Correction of anaemia with darbepoetin alfa in patients with chronic kidney disease receiving dialysis

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Abstract

Background. Darbepoetin alfa is a new recombinant erythropoietic protein with a 3-fold longer half-life than recombinant human erythropoietin (rHuEpo). The optimal starting dose and frequency of administration of darbepoetin alfa were investigated for treating renal anaemia in dialysis patients.

Methods. Two multicentre, sequential dose-escalation studies examined the i.v. route of administration of darbepoetin alfa in haemodialysis patients (n = 75) and the s.c. route in peritoneal dialysis patients (n = 47). Patients were randomized to receive darbepoetin alfa at doses ranging from 0.075 to 0.75 μg/kg/week administered as either a once weekly or a three-times weekly injection. Patients achieving the primary endpoint of a ≥1 g/dl increase in haemoglobin after 4 weeks continued darbepoetin alfa for up to 52 weeks. Safety was assessed by adverse event reports, changes in laboratory values and vital signs, and antibody screening.

Results. Darbepoetin alfa produced dose-related increases in haemoglobin over the first 4 weeks of treatment in both studies. Two dose levels (0.45 and 0.75 μg/kg/week) increased the haemoglobin by ≥1 g/dl in 60–80% of patients, and no difference between once weekly and three-times weekly dosing was apparent. For patients who continued treatment up to 52 weeks, haemoglobin was maintained between 10 and 13 g/dl from mean baseline values of 8.4 and 8.7 g/dl. The adverse event profile was similar to that associated with rHuEpo therapy, and no antibodies to darbepoetin alfa were detected.

Conclusions. Darbepoetin alfa is safe and effective for the treatment of anaemia in dialysis patients. The optimal weekly starting dose is 0.45–0.75 μg/kg and once weekly dosing is possible for both the s.c. and i.v. routes of administration.

Keywords: anaemia; chronic kidney disease; darbepoetin alfa; dialysis; novel erythropoiesis stimulating protein

Introduction

Patients with chronic kidney disease frequently suffer from anaemia, which can significantly affect their morbidity, mortality and quality of life. For more than a decade, recombinant human erythropoietin (rHuEpo) has been available as an effective treatment for anaemia in these patients because of its ability to increase haemoglobin concentration, reduce the need for red blood cell transfusions and mitigate symptoms associated with this condition [1–3].

Although rHuEpo has proven highly effective in treating renal anaemia, administration two or three-times weekly is recommended for most patients because of its short circulating half-life [4–6]. Unless a patient receives a kidney transplant, treatment must continue indefinitely. The chronic nature of the disease and its treatment means that multiple weekly injections of rHuEpo may be inconvenient for both patients and healthcare providers.

Research has indicated that the sialic acid-containing carbohydrate of erythropoietin determines its serum half-life [7]. Darbepoetin alfa is a glycoprotein that was designed by introducing two extra consensus N-linked glycosylation sites. Consequently, darbepoetin alfa has five N-linked carbohydrate chains, compared with rHuEpo, which has only three. The increased carbohydrate content of darbepoetin alfa results in a terminal half-life in humans that is 3-fold longer than that of rHuEpo [8]. This novel pharmacokinetic profile offered the opportunity for reduced dosing frequency compared with rHuEpo.

Two multicentre, sequential dose-escalation studies were conducted to examine the efficacy of darbepoetin alfa for treating anaemia in patients with chronic kidney disease.
kidney disease who were receiving haemodialysis or peritoneal dialysis.

**Subjects and methods**

**Patients**

Patients were recruited from nine European and three Canadian dialysis units. The ethics committees of the participating centres approved the study protocol, and all patients gave written informed consent.

Patients aged 18–75 years with chronic kidney disease and receiving haemodialysis or peritoneal dialysis for at least 2 months before the first planned dose of study drug were enrolled. Other entry criteria included a haemoglobin concentration <10 g/dl on two consecutive occasions (at least 24 h apart) and no rHuEpo therapy within 3 months before the first planned dose of study drug. Exclusion criteria included uncontrolled hypertension (diastolic blood pressure >100 mmHg), congestive heart failure (New York Heart Association Class III or IV), haematological disorders that could exacerbate anaemia, systemic infection or inflammatory disease, severe secondary hyperparathyroidism, or any other disorders that could interfere with the response to darbepoetin alfa. Red blood cell transfusions to treat anaemia and androgen therapy were prohibited within 1 and 3 months of the study start, respectively.

**Study drug**

Darbepoetin alfa (Aranesp®, Amgen Inc., Thousand Oaks, CA) was supplied as a clear, colourless, sterile protein solution in vials containing 5, 20 and 100 μg/ml.

**Study design**

These two multicentre, randomized, sequential, dose-escalation studies had similar designs: both studies investigated the optimal dose and frequency of administration of darbepoetin alfa for the treatment of renal anaemia, in addition to the safety profile of the product. One study investigated intravenously administered darbepoetin alfa in patients receiving haemodialysis, and the other investigated subcutaneously administered darbepoetin alfa in patients receiving peritoneal dialysis.

All patients completed a screening period within 2–3 weeks before the first dose of study drug. Ten eligible patients were then to be randomized to receive the starting dose of darbepoetin alfa (0.075 μg/kg/week) administered either once weekly (n = 5) or three times weekly (n = 5). Subsequent dose cohorts were to be enrolled at dose levels of 0.225, 0.45, 0.75, 1.5 and 4.5 μg/kg/week until the optimal haemoglobin rate of rise was established. A Safety Monitoring Committee, comprising of study group members, reviewed data after each cohort had completed 4 weeks of study drug administration, and made the decision whether or not to escalate to the next dose level. Patients who achieved ≥1 g/dl increase in haemoglobin concentration after 4 weeks continued darbepoetin alfa treatment for up to 52 weeks. Those patients who did not achieve this increase were withdrawn from the study and, after a 30-day period, could be re-enrolled at a higher dose level. After the dose escalation was completed, additional patients were enrolled at effective dose levels to extend the experience with the study drug. Patients who experienced an excessive increase in haemoglobin concentration (i.e. >3 g/dl over any 4-week period) or a haemoglobin concentration >13 g/dl had their dose of darbepoetin alfa reduced to the next lowest level. If a patient’s haemoglobin concentration increased to >14 g/dl, the dose of darbepoetin alfa was withheld until the haemoglobin concentration decreased to <12 g/dl, and dosing was then restarted at the next lowest dose level. After week 16, if the patient’s haemoglobin concentration was <10 g/dl, the dose could be increased by 25% increments to maintain haemoglobin values within the range of 10–13 g/dl.

To ensure an adequate supply of iron to support the erythropoietic response to darbepoetin alfa, patients with a screening serum ferritin level <200 μg/l received 200 mg of i.v. iron 2 weeks before the first dose of darbepoetin alfa. If the serum ferritin was <200 μg/l at any time during the study, 200 mg iron was administered intravenously every 2 weeks until the serum ferritin was >200 μg/l. Patients could also receive oral iron therapy throughout the study period.

**Study endpoints**

The primary endpoints of both studies were: the haemoglobin rate of rise over the initial 4 weeks of treatment; the haemoglobin value at 16 weeks of treatment; and the safety profile of darbepoetin alfa in this patient population. Safety was assessed by summarizing reports of adverse events. All adverse events were grouped according to body systems affected and by the preferred term within the body system, according to a modified World Health Organisation adverse reaction term (WHOART) dictionary. The secondary safety endpoints were changes in vital signs and laboratory measurements (including haematocrit, red blood cell count and reticulocyte count), changes in dose, serum darbepoetin alfa levels and antibody formation to darbepoetin alfa.

**Statistical analysis**

All patients who received at least one dose of study drug were included in the analyses of efficacy and safety. Patients were analysed according to the dose level and schedule assigned at randomization, irrespective of the dose and schedule they actually received. Patients who re-entered the study after withdrawal due to an insufficient increase in haemoglobin concentration were included in the efficacy analysis set at each of the dose-by-schedule combinations to which they were randomized.

The presence of a dose-by-schedule interaction was investigated with analysis of variance using an α = 0.1 (10%) level of significance for the primary endpoint (i.e. haemoglobin rate of rise over the initial 4 weeks of therapy). All other significance tests used the α = 0.05 (5%) level of significance. All tests were carried out against a two-sided alternative hypothesis. No adjustment was made for multiple comparisons. For all statistical comparisons, the treatment difference was estimated and an associated 95% confidence limit calculated.

Descriptive statistics were summarized for all endpoints by treatment group. For safety endpoints, summary statistics were tabulated by dose-by-schedule combination. If appropriate, data were pooled across dose schedule, and summary statistics were generated.
Results

Patient demographics

A total of 122 patients were randomized into the two studies between January 1997 and March 1999: 75 patients to receive darbepoetin alfa by the i.v. route, and 47 by the s.c. route (Table 1). The Safety Monitoring Committee recommended dose escalation until the 0.75 μg/kg/week dose cohort was completed in both studies, and all subsequent patients were enrolled at a dose level of either 0.45 or 0.75 μg/kg/week to gain further clinical experience at these doses. Three patients in the i.v. darbepoetin alfa study were withdrawn from study before receiving the first dose of study drug, and a further six patients re-entered the study once. Therefore, the i.v. dosing study had 78 patient-exposures to darbepoetin alfa. Nine patients receiving s.c. darbepoetin alfa re-entered the study once, and one patient re-entered twice. Therefore, the s.c. dosing study had 58 patient-exposures to darbepoetin alfa.

A total of 31 patients withdrew from study (22 for i.v. darbepoetin alfa; nine for s.c. darbepoetin alfa). The main reasons for withdrawal were failure to attain a haemoglobin response with the lower initial doses of darbepoetin alfa, receipt of a kidney transplant, patient request to withdraw, and death.

Efficacy evaluation

Haemoglobin rate of rise over initial 4 weeks. The results of both studies indicate a dose-related increase in haemoglobin concentration over the first 4 weeks of darbepoetin alfa treatment (Figure 1). This increase was statistically significant in both studies (P = 0.029 for patients receiving i.v. darbepoetin alfa; P = 0.003 for patients receiving s.c. darbepoetin alfa). No difference was apparent between the haemoglobin response for the two dose schedules (once weekly and three-times weekly). The proportion of patients achieving a haemoglobin response over the first 4 weeks was 60–80% with darbepoetin alfa administered at doses of 0.45 to 0.75 μg/kg/week, and 0–40% with the lower doses (0.075 and 0.225 μg/kg/week).

Haemoglobin values throughout the study. After the first 4 weeks of the study, patients’ haemoglobin values progressively increased from a mean baseline value of 8.4 g/dl in patients receiving i.v. darbepoetin alfa and 8.7 g/dl in patients receiving s.c. darbepoetin alfa, reaching a plateau of 11–13 g/dl at 16 weeks (Figure 2). After this time, haemoglobin was maintained between 10 and 13 g/dl for up to 52 weeks (Figure 3).

Safety. For patients receiving i.v. darbepoetin alfa, 67 of 72 patients (93%) experienced at least one adverse

Table 1. Baseline demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Mode of dialysis</th>
<th>i.v. administration (n=75)</th>
<th>s.c. administration (n=47)</th>
</tr>
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<tbody>
<tr>
<td>Sex (n%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>26 (35%)</td>
<td>24 (51%)</td>
</tr>
<tr>
<td>Men</td>
<td>49 (65%)</td>
<td>23 (49%)</td>
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<tr>
<td>Race (n%)</td>
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<tr>
<td>White</td>
<td>61 (81%)</td>
<td>39 (83%)</td>
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<td>Black</td>
<td>6 (8%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (7%)</td>
<td>5 (11%)</td>
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<tr>
<td>Other</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>55.4 (14.7)</td>
<td>53.7 (15.2)</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>Mean (SD)</td>
<td>8.4 (1.0)</td>
</tr>
<tr>
<td>Ferritin (μg/l)</td>
<td>Mean (range)</td>
<td>8.7 (1.1)</td>
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<tr>
<td>Mean (range)</td>
<td>319 (18–1400)</td>
<td>356 (69–1201)</td>
</tr>
<tr>
<td>PTH (pmol/l)</td>
<td>Median (range)</td>
<td>12.0 (0.7–160.3)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>Median (range)</td>
<td>6.0 (1.0–52.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.7 (0.8–105.0)</td>
</tr>
</tbody>
</table>
event during the study, most of which were mild to moderate in severity. The most frequently reported adverse events were hypotension (35%), vomiting (33%), headache (28%) and myalgia (28%). Most of these events were attributable to concurrent medical conditions and were consistent with those expected in this patient population. Thrombosis of the vascular access and hypertension were the most frequently reported treatment-related adverse events (7 and 6%, respectively).

For patients receiving s.c. darbepoetin alfa, 45 of 47 patients (96%) experienced at least one adverse event during the study, most of which were mild to moderate in severity. The most frequently reported adverse events were peritonitis (32%), peripheral oedema (30%), injection site pain (30%) and hypertension (30%). These events were typical of those expected in this patient population. Injection site pain and hypertension were the most frequently reported treatment-related adverse events (30 and 17%, respectively).

In general, no difference in the adverse event profile appeared to be attributable to dose cohort assignment or time on study, and no apparent increase in the incidence of adverse events with increased haemoglobin rate of rise was observed. Four patients died on study (three receiving i.v. darbepoetin alfa and one receiving s.c. darbepoetin alfa). All of the deaths were considered by the study investigators to be related to concurrent illness and not to the study drug.

For both the i.v. dosing and the s.c. dosing studies, mean values for vital signs did not change and no clinically meaningful changes in laboratory values were evident. The mean serum ferritin remained well above 100 µg/l throughout the studies, i.e. above the level recommended in the European Best Practice Guidelines [6] and the National Kidney Foundation Dialysis Outcomes Quality Initiative (DOQI) Guidelines [9] for maintenance of adequate iron stores.

No patient in either the i.v. dosing or the s.c. dosing study required a change in dose because of an adverse event. In patients who had their doses of darbepoetin alfa withheld due to a haemoglobin concentration > 14 g/dl, the haemoglobin decreased progressively after discontinuation of study drug, and was < 12 g/dl by week 5 for patients receiving i.v. therapy and <12 g/dl by week 8 for patients receiving subcutaneous therapy (Figure 4). Most of the patients who required dosing of darbepoetin alfa to be withheld were in the 0.75 µg/kg/week dose group (5/7 patients receiving i.v. therapy and 6/7 patients receiving s.c. therapy).

Patients’ serum was screened for antibodies to darbepoetin alfa using a radio-immunoprecipitation assay at regular intervals before, during and after administration of study drug, and all were negative.

Serum darbepoetin alfa levels
Weekly serum trough concentrations of darbepoetin alfa were determined by ELISA throughout the study. Minimal accumulation of the drug was found, with no statistically significant difference in serum levels over time. At weeks 12, 24, 36 and 48, mean serum concentrations were 1.07, 0.58, 1.49 and 0.38 ng/ml.
appeared to be in the range of 0.45–0.75 g/dl. Treatment, and the optimally effective starting dose of darbepoetin alfa was temporarily stopped, there was a steady decline in haemoglobin over the following 5–8 weeks. Interestingly, this decrease in haemoglobin was similar for both i.v. and s.c. administration, suggesting that the rate of decline is determined by destruction of circulating red blood cells rather than by drug clearance.

Further randomized studies examining the correction of renal anaemia with darbepoetin alfa compared with rHuEpo have subsequently been conducted. The first of these was in patients with chronic kidney disease not yet requiring dialysis, i.e. chronic renal insufficiency [16], and the second was in chronic kidney disease patients requiring dialysis [17]. The starting dose of darbepoetin alfa in both of these studies was 0.45 μg/kg administered once weekly. The results demonstrated that darbepoetin alfa could safely and effectively increase and maintain haemoglobin concentration within the target range of 11–13 g/dl at a reduced dose frequency relative to rHuEpo.

Two further randomized, comparative studies have examined the effect of switching dialysis patients from rHuEpo to darbepoetin alfa [18,19]. Patients on twice or three times weekly rHuEpo were converted to once weekly darbepoetin alfa, and patients on once weekly rHuEpo were converted to darbepoetin alfa once every other week. In the control group, patients carried on their rHuEpo dosing at either once, twice or three times weekly. In both studies, the mean haemoglobin remained stable throughout the study, and there was no significant difference between the treatment groups. The majority of patients (>95%) were able to maintain the reduced dose frequency of darbepoetin alfa throughout the study. The safety profile of darbepoetin alfa was similar to that of rHuEpo. An additional non-comparative study of over 700 dialysis patients has confirmed the ability of darbepoetin alfa to maintain haemoglobin levels at a reduced dosing frequency over a treatment period of 1 year [20].

The data from the studies reported in this paper, along with the other studies described above, confirm the efficacy and safety of darbepoetin alfa as an erythropoietic agent. As the secondary benefits of rHuEpo therapy (in terms of improved quality of life, increased well-being, increased exercise capacity and improved cardiac function) are related to correction of anaemia rather than to the drug itself, it is reasonable to assume that similar secondary benefits would occur with darbepoetin alfa. In serial screening tests, no antibodies against darbepoetin alfa have been detected in this study or any of the other reported studies.

In conclusion, darbepoetin alfa is safe and effective for the treatment of anaemia in patients with chronic kidney disease receiving dialysis. The optimum weekly starting dose appears to be in the range of 0.45–0.75 μg/kg, and once weekly dosing is possible for both
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the i.v. and s.c. routes of administration. The potential for a reduced dosing frequency of darbepoetin alfa may have significant advantages for both the patient and the healthcare worker, with a decrease in the number of injections required.

Contributors

In addition to the authors, the NESP 960245/246 Study Group comprised the following members and institutions (in alphabetical order): J. Bargman (Toronto General Hospital, Toronto, Canada), P. Barre (Royal Victoria Hospital, Montreal, Canada), G. A. Coles (Cardiff Royal Infirmary, Cardiff, UK), R. Gokal (Manchester Royal Infirmary, Manchester, UK), K. Jindal (Queen Elizabeth Hospital, Halifax, Canada), R. Richardson (Toronto General Hospital, Toronto, Canada), J. Walls (Leicester General Hospital, Leicester, UK), C. Tomson (Southmead Hospital, Bristol, UK), A. P. Maxwell (Belfast City Hospital, Belfast, UK), C. Winearls (The Churchill, Oxford, UK).

Acknowledgements. Barbara Jenkins, RN, Victoria Piccard, RN, Dylan Rosser, BSc and Annette Lloyd, RN assisted with the conduct of the study. Claire Fulton, MSc and John Kirkpatrick, MSc assisted with the statistical analysis of the trial results. Breege Traynor, RN and Mary Daly, RN were responsible for the safety monitoring of the trial. William Cobb, PhD and MaryAnn Foote, PhD, assisted with the writing of the manuscript.

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Received for publication: 30.4.02
Accepted in revised form: 28.10.02