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Switching from darbepoetin alfa to epoetin beta: results following an administrative switch in a single centre in Portugal

Fernando Carrera, Lino Oliveira

Dialysis Unit, Eurodial, Leiria, Portugal.

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ABSTRACT

The rationale for administering erythropoiesis-stimulating agents to patients with kidney disease-related anaemia is well established. The present study aimed to explore clinical outcomes and management of patients switched from darbepoetin alfa to epoetin beta.

This single-centre, retrospective, observational, cohort study involved adult haemodialysis patients at Eurodial in Leiria, Portugal, who, for administrative reasons, were all switched from intravenous darbepoetin alfa once a week to intravenous epoetin beta three times per week. The treatment goal was to maintain haemoglobin levels at >11 and ≤13 g/dL. Data were collected retrospectively for up to fourteen months: seven months before switching, and up to seven months afterwards.

Following the switch from darbepoetin alfa, 74 patients received at least one dose of epoetin beta and were included in the full analysis set. Mean values were calculated for all haemoglobin levels recorded during the final two months of the treatment period for each erythropoiesis-stimulating agent i.e. the two months before switching to epoetin beta (Evaluation Period P1) and the sixth and seventh months afterwards (Evaluation Period P2). The mean haemoglobin levels in the two evaluation periods were both 11.4 g/dL, with standard deviations of 1.0 and 1.2 g/dL, respectively (observed data).

The geometric mean weekly dose of erythropoiesis-stimulating agent was 17.8 µg/week (95% confidence interval 13.32, 23.79) in Evaluation Period 1 and 20.9 µg/week (95% confidence interval 16.37, 26.68) in Evaluation Period 2 (full analysis set, observed data). The median percentage dose change was -14.3%, although the quartile values (Q1, Q3 -43.8, 50.0%) showed the percentage change to be highly variable.

Mean haemoglobin levels could be maintained within the desired range using both darbepoetin alfa and epoetin beta, but it was not possible to draw conclusions relating to relative amounts of the two drugs required to achieve this, because of the variability of the dose data.

Key-Words:
Anaemia; chronic kidney disease; darbepoetin alfa; epoetin beta; erythropoiesis-stimulating agent; haemodialysis.

INTRODUCTION

The rationale for administration of erythropoiesis-stimulating agents (ESAs) to patients with kidney disease-related anaemia has become well established over the last twenty years, since epoetins first received a licence for clinical use. The last thirteen years have seen the publication of several sets of

guidelines produced by nephrology societies describing the use of ESAs[1-5]. The guidelines also recommend the best haemoglobin (Hb) targets that patients should achieve in terms of clinical outcomes and resource utilisation.

Current consensus is that intravenous (IV) administration of ESAs is the preferred route for patients receiving haemodialysis (HD). IV administration at the end of the dialysis treatment in patients receiving HD has the benefits of causing less patient discomfort and requiring less nursing time than subcutaneous (SC) administration. When using epoetins, the optimal administration interval is two to three times a week (using the IV route). When using darbepoetin alfa, this interval is once a week; it can even be extended effectively to once every other week in the maintenance phase[6], as we were the first to show in a previous study that demonstrated IV darbepoetin alfa administered once every two weeks to be an effective regimen in routine clinical practice[7].

Comparative studies between ESAs may aid clinicians in choosing the most appropriate option for anaemia management in the individual patient[8]. In 2008, all patients with chronic kidney disease (CKD) undergoing HD at Eurodial in Leiria, Portugal, were switched from darbepoetin alfa to epoetin beta at the same time. The switch was driven by administrative decisions and no other ESAs were prescribed.

This study describes the results of all patients receiving HD only three times a week, on the Monday/Wednesday/Friday shifts, attended always by the same two nephrologists (Fernando Carrera and Lino Oliveira) during the entire study period. The dialysis sessions lasted four hours each, and there was no change in target Hb levels or the dialysis format (conventional HD, Fresenius dialysis machines, Fresenius polysulfone membranes) throughout the study period. All patients went from IV darbepoetin alfa once a week to the equivalent weekly dose of epoetin beta, given intravenously three times a week.

This provided an unbiased source of information on the clinical management of subjects switched from darbepoetin alfa to epoetin beta. The data collected on these patients, in the pre- and post-switch periods, provide a valuable opportunity to investigate dose requirements and other parameters of anaemia management in the real-life setting following such a switch. The aim of this study was to explore the clinical outcomes and clinical management of patients in whom ESA therapy was switched from darbepoetin alfa to epoetin beta.

Since the 2001 launch of darbepoetin alfa for clinical use, several studies have documented the differences found in switching from epoetins to this new ESA[9-15]. Interestingly, to date there are only three reports of switching from darbepoetin alfa to an epoetin[16-18]. The switching studies show dose savings with darbepoetin alfa.

PATIENTS AND METHODS

This single-centre, retrospective, observational, cohort study included all adult patients undergoing HD at Eurodial in Leiria, Portugal, and switched from darbepoetin alfa once weekly to epoetin beta three times per week in April 2008. As previously mentioned, all patients in this study were under the care of the same two nephrologists (FC and LO), and were undergoing dialysis three times per week (on Mondays, Wednesdays and Fridays) for a mean duration of four hours per session, with no change in the dialysis format throughout the study. The goal of ESA treatment was to keep Hb levels at >11 and ≤13 g/dL, which accorded with the guidelines under which the patients had previously been treated.

Data were collected retrospectively for each patient for a maximum of fourteen months: seven months prior to the switch, and up to seven months post switch (Fig. 1). Required data were transcribed at the dialysis unit from medical records into a spreadsheet designed to clearly label the time periods and parameters to which the data points referred. The information collected included demographic data, patient characteristics (vascular access type, aetiology of CKD, start date of HD, body weight), dose data, Hb levels, use of iron therapy and measures of iron levels (transferrin saturation [TSAT] and serum ferritin), use of red blood cell (RBC) transfusions, laboratory data (Kt/V and levels of C-reactive protein [CRP], parathyroid hormone [PTH], albumin, and total protein), and death and cause of death.

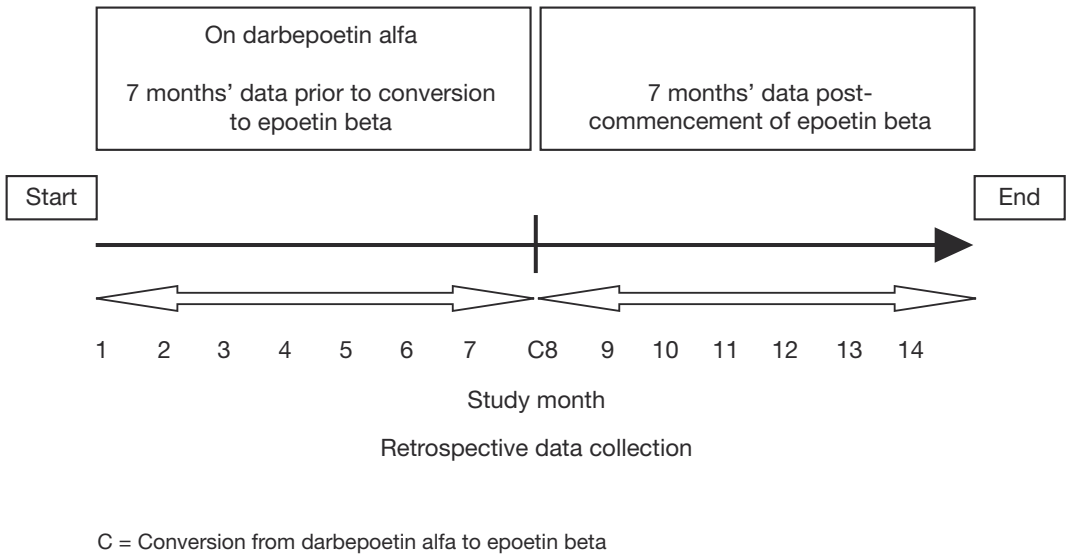


Figure 1

Study design and treatment schema.

Dose data were recorded by calendar month; doses were at a constant weekly dose within each month. Doses of epoetin beta were converted to µg using a conversion factor of 200 IU:1 µg. Patients were switched using the 200:1 conversion factor, unless dose modification was required at the time of the switch.

Statistical analysis

Summaries were produced based on the full analysis set, defined as patients who received at least one dose of epoetin beta following the switch, using observed data and last observation carried forward (LOCF) methodology.

For each patient, an evaluation period (EP) Hb level was calculated, defined as the mean of all Hb levels recorded in the final two months of the treatment period. This was the two months prior to switching to epoetin beta (EP1; study months 6 and 7) and the sixth and seventh months after switching to epoetin beta (EP2; study months 13 and 14). If only one Hb value was recorded for any patient during an EP, that value was taken as the EP Hb; if no Hb value was recorded during an EP, the patient's EP Hb value was defined as missing.

Hb levels were summarised by month and for the two EPs, and the change in Hb from EP1 to EP2 was calculated. For the EPs, Hb data (absolute levels and categories) were also summarised using LOCF as a sensitivity analysis. Where an Hb value was missing for a patient during an EP, the last available Hb value prior to the missing value was used; only Hb values recorded after the switch to epoetin beta were used for EP2 (no Hb values recorded pre-switch were carried forward to the post-switch period in the LOCF analysis).

Dose data were summarised as weekly dose each month and for the two EPs, and the change in weekly dose from EP1 to EP2 was calculated. Geometric mean doses were used to account for non-normal distribution of data. Doses of zero (due to dose being withheld) were included in the calculation, but where no dose was recorded, the value was defined as missing. For the calculations of geometric mean dose (involving a log-transformation of the data), a value of 1 µg was imputed as the dose if a subject was receiving a dose of zero at a particular time point. For the dose data, a sensitivity analysis was also performed to handle patients with a dose of zero or missing doses during an EP. In this analysis, the last dose during the treatment period was imputed as the EP dose – patients with no doses during one or both treatment periods were excluded.

RESULTS

Of the 84 patients enrolled in the study, 74 were included in the full analysis set, defined as all patients who received at least one dose of epoetin beta after switching from treatment with darbepoetin alfa. Eight patients died during the first seven months (while receiving darbepoetin alfa), one received no dose of drug throughout the study, and one received no dose of epoetin beta after the switch. Some data were available for all 74 patients in EP1 and for 67 patients in EP2. The seven missing patients not included in EP2 died following the switch. Deaths before the switch were due to lower-limb ischaemia, acute pulmonary oedema, multi-organ failure, bladder cancer, and mesenteric infarction (one each), while those after the switch were due to cerebrovascular accident, catheter sepsis and cachexia (one each); no data were available for three patients who died before the switch and four who died after the switch.

Patients had a mean (±SD) age at commencement of darbepoetin alfa of 63.9±15.6 years (Table I). Most were male (65%). Mean (±SD) time on dialysis was 49.3±39.9 months. The most common aetiology of CKD was hypertension, and the most frequent form of vascular access was arteriovenous fistula.

There was an initial trend to an increase in mean Hb level during treatment with darbepoetin alfa, and then a trend to a decrease, followed by stabilisation until study month 12 (fifth month after the switch) and then a trend to an increase at month 13 (sixth month after the switch) (Fig. 2). During EP1, prior to the switch, 42% of the patients had Hb ≤11 g/dL (and a substantial number (n=28, 42%) had Hb ≤11 g/dL during EP2) (Fig. 3); these patients presented a treatment challenge to maintain Hb within the target range. However, mean Hb remained within a narrow range, in line with target levels, throughout the study period. The mean Hb level in EP1 was the same as that in EP2 (both 11.4 g/dL, SD in EP1=1.0 g/dL, SD in EP2=1.2 g/dL). The sensitivity analysis using LOCF showed similar results (Table II), although the mean Hb was slightly lower in EP2 in this analysis. More than half of all patients had Hb levels ›11 g/dL in EP1 and EP2, but Hb levels were ≤9 g/dL or ›13 g/dL in fewer patients in EP1 than in EP2 (Fig. 3).

The geometric mean weekly ESA dose fell from month 1 to month 4, mirroring the rise in mean Hb level, and was then stable to month 7 (Fig. 2). The mean (±SD) dose conversion ratio (DCR) at the time of switch from darbepoetin alfa to epoetin beta was 231:1±147 (median=200:1). (A number of patients had a dose increase at the time of the switch. As previously stated, patients were switched using a 200:1 conversion factor, unless dose modification was required at this point.) During epoetin beta

Table I

Baseline characteristics

	FAS
Demographics, N	74
Male, n (%)	48 (65)
Age at commencement of darbepoetin alfa (years), mean±SD	63.9±15.6
Weight at commencement of darbepoetin alfa (kg), mean±SD	65.6±13.2
Patient characteristics, N	73*
Time since initiation of dialysis (months), mean±SD	49.3±39.9
Aetiology of CKD, n (%)	
Hypertension	22 (30)
Diabetic nephropathy	11 (15)
Chronic graft rejection	8 (11)
Pyelonephritis	8 (11)
Glomerulonephritis	4 (5)
ADPKD	3 (4)
Urological	2 (3)
Other	1 (1)
Unknown	14 (19)
Vascular access type, n (%)	
AVF	57 (78)
Graft	10 (14)
Catheter (Provisional)	2 (3)
Catheter (Permanent)	2 (3)
Unknown	2 (3)

*One patient removed due to an erroneous value.

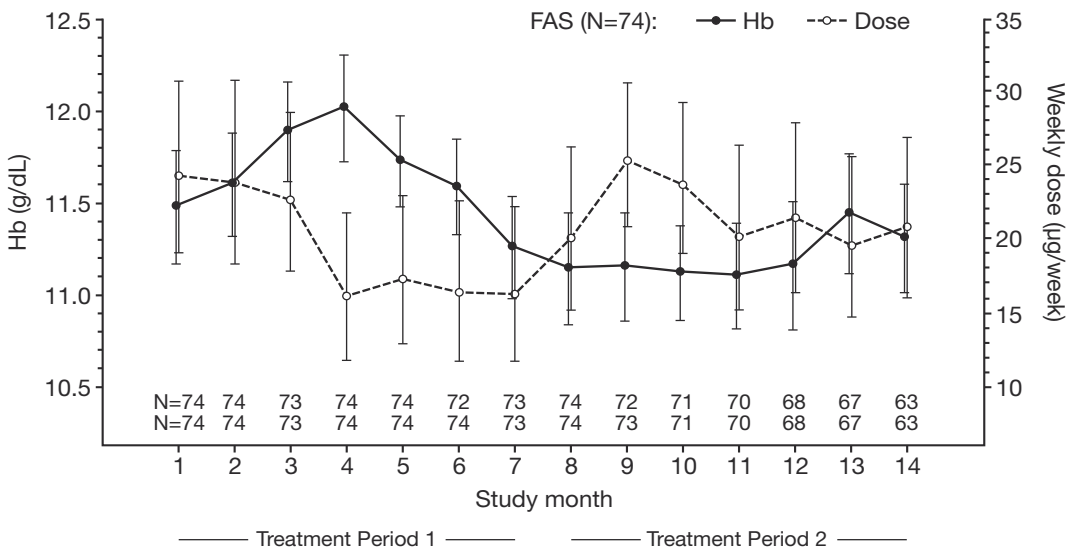
Full analysis set (FAS), Standard deviation (SD), Chronic kidney disease (CKD), Autosomal dominant polycystic kidney disease (ADPKD), Arteriovenous fistula (AVF).

Table II

Haemoglobin levels in the two evaluation periods

	Hb level (g/dL), mean (95% CI)
Observed data	
Evaluation period 1 (n=74)	11.41 (11.17, 11.64)
Evaluation period 2 (n=67)	11.38 (11.09, 11.67)
Change from evaluation period 1 to 2 (n=67)	0.014 (-0.331, 0.360)
LOCF	
Evaluation period 1 (n=74)	11.43 (11.19, 11.66)
Evaluation period 2 (n=74)	11.30 (11.01, 11.59)
Change from evaluation period 1 to 2 (n=74)	-0.128 (-0.484, 0.229)

Last observation carried forward (LOCF), Haemoglobin (Hb), Confidence interval (CI).



The dose of epoetin beta during Treatment Period 2 (months 8-14) was converted from International Units to µg using a 200:1 conversion factor (IU:µg)

Figure 2

Summary of mean haemoglobin level (95% CI) and geometric mean weekly dose (95% CI) by study month.

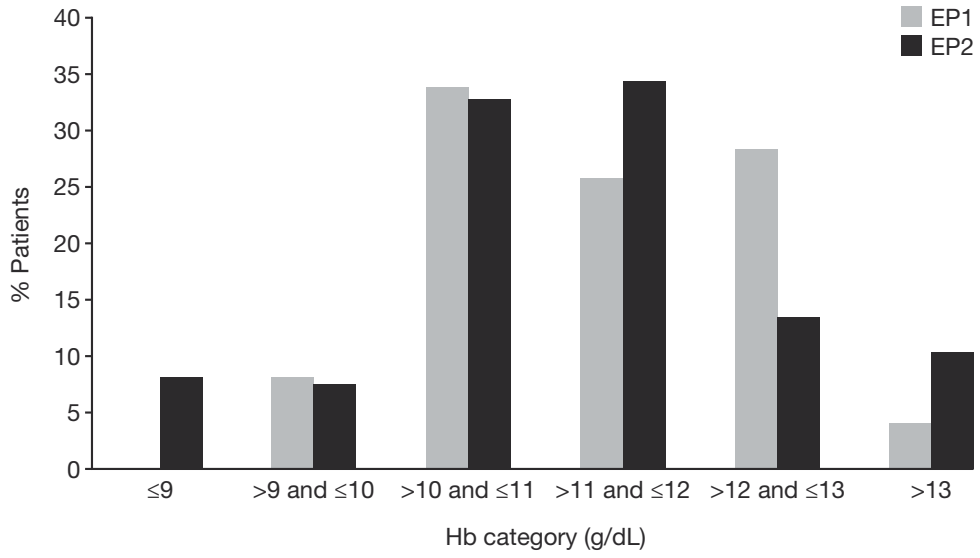


Figure 3

Percentage of patients in each haemoglobin category during the two evaluation periods (EP1 and EP2).

treatment, geometric mean weekly ESA dose rose in the first two months, fell over the next two months and then remained fairly stable. At the end of the study, the mean (±SD) DCR was 234:1±183. The geometric mean weekly dose was slightly lower in EP1, at 17.8 µg/week (95% CI 13.32, 23.79 µg/week), than

Table III

Mean weekly dose during the two evaluation periods

	Geometric mean, µg/week (95% CI)
Observed data	
Evaluation period 1 (n=74)	17.8 (13.3, 23.8)
Evaluation period 2 (n=67)	20.9 (16.4, 26.7)
Sensitivity analysis	
Evaluation period 1 (n=72)	26.82 (22.61, 31.80)
Evaluation period 2 (n=72)	24.45 (29.09, 29.74)

Confidence interval (CI).

Note: The dose of epoetin beta was converted from International Units to µg using a 200:1 conversion factor (IU:µg). In the sensitivity analysis, for patients with an evaluation period dose of zero, or for whom the evaluation period dose was missing, the last dose during the treatment period was imputed as the evaluation period dose — patients with no doses during one or both treatment periods were excluded.

in EP2, at 20.9 µg/week (95% CI 16.37, 26.68 µg/week) (Table III). The mean percentage dose change from EP1 to EP2 was 13.0% (95% CI -10.8, 36.8%). However, the median change was -14.3% (Q1, Q3 -43.8, 50.0%) (because of the skewed distribution of the data).

Results from the sensitivity analysis (n=72, as 2 patients did not receive a dose of darbepoetin alfa during the first treatment period) showed the geometric mean weekly dose to be 26.82 µg/week (95% CI 22.61, 31.80 µg/week) during EP1 and 24.45 µg/week (95% CI 20.09, 29.74 µg/week) during EP2. For the mean weekly dose, the mean percentage dose change from EP1 to EP2 was 15.2% (95% CI -7.4, 37.7%) but the median percentage change was -15.0% (Q1, Q3 -43.8, 50.0%) (again, because of the skewed distribution of the data).

Most patients received iron therapy throughout the duration of the study (94.6% during darbepoetin alfa treatment and 93.2% during epoetin beta treatment; 85.1% in EP1 and 77.6% in EP2, an absolute difference of -7.5%). More patients received RBC transfusions during epoetin beta treatment (six patients, 8%, received a total of eight transfusions) than during darbepoetin alfa treatment (three patients, 4%, received a total of three transfusions).

Laboratory data (not shown) were generally similar before and after the switch, although median PTH levels were higher during treatment with darbepoetin alfa than with epoetin beta.

DISCUSSION

The results of this switching study showed that it was possible to keep the mean Hb level at >11 and ≤13 g/dL using both darbepoetin alfa and epoetin beta. The goal was chosen by the treating physicians according to guideline recommendations in effect when patients were receiving treatment, prior to any subsequent changes in relation to target Hb levels. The ESA dose was stable from months 4-7, but after the switch an increased dose was required to maintain desired Hb levels, when considered in terms of mean percentage change. However, because of the skewed nature of the data, the mean and median percentage dose changes between the two EPs differed substantially; the mean was affected by a small number of particularly large values and therefore the median percentage change -14.3% (Q1, Q3 -43.8, 50.0%) may be considered a better representation of the midpoint of the data. The interquartile range, which includes 0, shows that the percentage change was highly variable across the population – such variability confounds attempts to draw any reliable conclusions from the dose data.

To place our results in a wider context, it is appropriate to acknowledge that pharmacokinetic and pharmacodynamic considerations relating to optimised use of ESAs have previously been described in detail[19]. Previously reported switching studies[9], both those in which the switch was from epoetin alfa or beta to darbepoetin alfa[10-15] and those in which the switch was from darbepoetin alfa to epoetin alfa or beta[16-18], have reported dose savings with darbepoetin alfa. Savings of up to 44% have been reported, depending on study design and patient population[20].

This is only the fourth reported study of a switch from darbepoetin alfa to an epoetin, and the first published article describing a non-selected population (with the non-selection the result of an administrative decision resulting in all CKD patients undergoing HD at our unit being switched from darbepoetin alfa to epoetin beta at the same time). In a previously published study, Biggar *et al.* determined the dose of epoetin beta required to maintain or achieve target Hb levels after switching from darbepoetin alfa in 90 patients on HD[16]. They found that there was a

dose penalty with epoetin beta (17%), and that significantly fewer patients achieved recommended Hb target levels following the switch (67.8% *vs*. 47.8%). In the current study, the variability of the dose data confounded attempts to draw any reliable conclusions regarding dosing, as previously mentioned. It is notable that a smaller percentage of patients were within the target range during EP2 than EP1 (48% *vs*. 54%) and Hb levels were below 9 g/dL or above 13 g/dL in fewer patients in EP1 than in EP2. The Biggar *et al*. study is similar to the current study in sample size. However, Biggar *et al*. selected only patients who had been on HD and receiving darbepoetin alfa for 24 weeks, which meant that only 68% of their cohort of 132 HD patients were included in the analysis. The current study included all patients undergoing HD (and treated always by the same two nephrologists) who had received at least one dose of epoetin beta after the switch (74/84, 88%).

The current study did not consider costs. However, these have been described in other work. In a pilot study, Orazi determined the cost-effectiveness of switching from weekly darbepoetin alfa to epoetin alfa two to three times weekly[18]. This study included a much smaller and more selected sample than the current study: only twelve patients, all of whom were clinically stable on HD and had received darbepoetin alfa for at least sixteen months. Anaemia was worse after the switch, with a mean Hb level of 11.4±0.5 in the month before conversion and 10.8±0.7 g/dL two months after conversion. At that point, the DCR was 234:1; to bring the mean Hb level back to >11 g/dL, the DCR was 414:1. This resulted in increased expenditure (€3410, 42% increase) compared with before the switch (€2400/month). These differences in Hb level and dose were more pronounced in the small, highly selected sample than in the current study, which found no difference in Hb level in the months following the switch and a mean (±SD) DCR at the end of the study of 234:1±183 in a non-selected population.

Data on adverse events were not collected during our study. However, more patients received RBC transfusions during treatment with epoetin beta than during treatment with darbepoetin alfa.

There are several limitations to this study, including the single-centre retrospective design, lack of a control arm (i.e., subjects who would remain on darbepoetin alfa throughout the study), and sample size. However, this design allowed the potential for information bias to be reduced; the amount of missing data in the final dataset was low and the quality and quantity of data captured were consistent across patients. While Hb levels during the EPs can be estimated with reasonable precision, the limited sample size may prevent any potentially important changes in Hb from being identified due to the uncertainty around the estimates. Also, the small sample size prevented the exploration of the DCR within subgroups of the study population.

In conclusion, these results showed that it was possible to keep the mean Hb level within the desired range using both darbepoetin alfa and epoetin beta, but it was not possible to draw any firm conclusions relating to the relative amounts of the two drugs required to achieve this, because of the variability of the dose data.

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Contributions: Fernando Carrera was the lead and corresponding author and was responsible for the study concept, design and implementation. He reviewed all drafts and approved the final draft prior to submission of the manuscript. Lino Oliveira was also responsible for the study design, participated in the data collection and reviewed all drafts. He approved the final draft prior to its submission. Ian Bridges (Amgen Ltd, Cambridge, UK) provided support with statistical analysis. Mourad Farouk (Amgen (Europe) GmbH, Zug, Switzerland) assisted with data interpretation. Lucy Hyatt and Caterina Hatzifoti (Amgen (Europe) GmbH) assisted in the writing and editing of this manuscript.

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Correspondence to:
Dr Fernando Carrera
Eurodial, Dialysis Unit
Rua da Carrasqueira, 19
2400-441 Parceiros
Leiria, Portugal
E-mail: fcarrera@mail.telepac.pt