Darbepoetin alfa administered once monthly maintains haemoglobin levels in stable dialysis patients

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Abstract

Background. Darbepoetin alfa, a glycoprotein that stimulates erythropoiesis by the same mechanism as endogenous erythropoietin, has a 3-fold longer terminal half-life than recombinant human erythropoietin, allowing for an extended dosing interval. Darbepoetin alfa is currently recommended for once-weekly and once every 2 weeks administration in patients with chronic renal failure (CRF). The objective of this study was to explore once-monthly administration in this patient population.

Methods. Clinically stable dialysis patients (mean haemoglobin concentration, 10.0–13.0 g/dl) receiving stable darbepoetin alfa therapy administered once every 2 weeks in a long-term treatment study were converted to darbepoetin alfa once every 3 weeks for 20 weeks and then, if haemoglobin concentrations were successfully maintained between 10.0 and 13.0 g/dl, were converted to darbepoetin alfa once every 4 weeks for 20 weeks. The darbepoetin alfa dose was titrated to maintain haemoglobin within a target range (−1.0 to +1.5 g/dl of baseline haemoglobin, and between 10.0 and 13.0 g/dl). Success with the extended dosing interval was defined as maintenance of mean haemoglobin ≥10.0 g/dl during a 4-week evaluation at the end of the dosing period.

Results. Of the 54 patients who entered the study, 38 patients were converted to darbepoetin alfa therapy administered once every 4 weeks. Of these, 36 patients were considered evaluable and 30 (83%) of those evaluable patients successfully maintained the target haemoglobin. For successful patients the mean (SD) haemoglobin during evaluation was 11.16 (0.60) g/dl, and the mean change in haemoglobin from baseline to evaluation was −0.26 g/dl (95% CI: −0.51, −0.01). The median change from baseline in average weekly darbepoetin alfa dose was 1.61 μg (95% CI: 0.00, 4.75). Adverse events were consistent with those expected for this patient population.

Conclusions. Darbepoetin alfa, administered once monthly, maintained haemoglobin effectively and safely in most dialysis patients stabilized previously on once every 2 weeks dosing. Once-monthly dosing may optimize anaemia management for patients with CRF and for health care providers.

Keywords: anaemia; Aranesp; chronic renal failure; dosing frequency; erythropoietin; novel erythropoiesis stimulating protein

Introduction

Anaemia is a common consequence of chronic renal failure (CRF) [1]. The impact of anaemia on the wellbeing of patients with kidney disease has long been recognized, causing symptoms of fatigue, dizziness and shortness of breath. Renal anaemia has been associated with cardiovascular complications including left ventricular hypertrophy [2] and congestive heart failure [3], reduced cognitive function and mental acuity [4], impaired quality of life [4,5] and the need for blood transfusions and their attendant risks.

The management of anaemia in CRF patients was transformed by the development of recombinant human erythropoietin (rHuEPO), which has been the mainstay therapy since its introduction more than a decade ago [6–8]. Treatment of anaemia in dialysis patients has been associated with improved quality of life [9], reduced hospitalizations [10] and reduced mortality [11]. To be effective, however, rHuEPO
Once-monthly administration of darbepoetin alfa in dialysis patients needs to be given as frequently as three times per week. This frequency of administration is a burden for both patients and health care providers.

Darbepoetin alfa is a unique erythropoietic protein that stimulates erythropoiesis by the same mechanism as endogenous erythropoietin and rHuEPO. Research indicates that the sialic acid-containing carbohydrate of rHuEPO determines its serum half-life and biological activity in vivo [12]. Recombinant HuEPO has three N-linked carbohydrate side chains, whereas darbepoetin alfa has five. The increased carbohydrate content of darbepoetin alfa delays drug clearance, thereby increasing serum half-life and biological activity when compared with rHuEPO. Darbepoetin alfa has been shown to have a serum half-life 3-fold longer than that of rHuEPO in dialysis patients, which allows for extended dosing intervals [13].

Darbepoetin alfa is available in the United States, Europe, Australia and Canada for the treatment of renal anaemia, based on studies demonstrating safety and efficacy with administration once-weekly or once every 2 weeks [14]. The objective of the current exploratory study was to investigate the possibility of once-monthly darbepoetin alfa administration in dialysis patients.

Subjects and methods

Patients

The study protocol was approved by the ethics committees of the participating dialysis centres. All patients gave written informed consent before any study-related procedures were performed.

Enrolled patients were selected from a previous long-term treatment study in which dialysis patients were receiving darbepoetin alfa once every other week. Eligibility criteria included a requirement that patients were on a stable dose of darbepoetin alfa (defined as being on the same prescribed dose/month ± 25% and same frequency and route of administration) administered intravenously or subcutaneously once every other week. Patients were required to be at least 18 years of age, have a mean baseline haemoglobin value of 10.0–13.0 g/dl, and serum ferritin ≥100 μg/l.

Patients with severe congestive heart failure (New York Heart Association Class III or IV), uncontrolled hypertension (pre-dialysis diastolic blood pressure > 100 mmHg), grand mal epilepsy, HIV, clinical evidence of uncontrolled hyperparathyroidism or systemic haematologic disease were excluded from the study, as were those scheduled for a living-related kidney transplant. Neither red blood cell transfusions nor major surgery were permitted within 12 weeks before the screening period.

Study drug

The darbepoetin alfa (Aranesp™, Amgen Inc., Thousand Oaks, California) used in this study is produced by recombinant DNA techniques and is expressed by cultured mammalian cells. Darbepoetin alfa was supplied in vials as a clear, colourless, sterile protein solution containing 20, 100, 500, 1000 or 1500 μg/ml protein.

Study design

This was a multicentre, open-label, exploratory study to evaluate the efficacy and safety of darbepoetin alfa therapy administered at an extended dosing interval for maintaining haemoglobin concentration in CRF patients receiving dialysis. Patients on stable darbepoetin alfa therapy administered once every 2 weeks were initially converted to darbepoetin alfa administered once every 3 weeks. The once every 3 weeks starting dose was determined by calculating the average weekly dose at the time of enrollment and multiplying by three. Patients remained on their current route of administration, either i.v. or s.c., for the duration of the study. After a 16-week dose titration period (to maintain haemoglobin concentration within −1.0 to +1.5 g/dl of the baseline value and between 10.0 and 13.0 g/dl), patients entered evaluation period 1 (weeks 17–20).

In patients whose mean haemoglobin remained ≥10.0 g/dl and ≤13.0 g/dl during evaluation period 1, the darbepoetin alfa dosing interval was further extended to once every 4 weeks. The once every 4 weeks starting dose was determined by calculating the average weekly dose administered during evaluation period 1 and multiplying by four. After a further 16-week dose titration period, patients entered evaluation period 2 (weeks 37–40).

Darbepoetin alfa dose was adjusted when two consecutive weekly haemoglobin values were outside the target range. Dose adjustments were made by ±25–50% of the baseline dose. If the haemoglobin concentration was still not within the target range after the weekly dose of darbepoetin alfa had been increased by 100%, the dosing interval was to be reduced, from 4 to 3 weeks or from 3 to 2 weeks, as appropriate. If serum ferritin levels decreased below 100 μg/ml, i.v. iron was administered according to the policy of each clinic to maintain iron levels above this minimum.

Adverse events and red blood cell transfusions were monitored throughout the study. Blood pressure was measured every 4 weeks. Blood samples were drawn every 12 weeks for serum albumin, creatinine, urea, serum ferritin levels and to screen for antibodies to erythropoietic proteins. A radioimmune precipitation (RIP) screening assay was used to detect seroreactivity to darbepoetin alfa. If specimens were reactive in the RIP screening, further testing was performed using a Biacore Immunoassay and a cell-based bioassay to confirm the presence of antibodies, and to determine whether they had neutralizing activity.

Study endpoints

The primary endpoint of this study was the percentage of patients who maintained a mean haemoglobin concentration ≥10.0 g/dl while receiving darbepoetin alfa at an extended dosing interval during evaluation period 1 (dosing once every 3 weeks) and evaluation period 2 (dosing once every 4 weeks). Secondary endpoints included the change in mean haemoglobin concentrations, the median change in the average weekly dose of darbepoetin alfa from screening/baseline to the evaluation periods for successful patients, and the assessment of safety variables.

Statistical analysis

The efficacy analysis for each evaluation period used a modified-intent-to-treat population (evaluable patients),
which included all patients who commenced darbepoetin alfa at the reduced frequency, but excluded patients who died or received a kidney transplant. The number and percentage of evaluable patients who successfully maintained haemoglobin (mean haemoglobin concentration \( \geq 10.0 \text{ g/dl} \)) during each evaluation period and the exact 95% confidence intervals (CIs) are presented. The mean change in haemoglobin (95% CI) from screening/baseline to each evaluation period for patients who successfully maintained haemoglobin is presented, along with the median change (95% CI from non-parametric approximation [15]) in average weekly dose of darbepoetin alfa.

Patients were considered evaluable for safety if they received at least one dose of darbepoetin alfa during the study. Adverse events are presented as the proportion of patients experiencing an event on one or more occasions (patient incidence). Descriptive statistics were used to summarize haemoglobin and haematocrit values at baseline and each study week; serum ferritin and blood pressure at baseline and every 4 weeks; and serum albumin, creatinine and urea at baseline and every 12 weeks.

Results

Patients

Fifty-four patients from Australia \( (n = 13) \), Austria \( (n = 2) \), Belgium \( (n = 10) \), France \( (n = 21) \), Germany \( (n = 7) \) and the UK \( (n = 1) \) were enrolled in this study and received darbepoetin alfa administered once every 3 weeks. This represented 39% of the patients who were maintained on once every other week dosing in the original study. Investigator and patient willingness to participate in this study, administrative issues and the eligibility criteria described previously were the only selection criteria applied to participate in this study.

The mean (SD) baseline haemoglobin concentration was 11.23 (0.75) g/dl, similar to the mean baseline haemoglobin concentration from the original study. The mean baseline dose for darbepoetin alfa was similar to that received by all patients on once every other week dosing in the original study. Demographic and baseline characteristics for patients on once every 3 weeks dosing \( (n = 54) \) and for patients who progressed to once every 4 weeks dosing \( (n = 38) \) are summarized in Table 1 and Figure 1.

Patient disposition and evalubility for the 54 patients are shown in Table 2. One patient died and was not evaluable for efficacy in the evaluation period, resulting in 53 patients who were evaluable for once every 3 weeks dosing.

Fifteen of the 53 patients did not progress to receive darbepoetin alfa once every 4 weeks for the following reasons (Table 2). Four patients had haemoglobin concentrations \( >13.0 \text{ g/dl} \) on once every 3 weeks dosing; four patients had haemoglobin concentrations \( <10.0 \text{ g/dl} \) on once every 3 weeks dosing; two patients increased dosing frequency per protocol at evaluation 1; two patients both had a haemoglobin concentration \( <10.0 \text{ g/dl} \) and increased dosing frequency per protocol; two patients were discontinued by investigators; and one patient chose to discontinue immediately after evaluation period 1. Thirty-eight patients received darbepoetin alfa once every 4 weeks. Two were not evaluable for efficacy in evaluation period 2, one due to death, the other because of renal transplant, resulting in 36 patients who were evaluable for once every 4 weeks dosing (Figure 1).

Efficacy of darbepoetin alfa

Percentage of patients who maintained haemoglobin concentration. During evaluation period 1, 44 of 53 evaluable patients \( (83\% \ [95\% \text{ CI}: 70\%, 92\%]) \) maintained a haemoglobin concentration \( \geq 10.0 \text{ g/dl} \) while receiving darbepoetin alfa once every 3 weeks.

Table 1. Patient demographic and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Once every 3 weeks dosing ( (n = 54) )</th>
<th>Once every 4 weeks dosing ( (n = 38) )</th>
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<tbody>
<tr>
<td>Sex ( (n)/% )</td>
<td>Male 34 (63%) 26 (68%)</td>
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<td></td>
<td>Female 20 (37%) 12 (32%)</td>
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<tr>
<td>Race ( (n)/% )</td>
<td>White 47 (87%) 34 (89%)</td>
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<td></td>
<td>Black 3 (6%) 2 (5%)</td>
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<tr>
<td></td>
<td>Other 4 (7%) 2 (5%)</td>
<td></td>
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<tr>
<td>Age (years) Mean (SD)</td>
<td>65.6 (15.8) 66.6 (16.2)</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/dl) Mean (SD)</td>
<td>11.23 (0.75) 11.33 (0.77)</td>
<td></td>
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<tr>
<td>Route of administration ( (n)/% )</td>
<td>I.v. 16 (30%) 9 (24%)</td>
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<tr>
<td></td>
<td>S.c. 38 (70%) 29 (76%)</td>
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<tr>
<td>Dialysis modality ( (n)/% )</td>
<td>Haemodialysis 50 (93%) 36 (95%)</td>
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<td></td>
<td>Peritoneal dialysis 4 (7%) 2 (5%)</td>
<td></td>
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<tr>
<td>Baseline dose of darbepoetin alfa (µg/week)</td>
<td>Median 15.00 15.00</td>
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<td></td>
<td>95% CI 11.50, 20.00 12.50, 24.00</td>
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Table 2. Reasons for lack of success in evaluable patients

<table>
<thead>
<tr>
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<th>Darbepoetin alfa</th>
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<tbody>
<tr>
<td></td>
<td></td>
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<tr>
<td>Once every 3 weeks dosing</td>
<td></td>
</tr>
<tr>
<td>Number of patients evaluable</td>
<td>53</td>
</tr>
<tr>
<td>Number of unsuccessful patients at evaluation 1</td>
<td>9  (17%)</td>
</tr>
<tr>
<td>Increased dosing frequency</td>
<td>2  (4%)</td>
</tr>
<tr>
<td>Haemoglobin &lt; 10.0 g/dl</td>
<td>5  (9%)</td>
</tr>
<tr>
<td>Increased dosing frequency and haemoglobin &lt; 10.0 g/dl</td>
<td>2  (4%)</td>
</tr>
<tr>
<td>Once every 4 week dosing</td>
<td></td>
</tr>
<tr>
<td>Number of patients evaluable</td>
<td>36</td>
</tr>
<tr>
<td>Number of unsuccessful patients at evaluation 2</td>
<td>6  (17%)</td>
</tr>
<tr>
<td>Increased dosing frequency</td>
<td>1  (3%)</td>
</tr>
<tr>
<td>Haemoglobin &lt; 10.0 g/dl</td>
<td>5  (14%)</td>
</tr>
<tr>
<td>Increased dosing frequency and haemoglobin &lt; 10.0 g/dl</td>
<td>0  (0%)</td>
</tr>
</tbody>
</table>
During evaluation period 2, 30 of 36 evaluable patients (83% [67%, 94%]) maintained a haemoglobin concentration ≥10.0 g/dl while receiving darbepoetin alfa once every 4 weeks. Reasons for non-success at both once every 3 week and once every 4 weeks dosing are presented in Table 2.

All patients, excluding those who died or received renal transplants, who were unsuccessful at maintaining their target haemoglobin concentration at the extended dosing interval (nine on once every 3 weeks dosing and six on once every 4 weeks dosing) were able to maintain the target haemoglobin concentration with a reduced dosing interval.

**Table 3.** Mean change in haemoglobin values and median change in darbepoetin alfa dose from baseline to evaluation period in successful, evaluable patients

<table>
<thead>
<tr>
<th></th>
<th>Once every 3 weeks</th>
<th>Once every 4 weeks</th>
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<tbody>
<tr>
<td>Mean haemoglobin (g/dl)</td>
<td>11.34 (0.76)</td>
<td>11.41 (0.79)</td>
</tr>
<tr>
<td>Average during evaluation (SD)</td>
<td>11.39 (1.07)</td>
<td>11.16 (0.6)</td>
</tr>
<tr>
<td>Change (95% CI)</td>
<td>0.05 (−0.26, 0.36)</td>
<td>−0.26 (−0.51, −0.01)</td>
</tr>
<tr>
<td>Median dose of darbepoetin alfa (µg/week)</td>
<td>15.00 (11.50, 20.00)</td>
<td>15.00 (10.00, 20.00)</td>
</tr>
<tr>
<td>Evaluation (95% CI)</td>
<td>17.19 (11.08, 20.75)</td>
<td>21.88 (12.00, 31.25)</td>
</tr>
<tr>
<td>Change (95% CI)</td>
<td>0.00 (−1.42, 0.43)</td>
<td>1.61 (0.00, 4.75)</td>
</tr>
</tbody>
</table>

*Evaluation 1.*  
*Evaluation 2.*

During evaluation period 2, 30 of 36 evaluable patients (83% [67%, 94%]) maintained a haemoglobin concentration ≥10.0 g/dl while receiving darbepoetin alfa once every 4 weeks. Reasons for non-success at both once every 3 week and once every 4 weeks dosing are presented in Table 2.

All patients, excluding those who died or received renal transplants, who were unsuccessful at maintaining their target haemoglobin concentrations at the extended dosing interval (nine on once every 3 weeks dosing and six on once every 4 weeks dosing) were able to maintain the target haemoglobin concentration with a reduced dosing interval.

**Mean change in haemoglobin concentrations.** There was no clinically significant change from baseline in mean haemoglobin concentrations when the darbepoetin alfa dosing interval was extended to once every 3 weeks and then to once every 4 weeks (Table 3 and Figure 2). During evaluation period 1 (dosing once every 3 weeks), the mean change in the average haemoglobin concentration from baseline to evaluation was 0.05 (95% CI: −0.26, 0.36) g/dl among the 43 successful patients. During evaluation period 2 (dosing once every 4 weeks), the mean change in average haemoglobin concentration was −0.26 (95% CI: −0.51, −0.01) g/dl among the 30 successful patients (Table 3).

**Median change in average weekly darbepoetin alfa dose.** The median change from baseline in average weekly darbepoetin alfa dose was 0.00 (95% CI: −1.42, 0.43) µg/week for those patients successful at evaluation period 1 and 1.61 (95% CI: 0.00, 4.75) µg/week for those patients successful at evaluation period 2, indicating that minimal or no dose increases were required to maintain haemoglobin at the extended dosing interval.

**Safety of darbepoetin alfa.** No differences were observed in the incidence or prevalence of adverse events between patients receiving once every 3 weeks and once every 4 weeks dosing. The most frequently reported adverse events were dyspnoea (17% patient incidence), arthralgia (15%), abdominal pain (13%), vomiting (13%), hypertension (11%), headache (11%) and bronchitis (11%). Only one serious adverse event...
(hypertension) was reported as related to treatment. Anti-hypertensive medication was initiated, and the serious adverse event resolved on therapy. No patients withdrew from study because of adverse events. Twelve patients (22%) had at least one red blood cell transfusion during the study; all transfusions were reported as associated with an adverse event, and none was considered related to darbepoetin alfa therapy. No clinically significant changes from baseline values were observed in clinical laboratory tests, including albumin, serum ferritin and blood pressure. Two deaths occurred during the study, one due to anorexia and the other to malnutrition. The deaths were not considered by the study investigators to be related to darbepoetin alfa. No anti-darbepoetin alfa antibodies were detected.

Discussion

Anaemia is a common problem for patients with CRF and is associated with a reduced quality of life and increased morbidity, hospitalizations and risk of mortality [16]. For more than a decade, rHuEPO has been the mainstay of anaemia management in CRF patients. However, rHuEPO has the disadvantage of requiring frequent administration (up to three times per week) due to its relatively short circulating half-life.

Darbepoetin alfa has a 3-fold longer half-life than rHuEPO [13], allowing for an extended dosing interval and simplified management of renal anaemia. The safety and efficacy of darbepoetin alfa have been demonstrated when given once weekly [14,17–19] and once every 2 weeks [14,18] to patients with anaemia associated with CRF. These studies have also shown that darbepoetin alfa may be administered both subcutaneously and intravenously with similar dosing requirements for both routes of administration. This is in marked contrast with rHuEPO where dose requirements for i.v. dosing are approximately one-third higher than for s.c. dosing [14,17,19]. Further studies have demonstrated the safety and efficacy of darbepoetin alfa administered once every 2 weeks for correction of anaemia in chronic renal insufficiency [20].

The goal of the current study was to determine if the darbepoetin alfa dosing interval could be further extended and still maintain haemoglobin concentrations above a therapeutic target of ≥10.0 g/dl in dialysis patients stabilized previously on darbepoetin alfa administered once every 2 weeks. Dialysis patients with haemoglobin concentration ≥10.0 g/dl while receiving darbepoetin alfa once every 2 weeks were converted initially to once every 3 weeks administration and then, if haemoglobin concentrations were successfully maintained, to once every 4 weeks administration. A mean haemoglobin concentration ≥10.0 g/dl was maintained in 44 of 53 evaluable patients (83%) receiving darbepoetin alfa once every 3 weeks and in 30 of 36 evaluable patients (83%) receiving darbepoetin alfa once every 4 weeks. Overall, there was minimal or no change in median dose requirements associated with less frequent administration at once every 3 weeks and once every 4 weeks.

The safety profile in patients receiving darbepoetin alfa once every 4 weeks was very similar to that observed in patients on the once every 3 weeks regimen, and both regimens were consistent with results reported previously in patients treated once weekly or once every 2 weeks [14,17–23]. Adverse events were consistent with those expected in a population of dialysis patients.

This exploratory study demonstrates that darbepoetin alfa, administered once monthly, maintains haemoglobin effectively and safely in most dialysis patients stabilized previously on once every 2 weeks dosing. Once-monthly dosing may optimize anaemia management for patients with CRF and for health care providers.
Once-monthly administration of darbepoetin alfa in dialysis patients

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