoms associated with anemia in patients with chronic kidney disease [11–13]. Some publications indicate that treating anemia with rHuEPO may reduce the risk of cardiovascular disease in this patient population [14–16]. Thus, optimizing the treatment of anemia in patients with chronic kidney diease has the potential to substantially reduce morbidity and mortality from cardiovascular disease.

While most patients undergoing dialysis receive rHuEPO, anemia remains highly prevalent and undertreated in patients who are not receiving dialysis [3, 17]. The undertreatment of anemia in patients with chronic kidney disease who are receiving dialysis and who are seen in outpatient settings may, in part, be due to poor compliance due to the need for frequent injections of rHuEPO.

Darbepoetin alfa is an erythropoiesis-stimulating glycoprotein that activates the same receptor as rHuEPO and endogenous erythropoietin [18]. Darbepoetin alfa has a higher sialic acid content and a terminal half-life that is threefold longer than that of rHuEPO (25.3 vs. 8.5 h) [18, 19]. As a result, darbepoetin alfa is effective when administered at less-frequent dosing intervals than rHuEPO. Darbepoetin alfa has been shown to be a safe and effective treatment for anemia in patients with chronic kidney disease who are either naive to rHuEPO or are converted from rHuEPO therapy to darbepoetin alfa therapy [20–23].

The present study was designed to evaluate efficacy and safety of initiating treatment with darbepoetin alfa at once-every-other-week intervals in anemic patients with chronic kidney disease who are not on dialysis and who are naive to rHuEPO therapy.

Patients and Methods

Patients

The institutional review boards of the participating centers approved the study protocol. All patients gave written, informed consent before any study-related procedures were performed.

Patients were eligible for enrollment, if they were ≥18 years of age, were clinically stable, and had a calculated creatinine clearance <40 ml/min according to the Cockcroft-Gault formula [24]. The patients were required to have mean baseline hemoglobin concentration <11.0 g/dl, determined by two values taken during the screening period at least 1 week apart. A transferrin saturation ≥20% or a ferritin level ≥100 μg/l was required [25] to ensure adequate iron stores to support erythropoiesis. Patients were excluded from the study, if they had received rHuEPO therapy within 12 weeks of enrollment, congestive heart failure (New York Heart Association Class III or IV), uncontrolled hypertension (two measurements with a diastolic blood pressure >110 mm Hg during the 2-week screening baseline period), a hematologic disorder, an active inflammatory process, a grand mal seizure within 1 year of enrollment, or major surgery within 12 weeks of enrollment. In addition, patients who had received a kidney transplant or were scheduled for a transplant, patients expected to initiate dialysis within 24 weeks of enrollment, and patients who had received red blood cell transfusions within 8 weeks of enrollment were excluded from the study.

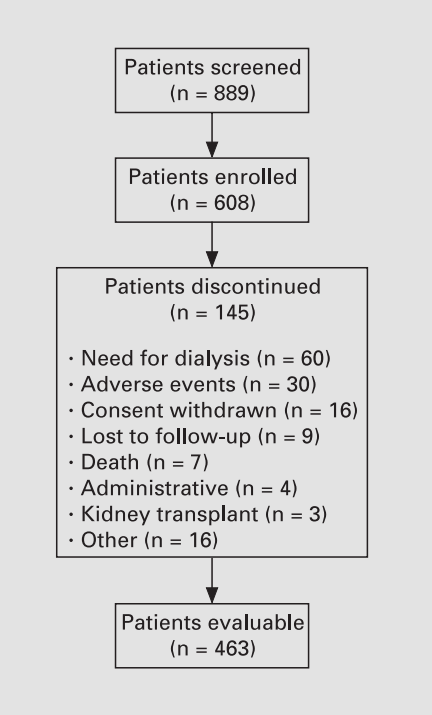

Fig. 1. Disposition of the study population.

Study Design

This multicenter, open-label study was designed to further evaluate efficacy and safety of darbepoetin alfa administered de novo once every other week for the treatment of anemia in patients with chronic kidney disease who are not receiving dialysis (fig. 1). After a 2-week screening and baseline period, the patients were initiated on subcutaneous administration of darbepoetin alfa (Aranesp; Amgen, Thousand Oaks, Calif., USA). Darbepoetin alfa was available in unit-dose strengths of 10, 15, 20, 30, 40, 50, 60, 80, and 100 μg. Each dose was calculated according to body weight and rounded to the nearest unit-dose strength. The initial dose in all patients was 0.75 μg/kg, rounded to the nearest unit-dose strength. Subsequent doses, given once every other week, were adjusted in individual patients as necessary to achieve a rate of rise in hemoglobin concentration from ≥1.0 g/dl to <3.0 g/dl over 4-week intervals, until the target hemoglobin concentration range (11.0–13.0 g/dl) was reached. If a patient's hemoglobin concentration was below the target range on two consecutive assessments, the dose of darbepoetin alfa was increased to the next higher unit-dose strength. After the hemoglobin concentration reached the target range, the dose of darbepoetin alfa was adjusted as necessary to

maintain the hemoglobin concentration within the target range. If a patient's hemoglobin concentration was above the target range for two consecutive assessments, the dose of darbepoetin alfa was reduced to the next lower dose strength as previously described [23]. Iron stores were assessed in all participants at a screening visit: at weeks 11 and 23 during the study and at week 25 (end of study assessment). Iron was administered as needed according to study-site-specific protocols at each individual study center to maintain adequate iron stores, defined as a transferrin saturation >20% or ferritin >100 μg/l. The amount of all iron supplements administered to patients (both oral iron and intravenous iron) is expressed as the weight of the entire molecule and not as elemental iron. The total period of treatment was 24 weeks.

The primary efficacy end point was the dose of darbepoetin alfa at the time the hemoglobin concentration was ≥11.0 g/dl. Secondary end points included the time required for the hemoglobin concentration to reach the target and the proportion of patients achieving the target. The number of red blood cell transfusions was recorded.

Safety was monitored throughout the study by reports of adverse events and changes in laboratory data. Laboratory tests were done at each center's local laboratory. Blood samples taken before the first dose of darbepoetin alfa and at the end of the study were tested for the presence of antibodies to erythropoietic proteins. All antierythropoietic protein antibody assays were done at Amgen using the Biacore 3000 assay [26].

Statistics

Unless otherwise stated, descriptive statistics are expressed as mean values with standard deviations (SD) or 95% confidence intervals (95% CI). For categorical variables, numbers were determined and percentages calculated. The time to reach the target hemoglobin concentration was analyzed using life table methods. Missing hemoglobin values were not imputed. All patients who completed 24 weeks of treatment were included in efficacy analyses. All patients who received at least one dose of darbepoetin alfa were included in the safety analyses.

Table 1. Demographics and baseline characteristics of the patients enrolled

Number of patients	608
Age, years	
Mean ± SD	63.8 ± 13.7
Range	21.0−99.0
Sex, n (%)	
Women	297 (49)
Men	311 (51)
Race, n (%)	
White	355 (58)
Black	190 (31)
Hispanic	34 (6)
Other	29 (5)
Weight, kg	
Mean ± SD	81.0 ± 19.2
Range	23.0−178.2
Primary causes of chronic kidney disease, n (%)	
Diabetes	289 (48)
Hypertension	123 (20)
Glomerulonephritis	35 (6)
Polycystic kidney disease	28 (5)
Urologic	9 (1)
Other	95 (16)
Unknown	29 (5)
Hemoglobin, g/dl	
Mean ± SD	9.8 ± 0.8
Range	6.4−11.0
Transferrin saturation, %	
n	532
Mean ± SD	28.0 ± 21.2
Range	4.0−247.0
Serum ferritin, μg/l	
n	578
Mean ± SD	222 ± 189
Range	13−1,650
Creatinine clearance, ml/min	
Mean ± SD	23.2 ± 9.26

Results

Six hundred and eight patients from 325 study centers in the United States, Canada, and Australia were enrolled into the study, and 463 (76%) completed 24 weeks of darbepoetin alfa treatment (fig. 1). Comparable proportions of men (51%) and women (49%) were enrolled (table 1). Most patients were of white or black race and the mean age at study entry was 63.8 ± 13.7 years. The patients' mean baseline hemoglobin concentration was 9.8 ± 0.8 g/dl, and the calculated creatinine clearance was 23.2 ± 9.3 ml/min. The most common causes of chronic kidney disease were diabetes (48%) and hypertension (20%). One hundred and forty-five patients discontinued the study early. The reasons for early discontinuation included initiation of dialysis (60 patients; 41%), kidney transplantation (3 patients; 2%), loss to follow-up (9 patients; 1.5%), protocol deviation (3 patients; 0.5%), withdrawal of consent (16 patients; 2.6%), adverse events (30 patients; 21%), and death (7 patients; 1%). These patients died of complications related to comorbidity, and no deaths were attributed to the treatment with darbepoetin alfa. The adverse events that led to discontinuation included hypertension (5 patients), convulsions (3 patients), sepsis (2 patients), and coronary artery disease (2 patients). The primary end point of the study, the mean dose of darbepoietin alfa at the time the hemoglobin value was ≥11.0 g/dl, was 63.6 ± 16.9 μg every other week. The mean darbepoetin alfa doses at baseline and during the last week of the study were 59.9 ± 15.8 and 51.6 ± 30.6 μg, respectively. Thus, the

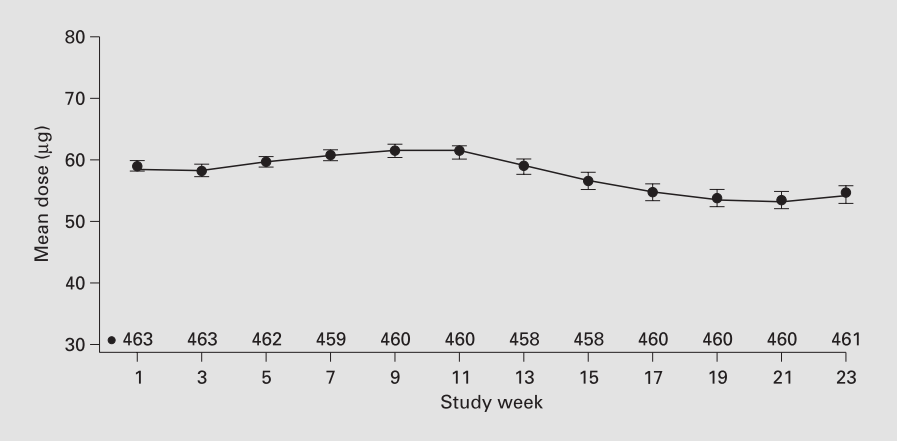

Fig. 2. Weekly darbepoetin alfa dose over time. Numerals above the study weeks indicate the number of patients with evaluable data. Vertical bars represent the SEM.

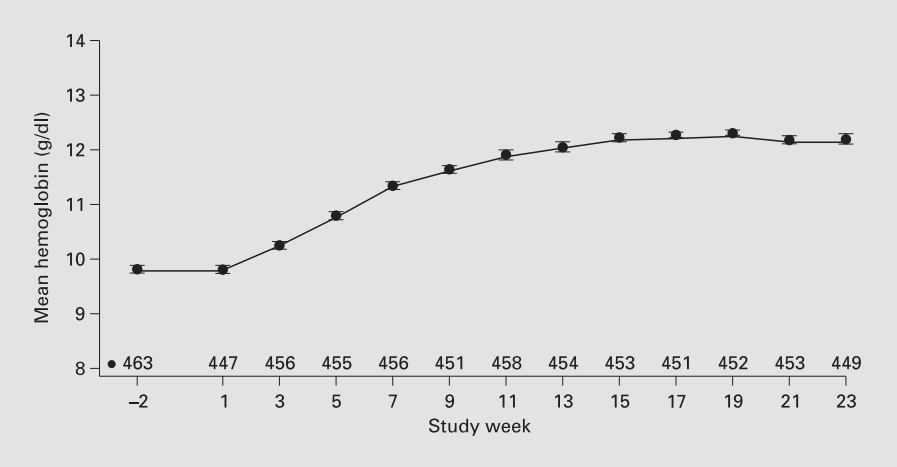

Fig. 3. Mean hemoglobin concentration over time. Numerals above the study weeks indicate the number of patients with evaluable data. Vertical bars represent the SEM.

mean darbepoetin alfa dose was relatively stable over the duration of the study (fig. 2). The mean time to reach the target range was 5.7 ± 4.5 weeks. The probability of achieving a hemoglobin response (estimated by life table analysis) reached 82% by week 11. The proportion of patients achieving the target hemoglobin level of 11.0–13.0 g/dl was 96% (95% CI: 94, 98). The hemoglobin values were maintained within the target range for the duration of the study (fig. 3). The mean change in hemoglobin concentrations between baseline and week 24 was 2.41 ± 1.24 g/dl (95% CI: 2.29, 2.52).

The mean rate of rise of the hemoglobin concentration ranged from 0.2 to 0.4 g/dl/week during the first 11 weeks of the study and from 0.0 to 0.1 g/dl for the duration of the study (fig. 4). Red blood cell transfusions were administered to 34 patients (5.7%). The mean number of transfusions administered was 1.9 ± 1.4. Most patients (3.2%) received a single transfusion; 1.3 and 1.2% of the patients received two or three transfusions, respectively.

The mean transferrin saturation measurements at baseline and at weeks 11, 23, and 25 were 28.1, 22.1, 26.7, and 25.4%, respectively. The mean ferritin levels at baseline and at weeks 11, 23, and 25 were 223.1, 123.3, 154.7, and 169.8 µg/l, respectively. Oral and intravenous iron was given to 60% and 16% of subjects respectively.

Darbepoetin alfa appeared to be safe and well tolerated in this study. At least one adverse event was reported for 505 of the patients (84%). Events reported with a frequency >5% were hypertension (24%), upper respiratory tract infection (10%), peripheral edema (9%), diarrhea (7%), renal failure (6%), and dizziness (6%). In general, these events were among those expected in a population of patients with chronic kidney disease. Seven patients (1.2%) died on study from comorbid conditions that were consistent with those expected for this study population. Laboratory tests did not change, apart from hemoglobin values and hematocrit, which would be expected with an

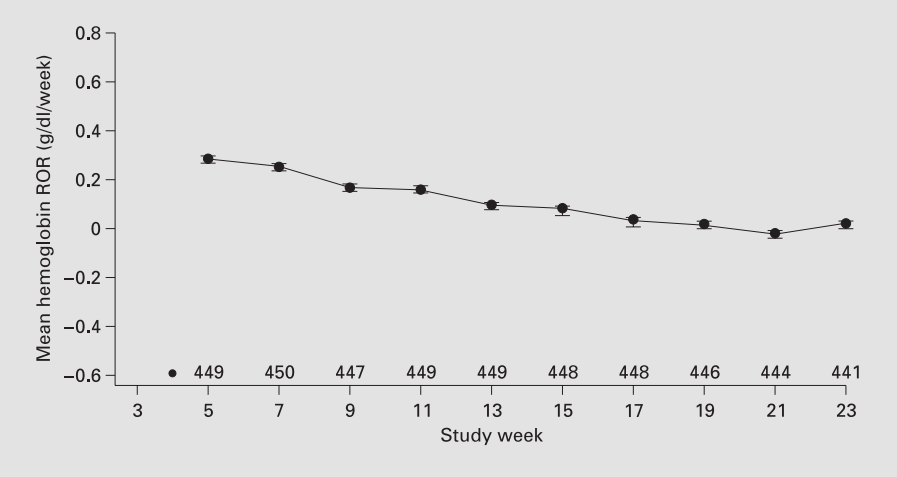

Fig. 4. Mean weekly hemoglobin rate of rise (Hb ROR) over time, calculated using a 4-week window. Numerals above the study weeks indicate the number of patients with evaluable data. Vertical bars represent the SEM.

erythropoietic agent. Blood samples taken before the first dose of darbepoetin alfa and at the end of study were negative for antibodies to erythropoietin in all patients.

Discussion

In this study, efficacy and safety of initiating treatment of anemia in rHuEPO-naive patients not on dialysis with once-every-other-week darbepoetin alfa administration were studied. The hemoglobin target level (11.0–13.0 g/dl) was achieved in 95% of the patients. The mean change in hemoglobin concentrations between baseline and week 24 was 2.41 ± 1.24 g/dl (95% CI: 2.29, 2.52). Red blood cell transfusions, which were administered to only 5.7% of all patients, were unlikely to have contributed substantially to this increase in hemoglobin.

The rate of rise of hemoglobin observed in this study was consistent with the rate of rise observed in other studies performed in patients with chronic kidney disease evaluating darbepoetin alfa administered once weekly [20] or every other week [23].

In general, the adverse events reported were representative of those seen in this patient population. No antibodies to erythropoietic protein were detected. These data indicate that darbepoetin alfa, administered once every other week, is highly effective and safe in correcting anemia in rHuEPO-naive patients with chronic kidney disease. Previous studies have shown that darbepoetin alfa is a safe and effective treatment for anemia in this patient population [20–22]. One other study [23] examined the efficacy and safety of once-every-other-week administration of darbepoetin alfa. In this paper, however, only 76 patients were studied. The large cohort of patients in our study confirms the utility of once-every-other-week administration of darbepoetin alfa for the correction and maintenance of hemoglobin in anemic patients with chronic kidney disease who are not receiving dialysis.

It is important to note that almost all patients received iron supplementation; however, the iron stores generally were well maintained in this study population, and oral iron administration appeared sufficient to maintain the iron stores for most patients.

A number of studies have shown that morbidity and mortality from cardiovascular disease are high in patients with chronic kidney disease [7, 10, 27, 28]. In addition, other data suggest that more patients with chronic kidney disease die than reach dialysis [29]. Other studies indicate that anemia is an independent risk factor for cardiovascular morbidity and mortality in this patient population [30, 31] and that treatment of anemia in these patients with rHuEPO may reduce the risk of cardiovascular disease [15, 16, 29, 31, 32]. These potential benefits of treating anemia on outcomes in patients with chronic kidney disease are not widely recognized. Moreover, no studies have demonstrated a survival benefit of correcting anemia in chronic kidney disease.

A number of studies have shown that while most patients who are undergoing dialysis receive rHuEPO, anemic patients with chronic kidney disease who are not receiving dialysis are treated with rHuEPO relatively infrequently [3, 17, 32]. The undertreatment of anemia in patients with chronic kidney disease who are not receiving dialysis may be due, in part, to the need for frequent injections of rHuEPO which makes treatment of anemia

difficult in the outpatient setting in which these patients are seen. The ability to treat anemia with less frequent administration of darbepoetin alfa may improve compliance with anemia treatment in patients not on dialysis by increasing convenience for the patients and their caregivers.

We conclude that darbepoetin alfa, when administered de novo once every other week in conjunction with either oral or intravenous iron, is safe and effective for the correction and maintenance of the hemoglobin concentration in anemic in patients with chronic kidney disease who are not receiving dialysis. The ability to achieve and maintain target hemoglobin concentrations with every-other-week administration of darbepoetin alfa is an important advance in the management of patients with renal anemia. Further clinical studies are in progress to determine if, in patients stable on darbepoetin alfa administered once every other week, administration can be extended further to once-monthly intervals.

Appendix

Additional Members of the United States, Canadian, and Australian Aranesp 990788 Study Group

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