

Original Article

Effectiveness of weekly darbepoetin alfa in the treatment of anaemia of HIV-infected haemodialysis patients*

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Abstract

Background. Anaemia is aggravated by the coexistence of chronic kidney disease (CKD) in patients infected with human immunodeficiency virus (HIV). Darbepoetin alfa effectively alleviates CKD-associated anaemia with less frequent dosing than recombinant human erythropoietin (EPO). The current study aimed to determine the efficacy, safety and cost-effectiveness of darbepoetin alfa compared with erythropoietin alfa (EPO-alfa) for treatment of anaemia in HIV-infected subjects receiving haemodialysis.

Methods. An open label, single arm, prospective study of 12 haemodialysis subjects with HIV infection was conducted for a duration of 6 months after switching from intravenous (i.v.) EPO-alfa two/three times weekly to i.v. darbepoetin alfa once weekly. The primary end point was the proportion of patients maintaining haemoglobin (Hb) levels ≥ 11 g/dl while a weekly dose of darbepoetin alfa was a secondary end point.

Results. Darbepoetin alfa, as effectively as EPO-alfa maintained the proportion of the subjects having Hb levels ≥ 11 g/dl at an average weekly dose of 40.60 μ g compared with an equivalent dose of 51.84 μ g for EPO-alfa. Antiretroviral therapy and HIV infection stage remained the same for each specific patient throughout the study period, including the last 6 months of EPO-alfa therapy. No difference in the incidence of adverse effects was observed after switching from EPO-alfa to darbepoetin alfa.

Conclusions. Lower doses of darbepoetin alfa at extended dosing interval is as safe and effective as EPO-alfa for treating anaemia, suggesting that darbepoetin alfa is a more cost-effective therapeutic alternative to EPO-alfa in the management of anaemia associated with HIV infection in subjects receiving haemodialysis.

Keywords: anaemia; chronic kidney disease; darbepoetin alfa; erythropoietin alfa; human erythropoietin; human immunodeficiency virus

Introduction

Anaemia is the most common haematological abnormality associated with human immunodeficiency virus (HIV) infection, affecting the majority of the infected patients, depending on the severity of their disease [1,2]. The degree of anaemia correlates with mortality in HIV patients, independent of immunological and virological parameters such as CD4⁺ lymphocyte count and the HIV-viral load [3]. Furthermore, correction of anaemia reduces the mortality, independent of the immunological or virological status of HIV patients [3]. With the recent success of highly active antiretroviral therapy (HAART), increased attention is being paid to improving the duration and the quality of life in people with HIV infection. In addition to negatively impacting the well-being of patients, anaemia can serve as an early clue to the presence of nutritional deficiency, opportunistic infection or occult malignancy. Identifying such conditions at an earlier stage and instituting appropriate therapy may improve outcomes [3].

The pathogenesis of anaemia associated with HIV-infection is complex and multifactorial, involving direct effects of HIV on erythroid precursors, presence of opportunistic infections and a multitude of adverse effects associated with antiretroviral therapy [3]. Establishing the cause or causes of anaemia, therefore, presents a challenge in HIV-infected individuals. Furthermore, the magnitude of the effect of viral infection on worsening anaemia is not well characterized, and the relative contribution of HIV-infection to anaemia, in concert with other factors that affect response to treatment with recombinant human erythropoietin (EPO), is unknown [4]. The coexistence of chronic kidney disease (CKD) with HIV-infection aggravates anaemia and increases resistance to the

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action of EPO [4]. EPO is safe and at large doses alleviates anaemia of HIV-infected patients with end-stage renal disease who undergo haemodialysis [4,5].

Darbepoetin alfa is a newer erythropoiesis stimulating agent, with demonstrated efficacy and safety in the treatment of anaemia associated with CKD at a reduced dosing frequency compared with EPO [6–9]. Furthermore, several studies have demonstrated that haemodialysis patients treated with EPO require lower equivalent doses when switched to darbepoetin alfa [9,10]. As the global costs of treating HIV-infected patients with concomitant CKD requiring haemodialysis are very high, cost-effective therapy alternatives with similar efficacy to EPO are desirable for the treatment of their anaemia. Therefore, this current study was undertaken to determine the efficacy, safety and cost-effectiveness of darbepoetin alfa administered intravenously (i.v.) once weekly instead of i.v. EPO-alfa administered two/three times weekly for the treatment of anaemia in HIV-infected subjects who were currently undergoing haemodialysis (12 subjects) in our hospital. To the best of our knowledge, this is the largest European study of its kind performed in a single centre.

Patients and methods

Subjects

Twelve haemodialysis subjects with HIV infection were included in this study. The average age of the study subjects was 46.75 ± 10.6 years (maximum 61; minimum 27); seven subjects were black (58%) and five Caucasian (42%); eight had HIV-1 infection and the remaining four were infected with HIV-2. The average time period since HIV infection diagnosis was 4.45 ± 2.76 years (maximum 10.75; minimum 1.32). According to the 1993 CDC revised classification of HIV infection, five subjects met the criteria for AIDS, being in the following stages: A3 ($n=1$), C1 ($n=1$), C2 ($n=2$) and C3 ($n=1$). The HIV infection stages of the remaining study subjects were B2 ($n=4$), B1 ($n=2$) and A1 ($n=1$) [11].

Ten patients were under HAART. The two remaining subjects were not treated with any kind of anti-HIV therapy. In one case no such therapy was considered necessary and the other refused it against expert medical opinion.

The aetiologies of their CKD were HIV-associated nephropathy ($n=2$), reflux nephropathy ($n=1$), autosomic dominant polycystic kidney disease ($n=1$), hypertension ($n=1$), analgesic nephropathy ($n=1$), renal aspergillosis ($n=1$), oxalosis ($n=1$) and unknown ($n=4$).

Study design

This was an open label, single arm and prospective study, with 6-month duration, undertaken after switching from i.v. EPO-alfa two/three times weekly to i.v. darbepoetin alfa once weekly. Inclusion criteria were adult subjects (≥ 18 years) on haemodialysis for at least 6 months with regular EPO-alfa treatment, documented HIV infection, stable haemoglobin (Hb) levels of at least 10 g/dl, adequate iron stores with transferrin saturation $\geq 20\%$ and ferritin

serum levels >150 ng/ml. Of the 12 patients, two were treated with EPO-alfa twice weekly and the remaining 10 were on a three times weekly schedule. The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the independent Ethics Committee of Hospital de Santa Cruz. All subjects signed a written informed consent prior to enrolment.

Treatment protocol

The initial weekly dose of darbepoetin alfa was equivalent to the weekly dose of EPO-alfa administered during the last month before the switch. The conversion formula of $1 \mu\text{g}$ darbepoetin alfa = 200 IU EPO was used to equate the protein mass of the two molecules [12].

The first 16 weeks of the study were considered as the dose adjustment period, during which the Hb levels were kept between -1.5 and $+1.5$ of the basal values and always in the range of 10–13 g/dl. Darbepoetin alfa dose adjustments were made every 4 weeks with a 25% increment if Hb levels were 1.5 g/dl below or above the basal values. The treatment protocol also specified withdrawal of darbepoetin alfa should the Hb levels rise above 14 g/dl. In such situations, darbepoetin alfa administration was resumed only after a documented Hb value below 13 g/dl and with a subsequent 25% reduction in its dose. The treatment protocol allowed administration of packed red blood cells if clinically justified. All patients were treated with i.v. iron sucrose, and the doses were adjusted monthly to maintain adequate iron stores (serum ferritin between 200 and 800 ng/ml). Iron availability was also monitored using transferrin saturation with target values above 20%. The last 8 weeks of the study were considered as the evaluation period. The same protocol in the dose adjustment period was used to modify darbepoetin alfa dose during the evaluation period.

End points

The primary end points were the average Hb levels and the proportion of subjects that maintain an Hb level ≥ 11 g/dl during the evaluation period, as recommended by the *European Best Practice Guidelines* (EBPG) [13]. The weekly dose of darbepoetin alfa was considered as a secondary end point. Additional secondary end points included average ferritin concentrations, CD4^+ T lymphocyte count, HIV-viral load, dialysis adequacy (Kt/V), C-reactive protein (CRP) levels and the average parathyroid hormone (PTH) intact levels.

Adverse effects

During the 6-month darbepoetin alfa therapy, the subjects were assessed at each dialysis session for possible adverse effects of the drug, namely hypertension, number of hypotensive episodes, incidence of infections (opportunistic or others), myalgia, nausea and diarrhoea.

Statistical analysis

The proportion of the subjects who reached the target Hb level ≥ 11 g/dl during the last 2 months of EPO-alfa was calculated and compared with the proportion of patients

with Hb ≥ 11 g/dl during the evaluation period. The mean \pm SD of Hb levels 6 months prior to the initiation of darbepoetin alfa administration (baseline) and during the evaluation period were also calculated. The average weekly doses [confidence interval (CI) of 95%] of EPO-alfa during the last 2 months prior to darbepoetin alfa therapy were calculated and compared with the average weekly doses (95% CI) of darbepoetin alfa during the evaluation period. The Hb levels during the evaluation period were compared with the baseline values. Figure 1 shows the ratio of the dose of erythropoiesis stimulating agent (ESA) to the Hb level throughout the study.

The statistical differences were analysed using the paired *t* Student or the Wilcoxon signed ranks test for continuous variables with or without a normal distribution, respectively. Similar methods were used to establish statistical significance for the differences observed in other selected variables. A value of $P < 0.05$ was considered to be statistically significant. The SPSSTM (*Statistical Package for the Social Sciences*) version 13.0 was used for the statistic calculations.

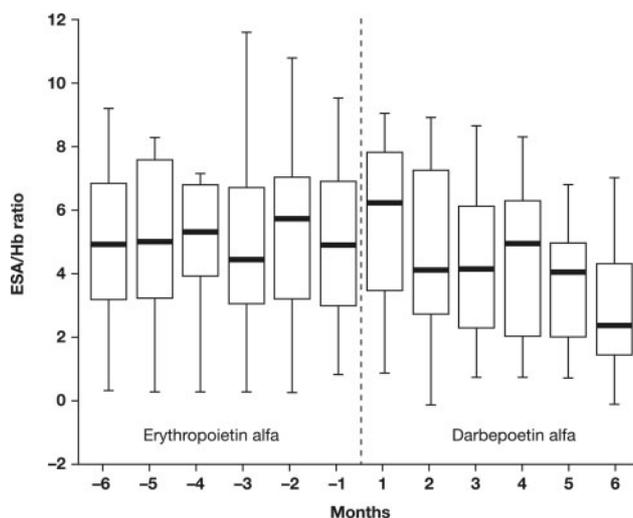


Fig. 1. Ratio of dose of ESA to Hb level throughout the study.

Results

End points

During the evaluation period of darbepoetin alfa therapy, all subjects reached the target Hb level ≥ 11 g/dl, as recommended by the EBPG, in comparison with only nine subjects (75%) in the last 2 months of EPO-alfa therapy prior to switching to darbepoetin alfa. The mean Hb levels were 11.69 ± 1.01 g/dl during the EPO-alfa therapy and 12.32 ± 1.02 g/dl during the evaluation period of darbepoetin alfa therapy (Table 1).

The average weekly dose (95% CI) of darbepoetin alfa was $40.60 \mu\text{g}$ (26.90; 61.28) whereas that of EPO-alfa was 10 368 U (6318; 17 016), corresponding to a darbepoetin alfa equivalent dose of $51.84 \mu\text{g}$. The difference between the doses of EPO-alfa and darbepoetin alfa was statistically significant ($P = 0.02$). No statistically significant differences were observed in other selected secondary end points between the evaluation and the baseline periods (Table 1).

The average weekly doses of i.v. iron sucrose were 91.67 ± 35.89 mg during the EPO-alfa period and 95 ± 23.16 mg during the darbepoetin alfa evaluation period ($P = \text{NS}$). There were also no significant differences in the average ferritin concentrations or average transferrin saturation (28 vs 31%) between both periods.

Adverse effects

The incidence of adverse effects of darbepoetin alfa, as contemplated in the surveillance protocol of the study, was similar to that registered for the treatment with EPO-alfa. No subject needed blood transfusions during the period of darbepoetin alfa therapy. There were no changes in the antiretroviral drug regimen or HIV stage during the dose adjustment or evaluation periods of the study and they remained equal to those documented during baseline.

Table 1. Comparison of darbepoetin alfa therapy with erythropoietin alfa for treatment of anaemia in HIV-infected subjects receiving haemodialysis

Study end points	EPO-alfa	Darbepoetin alfa	P-value
Primary end points			
Haemoglobin concentration (mean \pm SD)	11.69 ± 1.10 g/dl	12.32 ± 1.02 g/dl	NS
Subjects achieving haemoglobin level ≥ 11 g/dl n (%)	9 (75%)	12 (100%)	NS
Secondary end points			
EPO-alfa dose, mean (CI 95%)	10 368 u/week (6318; 17 016)	–	–
Darbepoetin alfa dose, mean (CI 95%)	–	$40.60 \mu\text{g}/\text{week}$ (20.90; 61.28)	–
Darbepoetin equivalent dose (1 μg darbepoetin = 200 IU EPO)	$51.84 \mu\text{g}/\text{week}$	$40.60 \mu\text{g}/\text{week}$	0.02
Ferritin (mean \pm SD)	448 ± 302 ng/ml	509 ± 311 ng/ml	NS
PTH (intact) (mean \pm SD)	678 ± 651 pg/ml	554 ± 637 pg/ml	NS
Kt/V (mean \pm SD)	1.32 ± 0.24	1.39 ± 0.46	NS
C-reactive protein (mean \pm SD)	1.18 ± 2.66 mg/dl	1.25 ± 3.11 mg/dl	NS
CD4 ⁺ count (mean \pm SD)	331 ± 180 cel/mm ³	305 ± 195 cel/mm ³	NS
HIV viral load [median (max; min)]	50 (10 ² ; 50)	50 (10 ² ; 50)	NS

Discussion

The findings of this study demonstrate that lower doses of i.v. darbepoetin alfa at less frequent dosing can, as effectively and safely as i.v. EPO-alfa, maintain Hb levels within the EBPG recommended target range in HIV-infected subjects receiving haemodialysis.

Due to its pharmacokinetic characteristics, darbepoetin alfa significantly differs from EPO. The terminal elimination half-life of darbepoetin alfa is 25.3 h following i.v. administration whereas that of EPO is 8.5 h [14]. Due to its longer elimination half-life, darbepoetin alfa can be administered less frequently than EPO while still maintaining the same level of erythropoietic efficacy both in haemodialysis patients and in patients with chronic renal insufficiency not yet requiring haemodialysis [6,8,15]. In addition to an extended dosing frequency, our findings in HIV-infected subjects requiring haemodialysis demonstrate that a 22% lower dose of darbepoetin alfa is adequate to maintain Hb levels in the range recommended by the EBPG [13].

It is noteworthy that the number of subjects reaching the target Hb level of ≥ 11 g/dl was 25% higher during the evaluation period of darbepoetin alfa therapy than the last 2 months of the treatment with EPO-alfa. This difference, however, did not reach statistical significance.

Regarding the dose reduction of the ESA observed after the switch, it is important to discuss the administration route. Compared with the i.v. route, the subcutaneous (s.c.) administration of EPO-alfa allows the use of lower doses maintaining adequate Hb levels, while darbepoetin alfa apparently maintains the same efficacy regardless of the administration route [8,16]. Therefore, it is possible that a comparison between s.c. EPO-alfa and i.v. darbepoetin alfa does not produce a dose reduction of the magnitude observed in the present study. However, the i.v. route may be preferable in the HIV-infected haemodialysis population not only because of patient comfort and convenience but also because the s.c. route is, at least theoretically, potentially associated with a higher risk of parenteral exposure of healthcare personnel to HIV compared with i.v. administration during the haemodialysis session. On the other hand, that same risk is expected to rise as the frequency of weekly administrations also increases, underlining the benefit of having an ESA that maintains its efficacy with a lower frequency of administration.

The other aspect relevant to the discussion of the observed dose reduction is the conversion factor used. Although 200 IU of EPO contain the same peptic mass as 1 μ g of darbepoetin alfa, it is true that some studies have shown that a fixed ratio of 200:1 is not necessarily predictive of an adequate conversion between the two molecules [17]. Therefore, the difference observed in the doses of the two erythropoiesis stimulating agents may not have been of the

reported magnitude if we had used a different conversion factor.

However, the treatment of anaemia in HIV-infected patients receiving haemodialysis is of economic significance. Given that, using the 200:1 conversion factor, lower doses of darbepoetin alfa were adequate for maintaining Hb levels in the EBPG recommended range and considering that the cost of 1 μ g of darbepoetin alfa is the same as 200 IU of EPO throughout the European Union, darbepoetin alfa therapy appears to be more economical than the treatment with EPO-alfa in this group of patients. Similarly, less frequent dosing of anaemia treatment, as is possible with darbepoetin alfa, may decrease healthcare costs especially in relation to reduced nursing time. Possible confounding factors related to HIV positive status, specifically HIV infection stage, HIV viral load and the type of antiretroviral therapy was similar before and after the switch of the erythropoietic molecules.

Therefore, our findings suggest that darbepoetin alfa is a more cost-effective therapeutic alternative to EPO-alfa in treating anaemia of HIV positive patients receiving haemodialysis over a wide spectrum of HIV infection stages including AIDS.

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Conflict of interest statement. Dr Fernando Carrera is a scientific consultant to Amgen (Europe). The other authors have declared no conflicts of interest.

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