Treatment of anaemia in dialysis patients with unit dosing of darbepoetin alfa at a reduced dose frequency relative to recombinant human erythropoietin (rHuEpo)

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Abstract

Background. Darbepoetin alfa is an erythropoietic agent with a 3-fold longer elimination half-life than recombinant human erythropoietin (rHuEpo), which allows less frequent dosing. This study investigated the safety and efficacy of darbepoetin alfa for treating anaemia in dialysis patients, using a dosing regimen that was independent of the patient’s body weight (unit dosing).

Methods. Dialysis patients (n=341) maintained on rHuEpo treatment (alfa or beta) were switched to darbepoetin alfa at a reduced dosing frequency, but by the same route of administration [intravenous (i.v.) or subcutaneous (s.c.)]. Patients receiving rHuEpo two or three times weekly changed to once-weekly darbepoetin alfa, and those receiving rHuEpo once weekly changed to once every other week darbepoetin alfa. The unit doses of darbepoetin alfa (10–150 μg) were titrated to maintain haemoglobin concentrations within 1.0 and 1.5 g/dl of the individual mean baseline haemoglobin and between 10 and 13 g/dl for 24 weeks.

Results. Mean change in haemoglobin from baseline to the evaluation period (weeks 21–24) was 0.13 g/dl (95% CI, 0.01, 0.25), which was not clinically relevant. An analysis by route of administration revealed that mean haemoglobin concentrations within 1.0 and +1.5 g/dl of the individual mean baseline haemoglobin and between 10 and 13 g/dl for 24 weeks.

Conclusions. The treatment of renal anaemia in dialysis patients with unit doses of darbepoetin alfa effectively and safely maintains target haemoglobin concentrations with less frequent dosing. Darbepoetin alfa was well tolerated.

Keywords: darbepoetin alfa; dose requirements; intravenous; renal anaemia; subcutaneous; unit dosing

Introduction

Due to its specific pharmacokinetic characteristics, darbepoetin alfa significantly differs from recombinant human erythropoietin (rHuEpo) in a number of critical aspects [1]. As it has a longer elimination half-life [2], darbepoetin alfa can be administered less frequently than rHuEpo while still maintaining the same level of erythropoietic efficacy both in dialysis patients [3–9],
and in patients with chronic renal insufficiency not yet requiring dialysis [10,11]. Moreover, it has been shown that, in contrast to rHuEpo, there is no difference in intravenous (i.v.) and subcutaneous (s.c.) dose requirements for darbepoetin alfa [8,12]. This observation is significant, since currently it has been common practice in Europe to administer rHuEpo by the s.c. route to haemodialysis (HD) patients for economic reasons, and in these patients the i.v. route of administration would otherwise be the route of choice.

It is currently recommended that the initial dose of darbepoetin alfa be determined on a μg/kg body weight basis, and then dose adjustments be based on ±25% of the initial dose [1]. As darbepoetin alfa is provided as prefilled syringes, corresponding to unit doses ranging from 10 to 150 μg, this study assessed the efficacy and safety of unit dosing at a reduced dosing frequency for maintaining haemoglobin concentrations within a defined target range in dialysis patients.

Subjects and methods

This multicentre, open label, single-arm study in 343 patients with end-stage renal disease (ESRD) evaluated the effectiveness of unit doses of darbepoetin alfa administered either i.v. or s.c. for the treatment of renal anaemia. The study design is presented schematically in Figure 1. Clinically stable ESRD patients (≥18 years of age) with mean haemoglobin concentrations between 10 and 13 g/dl, receiving HD or peritoneal dialysis (PD) for at least 6 months were recruited from 19 European dialysis centres. The study protocol required that patients were receiving a stable dose of rHuEpo (alfa or beta) given once, twice or three times weekly i.v. or s.c., for at least 8 weeks prior to entry to the study. To ensure adequate iron stores for supporting erythropoiesis, entry criteria specified that serum ferritin had to be ≥100 μg/l or transferrin saturation ≥20%.

Patients were excluded if they had: NYHA class III or IV congestive heart failure, uncontrolled hypertension (defined as a predialysis diastolic blood pressure ≥110 mmHg during the screening period), evidence of uncontrolled hyperparathyroidism, treatment for grand mal epilepsy, haematological, inflammatory, or infectious conditions that might interfere with the erythropoietic response, or had red blood cell transfusions within the 12 weeks before screening. Pregnant or lactating females were also excluded.

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

After an initial 3-week screening/baseline period, patients receiving rHuEpo were switched to darbepoetin alfa at a reduced dosing frequency using the same route of administration. Patients receiving rHuEpo once weekly changed to darbepoetin alfa once every other week, and patients receiving rHuEpo twice or three times weekly changed to darbepoetin alfa once weekly. The initial dose of darbepoetin alfa was based on the rHuEpo dose at the time of entry into the study, using a formula equating the peptide mass of the two molecules (200 IU rHuEpo = 1 μg darbepoetin alfa, e.g. 6000 IU rHuEpo = 30 μg darbepoetin alfa) [1]. Human serum albumin (HSA)-free darbepoetin alfa was available for administration at the following unit doses: 10, 15, 20, 30, 40, 50, 60, 80, 100, 130 or 150 μg. A period of 20 weeks (weeks 1–20) after the first dose of darbepoetin alfa was used for

![Fig. 1. Study design.](image-url)
dose-titration and stabilization of haemoglobin. This was followed by a 4-week evaluation period (weeks 21–24) during which efficacy end-points were assessed.

The primary efficacy end-point was the change in haemoglobin between baseline and the evaluation period. Secondary end-points included dose and frequency of darbepoetin alfa administered during the study. Safety variables assessed the nature, frequency, severity, relation to treatment, and outcome of all adverse events. Laboratory parameters and darbepoetin alfa seroreactivity were also monitored.

Darbepoetin alfa dosing was adjusted to maintain each patient’s haemoglobin concentration within a target range of −1.0 to +1.5 g/dl of the mean baseline haemoglobin, and between 10 and 13 g/dl throughout the 24-week study period. If a patient’s haemoglobin fell below target range on two consecutive assessments, the dose of darbepoetin alfa was increased to the next higher unit dose. Conversely, if a patient’s haemoglobin increased above target range on two consecutive assessments, then the dose of darbepoetin alfa was decreased to the next lower unit dose. Any change in dose was one step up or down in the list of provided unit doses. Intravenous iron supplementation was administered according to individual dialysis unit policy to maintain serum ferritin \( \geq 100 \mu g/l \).

Statistical analysis

The primary efficacy analysis compared the mean change in haemoglobin concentration between the baseline and evaluation periods. Based on a previous darbepoetin alfa study [8], where a standard deviation of 0.8 g/dl was observed, it was estimated that a sample size of 350 patients, with a 90% power and a 5% significance level, would allow a detection of a change in haemoglobin concentration between baseline and a period 21–24 weeks later, of more than 0.14 g/dl.

Summary statistics (mean or geometric mean, median, SD, and range for continuous variables, and number and percentage of subjects in each category for categorical variables) are presented for all efficacy and safety end-points. Two-sided confidence intervals (CI) are presented for all efficacy analyses.

Exploratory analyses of prognostic factors relating to haemoglobin made adjustments for frequency, route and dose of rHuEpo at study entry, screening/baseline haemoglobin concentration and modality of dialysis.

An intent-to-treat (ITT) analysis was chosen for the analysis of efficacy, and safety was analysed in all patients who received a dose of darbepoetin alfa. 343 patients were included in the ITT efficacy analysis and 341 in the safety analysis. The ITT population consisted of all patients assigned a study number. The safety population consisted of all patients in the ITT population who received at least one dose of darbepoetin alfa. All statistical analyses were performed with the SAS System Version 8.2.

Results

343 patients were recruited into the study. Two patients withdrew prior to the administration of darbepoetin alfa (both lost to follow-up), thus 341 dialysis patients were converted from rHuEpo to darbepoetin alfa treatment. Baseline characteristics and demography for this patient population were similar regardless of route of administration (Tables 1 and 2). Most patients were on HD \((n = 329; 96\%)\), with only a few receiving PD \((n = 14; 4\%)\). At baseline, 119 (35%) were receiving rHuEpo [alfa \((n = 51; 31\%); beta \((n = 68; 38\%)\)] three times a week, and 147 (43%) were receiving rHuEpo [alfa \((n = 70; 42\%); beta \((n = 77; 44\%)\)] twice a week. Only 77 (22%) patients were receiving rHuEpo [alfa \((n = 45; 27\%); beta \((n = 32; 18\%)\)] once a week. There were more patients receiving rHuEpo s.c. \((n = 267; 78\%)\) than i.v. \((n = 76; 22\%)\). At baseline, patients’ median weekly dosing requirements of rHuEpo were higher (33%) by the i.v. than by the s.c. route of administration (90.0 vs 67.7 IU/kg, respectively). The mean haemoglobin concentration at baseline was 11.2 g/dl.

313 (91%) patients completed the 20-week dose titration period, and 310 (90%) completed the evaluation period to week 24. 343 patients were included in the ITT efficacy analysis set, and 341 in the safety analysis set. Over the 24-week study period, 33 patients discontinued treatment for the following reasons: death during study (16, one further death occurred after withdrawal, but within the 30 day study follow-up period), kidney transplantation (6), adverse event (5), lost to follow up (3), withdrawal requested (3). Discontinuations were for reasons expected for this type of patient population. This is discussed further in the analysis of safety. Patient disposition is summarized in Figure 2.

Both i.v. and s.c. darbepoetin alfa effectively maintained haemoglobin concentrations throughout the study, and mean haemoglobin concentrations were above 11 g/dl throughout the evaluation period (Figure 3).

There was no clinically significant mean change in haemoglobin from baseline to the evaluation period [0.13 g/dl (95% CI: 0.01, 0.25)]. Analysis of the data revealed a difference between the i.v. and s.c. darbepoetin alfa routes of administration for mean haemoglobin concentration. The administration of darbepoetin alfa by the i.v. route resulted in higher mean haemoglobin concentrations at steady state than was observed after s.c. darbepoetin alfa (Figure 4).

Following i.v. administration, mean haemoglobin

<table>
<thead>
<tr>
<th>Table 1. Patient demography</th>
<th>Darbepoetin alfa ((n = 343))</th>
<th>i.v. ((n = 76))</th>
<th>s.c. ((n = 267))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47 (62%)</td>
<td>139 (52%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>29 (38%)</td>
<td>128 (48%)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>74 (97%)</td>
<td>264 (99%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)*</td>
<td>61.4 (± 15.0)</td>
<td>63.0 (± 14.8)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>63.9 (± 12.4)</td>
<td>67.1 (± 15.1)</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Mean (± SD).</td>
<td></td>
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</tbody>
</table>
concentrations during the evaluation period had increased by 0.58 g/dl (95% CI, 0.33, 0.82) compared with baseline. In contrast, there was no change in the mean haemoglobin concentration from baseline to the evaluation period following s.c. administration (0.00 g/dl, 95% CI, 0.13, 0.13). With regard to frequency of administration, the mean change in haemoglobin from baseline to the evaluation period was 0.11 g/dl (95% CI, −0.03, 0.24) in patients receiving the drug once a week, and 0.19 g/dl (95% CI, −0.06, 0.44) in patients receiving darbepoetin alfa once every other week, further confirming that darbepoetin alfa is effective in maintaining haemoglobin concentrations at reduced frequencies of administration.

Table 2. Patient baseline characteristics

<table>
<thead>
<tr>
<th>Cause of renal failure</th>
<th>Darbepoetin alfa (n = 343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>i.v. (n = 76)</td>
</tr>
<tr>
<td>Other</td>
<td>22 (29%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (17%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>Unknownc</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Urological</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Dialysis modality</td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>76 (100%)</td>
</tr>
<tr>
<td>PD</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Time since first dialysis (months)a</td>
<td>34.7 (16.6, 92.2)</td>
</tr>
<tr>
<td>Baseline rHuEpo (IU/kg/week)a</td>
<td>90.0 (55.0, 130.7)</td>
</tr>
<tr>
<td>Frequency of rHuEpo</td>
<td></td>
</tr>
<tr>
<td>Once per week</td>
<td>27 (36%)</td>
</tr>
<tr>
<td>Twice per week</td>
<td>26 (34%)</td>
</tr>
<tr>
<td>Three times per week</td>
<td>23 (30%)</td>
</tr>
<tr>
<td>Baseline Hb concentration (g/dl)b</td>
<td>11.3 (± 0.7)</td>
</tr>
<tr>
<td>Serum ferritin (µg/l)c</td>
<td>489.5 (313.3, 777.0)</td>
</tr>
</tbody>
</table>

3Median (quartiles); bMean (± SD); cUnknown category includes 'suspected' unconfirmed causes.

Screening/baseline patients = 343

IV rHuEPO = 76 patients
1x/week = 27 (36%) patients
2x/week = 26 (34%) patients
3x/week = 23 (30%) patients

Allocated IV darbepoetin alfa = 76
1x/week = 49
1x/every other week = 27

20 week dose titration (weeks 1-20)(n=76)
1x/week = 49
1x/every other week = 27

4 week evaluation (weeks 21-24)(n=72)
1x/week = 47
1x/every other week = 25

SC rHuEPO = 267 patients
1x/week = 50 (19%) patients
2x/week = 121 (45%) patients
3x/week = 96 (36%) patients

Allocated SC darbepoetin alfa = 267
1x/week = 217
1x/every other week = 50

20 week dose titration (weeks 1-20)(n=265)
1x/week = 213
1x/every other week = 51
1x/every three weeks = 1

4 week evaluation (weeks 21-24)(n=241)
1x/week = 190
1x/every other week = 50
1x/every three weeks = 1

Fig. 2. Patient disposition.
Investigation of the mean weekly darbepoetin alfa dosing requirements by route of administration during the evaluation period revealed that relative to baseline, i.v. dosage requirements decreased (25.2 to 21.5 µg, \( P = 0.004 \)), while s.c. dosage requirements increased slightly from baseline to the evaluation period (20.8 to 22.7 µg, \( P = 0.014 \)). However, at a time when steady state is expected to be reached, the mean dose of study drug was not different in both the i.v. and s.c. treatment groups (Figure 5). The ratio (95% CI) of i.v. to s.c. darbepoetin alfa doses was 1.21 (1.05, 1.40) at baseline reflecting the higher i.v. rHuEpo dose requirements at the time that patients switched to darbepoetin alfa. At evaluation, the ratio was 0.95 (0.78, 1.14), indicating that overall, the administered doses by the i.v. and s.c. routes were not different. The percentage change in dose requirements from baseline to the evaluation period in all patients, regardless of route of administration, was not significant (2.31%, 95% CI, −3.73, 8.73). However, when analysed by route of administration, there was a significant decrease in i.v. dose requirements (−17.3%, 95% CI, −27.1, −6.1), and a significant, but not considered clinically relevant, increase in weekly s.c. dose requirements (8.9%, 95% CI, 0.8, 16.6).

Analysis of s.c. dose requirements by baseline haemoglobin concentration revealed that a number of patients entering the study had sub-optimal haemoglobin concentration while receiving s.c. rHuEpo. Subcutaneously treated patients (\( n = 116 \)) with a baseline haemoglobin <11.0 g/dl experienced a significant adjusted mean haemoglobin increase of 0.45 g/dl (95% CI, 0.13, 0.77) following darbepoetin alfa treatment, which was accompanied by a significant increase in mean weekly dose requirements of 13.6% (95% CI, 2.7, 25.7). However, in s.c.-treated patients whose baseline haemoglobin concentration was \( \geq 11.0 \) g/dl (\( n = 151 \)), there was no significant change in adjusted mean haemoglobin (0.26 g/dl, 95% CI, −0.58, 0.06) and no significant change in weekly dose (5.3%, 95% CI, −4.0, 15.5). In contrast, i.v. patients (\( n = 29 \)) with a baseline haemoglobin <11.0 g/dl experienced an adjusted mean haemoglobin increase of 1.01 g/dl (95% CI, 0.53, 1.48) following darbepoetin alfa treatment, which was accompanied by a decrease in mean weekly dose requirements of −13.7% (95% CI, −34.0, 12.9). Similarly, in i.v.-treated patients (\( n = 47 \)) whose baseline haemoglobin concentration was \( \geq 11.0 \) g/dl, there was also an increase in adjusted mean haemoglobin of 0.4 g/dl (95% CI, −0.01, 0.8) that was accompanied by a decrease in weekly dose requirements of −19.5% (−28.9, −8.7).

Fig. 3. Mean (±SD) haemoglobin concentration over time by route of administration.

Fig. 4. Change in (95%) haemoglobin concentration between baseline and the evaluation period by route of administration.
The frequency of darbepoetin alfa administration during the evaluation period was also evaluated. One hundred per cent (68/68) of patients completed the evaluation period on dosing once every second week. Ninety-seven per cent (234/242) completed the evaluation period on once-weekly dosing. Moreover, 75% (236/313) did not require a dose change during the evaluation period, and a further 20% (62/313) required only one dose change.

Safety

HSA-free darbepoetin alfa was well tolerated in this study. The overall safety data for this study were consistent with that expected for a population of ESRD patients undergoing dialysis. Overall, 78% of patients reported an adverse event. The most commonly occurring events were hypotension (22%), hypertension (18%) and myalgia (17%). Twenty-nine patients (9%) experienced one or more adverse events that the investigator reported as being possibly related to darbepoetin alfa treatment. Consistent with the approved labelling for darbepoetin alfa, these included mild and transient injection-site pain (5%), mostly following the first s.c. administration; hypertension (2%) and headache (1%). Analyses of the adverse event profile by age, sex, dialysis modality, baseline haemoglobin concentration, and administration route revealed no notable differences in the incidence rates for any of these subgroups.

Five patients (1%) withdrew from the study due to adverse events (pulmonary oedema, hypertensive encephalopathy, hypertension and pulmonary oedema, erythema multiforme, pruritus and urticaria), and there were 17 deaths (5%) over the duration of the study. One death from a cerebrovascular accident in an 87-year-old male with a history of cardiac disease was reported as possibly related to study drug because of an elevated haemoglobin concentration at the time of death. There were no changes in clinical laboratory data associated with darbepoetin alfa treatment and no antibody formation was observed in any patient.

Mean transferrin saturation was 30% at baseline and was maintained above 20% throughout the study. Median serum ferritin was 436 µg/l at baseline and was maintained above 100 µg/l throughout the study (422 µg/l at week 24). Therefore both parameters were above the level recommended in the European Best Practice Guidelines [13] and the National Kidney Foundation DOQI Guidelines [14] for maintenance of adequate iron stores. Mean systolic and diastolic blood pressure were stable, and there was little change in the use of antihypertensive medications throughout the study.

Discussion

The results of this study demonstrate that unit dosing of darbepoetin alfa in stable dialysis patients can effectively and safely maintain haemoglobin concentrations within the recommended target range after switching from rHuEpo (alfa or beta) to darbepoetin alfa at reduced dose frequency.

Mean haemoglobin concentrations were maintained above 11 g/dl throughout the evaluation period, regardless of route, and frequency of administration. It is of note that i.v. darbepoetin alfa administration resulted in a higher increase in haemoglobin concentration compared with s.c. darbepoetin alfa. Following i.v. administration, there was an increase in haemoglobin of ~0.6 g/dl relative to baseline, which was, moreover, associated with a decrease of i.v. weekly
dose requirements of over 17%. While overall s.c. weekly dose requirements increased over the study period, this appears to be due to the fact that patients with baseline haemoglobin concentrations $<11.0$ g/dl were sub-optimally controlled while being treated with s.c. rHuEpo. The dose of s.c. darbepoetin alfa was subsequently increased in these patients over the course of the study, and this was associated with a haemoglobin increase of almost 0.5 g/dl. In contrast, in patients with a haemoglobin concentration above 11 g/dl and treated by the s.c. route, no change in haemoglobin concentration, or in darbepoetin alfa dose was observed from baseline to the evaluation period. Moreover, regardless of Hb category at baseline ($<11.0$, $\geq 11.0$ g/dl), following i.v. administration there was an increase in Hb concentration that was associated with a decrease in weekly dose requirements. The observation that i.v. and s.c. darbepoetin alfa dose requirements were not different at evaluation, results mainly from the decrease in i.v. dose requirements during the course of the study. This contrasts markedly with the previous decade of experience with rHuEpo.

The randomized cross-over study by Kaufman et al. [15] confirmed a number of previous reports, and demonstrated that dose requirements for rHuEpo when administered i.v. are approximately one-third higher than for s.c. dose requirements in order to maintain a similar haemoglobin concentration. In the present study, at baseline there was an $\sim 30\%$ higher dose of rHuEpo by the i.v. route compared with the s.c. route. However at evaluation, no such dosing difference is evidenced for darbepoetin alfa. This observation may be due to the longer circulating half-life of the molecule relative to that of rHuEpo. The terminal elimination half-life of darbepoetin alfa is 25.3 h following i.v. administration and 48.8 h by the s.c. route [2], whereas that of rHuEpo has been shown to be 8.5 h by the i.v. route, and from historical data to be in the range of 16–24 h by the s.c. route [2]. It has been hypothesized that a minimal threshold concentration of an erythropoietic agent is required to be maintained during a significant period of the dosing interval for effective erythropoiesis [16]. Given that the ratio of the i.v. to s.c. elimination half-life is higher for darbepoetin alfa than for rHuEpo, serum concentrations following i.v. administration would remain above the threshold for the stimulation of erythropoiesis for a proportionally longer time period of the dose interval by the i.v. route for darbepoetin alfa as compared with rHuEpo, and for a period of time which would lead to a pharmacodynamic response comparable to that obtained after the same dose of s.c. darbepoetin alfa. Thus, the pharmacokinetic characteristics of darbepoetin alfa may explain why there is no difference in dose requirements for the i.v. and the s.c. routes of administration.

The observation that i.v. and s.c. darbepoetin alfa requirements are not different in the present non-randomized study is consistent with the results from previous randomized [8] and non-randomized [5,12] studies. The clinical implications of these findings with darbepoetin alfa are of practical clinical significance, and could lead to changes in the management of renal anaemia. It has been common practice in Europe to administer rHuEpo by the s.c. route to HD patients essentially for economic reasons, as there is a demonstrated-dose-sparing effect. Using darbepoetin alfa by the i.v. route in HD patients may provide improved outcomes as compared with i.v. rHuEpo. These data also suggest that this can be achieved within the recommendations of the European Best Practice Guidelines for target haemoglobin concentrations in the treatment of renal anaemia [13]. Furthermore, the ability to dose patients less frequently with darbepoetin alfa may have economic implications for healthcare providers, especially in relation to reduced nursing time, and not withstanding the improved convenience for the patients. It is anticipated that future studies will address these issues.

In conclusion, this study indicates that renal anaemia treatment with unit doses of darbepoetin alfa in dialysis patients can effectively and safely maintain haemoglobin concentrations with either once-weekly or once every other week administration. In common with a previous darbepoetin alfa trial in dialysis patients, i.v. and s.c. dose requirements were not different. Clinically, i.v. darbepoetin alfa may provide improved outcomes over i.v. rHuEpo, at a reduced frequency of administration, and with the advantage of sparing patients the discomfort of repetitive s.c. injections. The results of this study suggest that darbepoetin alfa, given once weekly or once every other week is an effective therapy for ESRD patients on HD.

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