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ORIGINAL RESEARCH

Switch from epoetin to darbepoetin alfa in hemodialysis: dose equivalence and hemoglobin stability

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Aim: The objective of the study reported here was to describe dose equivalence and hemoglobin (Hb) stability in a cohort of unselected hemodialysis patients who were switched simultaneously from epoetin alfa to darbepoetin alfa.

Methods: This was a multicenter, observational, retrospective study in patients aged ≥18 years who switched from intravenous (IV) epoetin alfa to IV darbepoetin alfa in October 2007 (Month 0) and continued on hemodialysis for at least 24 months. The dose was adjusted to maintain Hb within 1.0 g/dL of baseline.

Results: We included 125 patients (59.7% male, mean [standard deviation (SD)] age 70.4 [13.4] years). No significant changes were observed in Hb levels (mean [SD] 11.9 [1.3] g/dL, 12.0 [1.5], 12.0 [1.5], and 12.0 [1.7] at Months –12, 0, 12 and 24, respectively, P=0.409). After conversion, the erythropoiesis-stimulating agent (ESA) dose decreased significantly (P<0.0001), with an annual mean of 174.7 (88.7) international units (IU)/kg/week for epoetin versus 95.7 (43.4) (first year) and 91.4 (42.7) IU/kg/week (second year) for darbepoetin (65% and 64% reduction, respectively). The ESA resistance index decreased from 15.1 (8.5) IU/kg/week/g/dL with epoetin to 8.1 (3.9) (first year) and 7.9 (4.0) (second year) with darbepoetin (P<0.0001). The conversion rate was 354:1 in patients requiring high (>200 IU/kg/week) doses of epoetin and 291:1 in patients requiring low doses.

Conclusion: In patients on hemodialysis receiving ESAs, conversion from epoetin alfa to darbepoetin alfa was associated with an approximate and persistent reduction of 65% of the required dose. To maintain Hb stability, a conversion rate of 300:1 seems to be appropriate for most patients receiving low doses of epoetin alfa (≤200 IU/kg/week), while 350:1 would be better for patients receiving higher doses.

Keywords: chronic kidney disease, darbepoetin alfa, dose equivalence, epoetin alfa, hemodialysis, hemoglobin

Introduction

Anemia is the complication that has the greatest impact on perceived quality of life in patients with chronic kidney disease on hemodialysis. Therapy with erythropoiesis-stimulating agents (ESAs) significantly reduces the need for transfusions, hospital admissions, and overall mortality.[1–4]

"Epoetin alfa" is a recombinant erythropoietin with the same amino acid sequence as human erythropoietin (EPO).[5] Subcutaneous (SC) administration has a higher therapeutic effect than intravenous (IV) administration, because the effect of epoetin alfa on erythropoiesis depends more on peak levels than on through levels.[5,6] However, it is almost exclusively used intravenously in hemodialysis patients to avoid the production of anti-EPO antibodies.[2]

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In comparison to epoetin alfa, darbepoetin alfa contains an increased amount of sialic acid-containing carbohydrate chains.[7–9] It shows a much longer elimination half-life than epoetin alfa, with prolonged erythropoietic effect.[10–15] Another peculiarity is the equivalence of IV and SC dosing requirements.[1,10,16] The initially recommended conversion factor was 200 international units (IU) of epoetin alfa per 1 μg of darbepoetin alfa.[12] However, several studies have found that, after switching from epoetin alfa to darbepoetin alfa, a mean dose reduction of between 17% and 39% is required to maintain stable hemoglobin (Hb) levels.[3,17–23] Further, there is wide inter-patient variability in the conversion rate.[23,24] Despite the fact that label instructions remain unchanged, all these observations have resulted in nephrologists using a conversion rate of 250:1 in clinical practice.[20–23]

Due to a decision of the Central Purchasing Center of the Basque Health Service, Spain, the type of ESA was changed simultaneously for all hemodialysis patients in the area. The present study aimed to assess the effect on Hb levels and dose requirements of switching from epoetin alfa to darbepoetin alfa in a cohort of unselected hemodialysis patients.

Materials and methods

We performed an observational, retrospective study of ten dialysis units in the Basque Country, Spain, with data collected from March to May 2011. The main inclusion criteria were patients aged ≥18 years who switched from epoetin alfa to darbepoetin alfa in October 2007 (index date) who had been on hemodialysis for at least 15 months before the index date and remained on hemodialysis for at least 24 months after switching. Only patients with active neoplasia or bleeding were excluded. The study was conducted in accordance with the Helsinki Declaration and the guidelines for Good Clinical Practice. The study protocol was approved by the ethics committee in each participating center. Institutional review board/ethics committee approval was obtained for experimental investigation on human subjects.

The date of switch was considered the index date (Month 0). The conversion rate was left to the discretion of each nephrologist. Both ESAs were administered intravenously using pre-filled syringes. The administration frequency of epoetin alfa was 2–3 times/week and darbepoetin alfa was administered once or twice weekly (two times/week for doses >80 μg/week). Hb was measured monthly, and the ESA dose was adjusted to maintain Hb within 1.0 g/dL of the baseline value. All patients received IV iron 100 mg/month, except if ferritin levels exceeded 600 mg/dL. If ferritin levels decreased to below 200 mg/dL, the dose of IV iron was increased to 100 mg/week. The target for ferritin was 300–500 mg/dL.

The retrospective follow-up period was 36 months: –12 and +24 months relative to the index date. We collected data on Hb, ESA dose, iron dose, weight, bleeding, transfusion of red blood cells, quality of hemodialysis water, serum ferritin, transferrin saturation index (TSI), and C-reactive protein (CRP). Aluminum levels were monitored twice a year. Charlson index was collected annually. Only adverse reactions leading to the discontinuation of darbepoetin alfa were collected.

Statistical analysis

All ESA doses were converted to IU/kg/week using the 200:1 conversion rate. The erythropoiesis-stimulating agent resistance index (ERI) was calculated by dividing the ESA dose by the Hb level.[22]

Changes from baseline at post-baseline visits were evaluated using paired *t*-test, Wilcoxon signed-rank test, or McNemar's test as appropriate. Changes in continuous variables over time were evaluated using repeated-measures analysis of variance. Univariate and multivariate linear regression models were used to investigate the influence of several variables on the ERI. Statistical analyses were performed using SAS software (v 9.2; SAS Institute, Cary, NC, USA).

Results

Patients

There were 242 prevalent hemodialysis patients at the index date. Of these, 125 were included in the study (67 were excluded due to kidney transplant, 17 due to change to peritoneal dialysis, three due to active neoplasia or bleeding, and 30 due to death).[25]

Patient characteristics are summarized in Table 1. The main comorbidities were hypertension (82.4%), peripheral vascular disease (21.6%), diabetes with end organ damage (20.8%), cerebrovascular disease (17.6%), chronic pulmonary disease (13.6%), arrhythmia (12.8%), coronary disease (12.8%), myocardial infarction (10.4%), and congestive heart failure (10.4%).

The mean dry weight, Charlson index, and TSI levels remained unchanged after conversion. Ferritin and CRP levels showed a moderate but significant increase over time. The bacterial content and aluminum levels in the water for hemodialysis decreased (Table 2).

Hb levels over time

No significant changes in mean and median monthly values of Hb were observed through the follow-up period

Table 1 Population characteristics at the time of switch from epoetin alfa to darbepoetin alfa

Characteristic	Patients on hemodialysis (n=125)
Age (years), mean (SD)	70.4 (13.4)
Range	27.3–106.7
Male, %	59.7
Dry weight (kg), mean (SD)	66.6 (15.3)
Range	40.0–119.5
Time since CKD diagnosis (months), median (range)	68 (4–615)
Time on hemodialysis (months), median (range)	25 (3–305)
Prior transplantation, %	14.0
Charlson index, mean (SD)	7.5 (2.2)
TSI (%), mean (SD)	26.5 (10.0)
Serum ferritin (ng/mL), median (range)	376 (36–1,987)
CRP (mg/dL), median (range)	0.6 (0.1–17.4)
Characteristics of water for hemodialysis	
Conductivity (µS/cm), mean (SD)	3.0 (1.2)
Temperature (°C), mean (SD)	20.3 (3.8)
Bacterial content (CFU/mL), median (range)	2 (0–2)
Aluminum levels (mg/L), median (range)*	ND (ND–16.5)

Note: *The lowest detection level was 1 µg/L.
Abbreviations: CKD, chronic kidney disease; CRP, C-reactive protein; ND, undetectable; SD, standard deviation; TSI, transferring saturation index.

(mean [SD] 11.9 [1.3] g/dL at Month −12, 12.0 [1.5] at Month 0, 12.0 [1.5] at Month 12, 12.0 [1.7] at Month 24, P=0.409; Figure 1). Only a slight, nonsignificant increase in mean Hb levels was observed within the first 3 months after the switch (12.3 [1.4] g/dL at Month 3), which quickly returned to prior levels (12.1 [1.6] g/dL at Month 4, 11.9 [1.4] g/dL at Month 6) after minor dose adjustments during the first 2 months of darbepoetin alfa (Figure 2).

Patients were on target levels (10–12 g/dL) for a mean (SD) of 4 (3) months with epoetin alfa and 8 (5) months with darbepoetin alfa, which represents 42.6% (25.2) and 44.2% (21.0) of the time, respectively (P=0.616). The coefficient of variation (SD/mean*100) of the Hb levels did not change between the two periods: 11.4% (95% confidence interval [CI] 10.8%–12.0%) with epoetin alfa; 11.9% (95% CI 11.4%–12.4%) with darbepoetin alfa.

No significant changes over time were observed in the number of bleedings or transfusions (data not shown). The percentage of patients suffering a bleeding episode or requiring a blood transfusion was <1% in all months.

ESA doses over time

The ESA dose with epoetin alfa did not show significant variation in the year prior to the switch (annual mean of 174.7 [88.7] IU/kg/week [54.1 (29.8) µg/week]; Figure 2 and Table 3). After conversion, the ESA dose decreased abruptly and significantly (P<0.0001), and, from then on, remained unchanged. Between Months 0 and 12, the mean dose was 95.7 (43.4) IU/kg/week (23.3 [12.5] µg/week). A slight but nonsignificant additional decrease was observed during the second year (mean 91.4 [42.7] IU/kg/week; Table 3). The conversion rate at baseline for the overall group was 332:1.

Resistance index

The ERI decreased from an annual mean of 15.1 (8.5) IU/kg/week/g/dL with epoetin alfa to 8.1 (3.9) during the first year and 7.9 (4.0) during the second year with darbepoetin alfa (Table 3 and Figure 3).

No significant relationship with the ERI was observed for iron dose, quality of hemodialysis water, or CRP levels (data not shown). The Charlson index was the only variable significantly associated with ERI (P=0.007), independently from the type of ESA used.

Results according to baseline ESA dose

There were significant differences in the reduction of ESA dose between subgroups defined by their baseline dose:

Table 2 Changes in patient characteristics and hemodialysis water over time

Characteristic	Epoetin alfa	Darbepoetin alfa		
		First year	Second year	*P*-value
Dry weight (kg), mean (SD)	66.5±15.1	65.8±14.6	64.6±14.2	0.609
Charlson index, mean (SD)	7.4 (2.3)	7.5 (2.4)	7.3 (2.5)	0.791
Serum ferritin (ng/mL), median (Q1, Q3)	314 (199, 467)	346 (220, 494)	372 (268, 593)	0.038
TSI (%), mean (SD)	28.7±13.0	26.8±9.6	26.5±10.0	0.710
CRP (mg/dL), median (Q1, Q3)	0.5 (0.2, 1.6)	0.9 (0.3, 3.4)	1.5 (0.5, 2.8)	0.025
Characteristics of water for hemodialysis				
Conductivity (µS/cm), mean (SD)	3.4±2.0	2.8±2.7	2.4±0.98	0.439
Bacterial content (CFU/mL), median (Q1, Q3)	7 (0, 7)	0 (0, 0)	1 (0, 1)	<0.001
Aluminum levels (mg/L), median (Q1, Q3)*	ND (ND, 6.4)	ND (ND, ND)	ND (ND, ND)	0.003

Note: *The lowest detection level was 1 µg/L.
Abbreviations: Q1, 25th percentile; Q3, 75th percentile; CRP, C-reactive protein; ND, undetectable; SD, standard deviation; TSI, transferring saturation index.

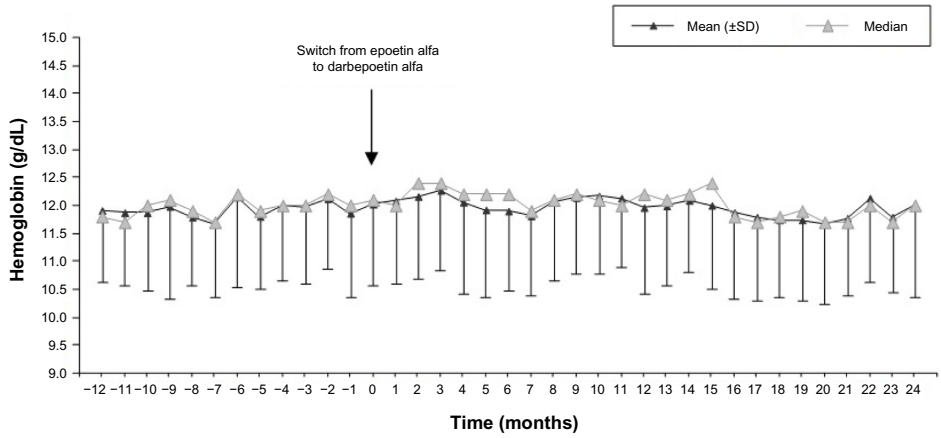

Figure 1 Changes in hemoglobin levels over time.
Abbreviation: SD, standard deviation.

patients requiring high doses had a greater reduction than patients on medium or low doses (Table 3). The resulting conversion rate was 291:1 for patients on low doses of epoetin alfa (≤200 IU/kg/week) and 354:1 for patients requiring doses >200 IU/kg/week.

Safety

There were no discontinuations of darbepoetin alfa due to adverse reactions during the follow-up period.

Discussion

The present study analyzed the switch from epoetin alfa to darbepoetin alfa in hemodialysis patients. After the switch, the mean ESA dose decreased by 65%, and this reduction was maintained during the subsequent 2 years, without noticeable changes in Hb levels. Thus, an approximately double efficiency of darbepoetin alfa treatment was observed. Further, the median values of ESA dose and ERI were much closer to the mean values after the switch. These findings support that there are more "resistant" patients with epoetin alfa,[17] in whom the conversion rate would be even higher than 350:1.

Our results are consistent with those from randomized and controlled trials;[3,26] however, the dose reduction was higher in our study, which could be related to the higher proportion of individuals requiring high ESA doses. In prior studies, there was a gradual reduction in the dose of ESA in the first year after conversion due to progressive dose adjustments in response to Hb levels above targets. In our experience, using a conversion rate of about 330:1, we achieved the early stabilization of Hb and dose of darbepoetin alfa.

The quality of water for hemodialysis improved during the study, from baseline values fulfilling requirements of "pure water" to final values close to those for

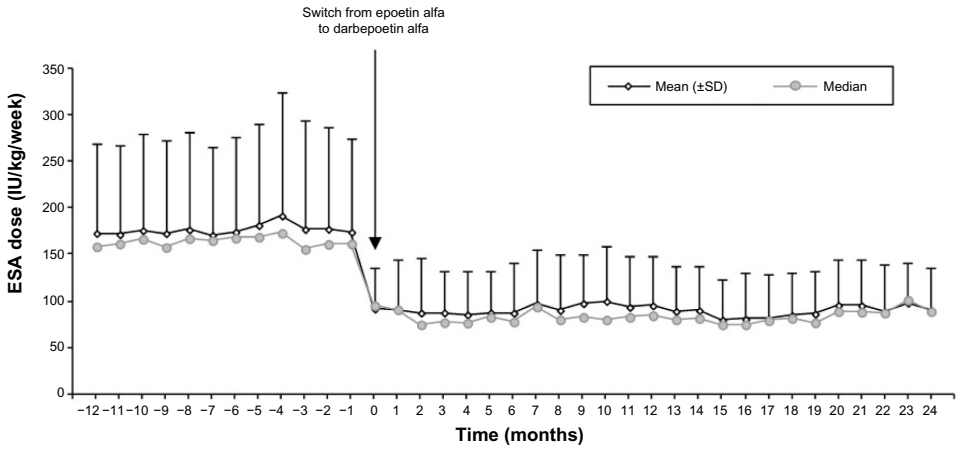

Figure 2 Changes in erythropoiesis-stimulating agent (ESA) dose over time.
Note: Darbepoetin doses were converted at a 1:200 conversion rate.
Abbreviation: SD, standard deviation.

Table 3 Absolute and relative changes in erythropoiesis-stimulating agent (ESA) dose and erythropoiesis-stimulating agent resistance index (ERI)

Parameter	Dose of epoetin alfa at conversion[a]			
	Low (<150 IU/kg/week) (n=50)	Intermediate (150–200 IU/kg/week) (n=33)	High (>200 IU/kg/week) (n=41)	Total (n=125)
ESA dose (IU/kg/week), mean (SD)				
Epoetin alfa[b]	93.0 (33.6)	175.5 (14.4)	273.6 (65.3)	174.7 (88.7)
Darbepoetin alfa				
First year	67.1 (36.8)	118.2 (30.1)	118.5 (37.8)	95.7 (43.4)
Second year	69.7 (34.4)	103.3 (35.8)	114.1 (45.8)	91.4 (42.7)
ESA dose reduction (%), mean (SD)[c]				
First year	47.9 (18.2)	66.7 (17.4)	76.3 (36.9)	65.5 (30.2)
Second year	46.0 (21.4)	58.3 (20.2)	79.8 (32.7)	64.4 (30.2)
ERI (IU/kg/week/g/dL), mean (SD)				
Epoetin alfa[b]	7.6 (2.9)	15.1 (1.9)	24.4 (7.3)	15.1 (8.5)
Darbepoetin alfa				
First year	5.5 (3.1)	10.0 (2.8)	10.3 (3.5)	8.1 (3.9)
Second year	5.9 (3.1)	9.4 (3.8)	9.7 (4.2)	7.9 (4.0)
ERI reduction (%), mean (SD)[c]				
First year	48.6 (19.0)	67.8 (19.5)	77.4 (37.8)	66.3 (31.2)
Second year	45.2 (22.2)	61.3 (23.1)	81.6 (33.6)	65.8 (31.7)

Notes: [a]Not available in one patient; [b]mean dose during the year before conversion; [c]mean of individual percent differences, calculated by dividing the difference between the mean darbepoetin alfa dose and the mean epoetin alfa dose by the mean epoetin alfa dose.
Abbreviations: SD, standard deviation; IU, international units.

"ultrapure water".[27,28] A good hemodialysis water quality can decrease the ERI.[29–31] However, the bacterial and aluminum contents with epoetin alfa were already very low relative to the maximum levels allowed for pure water (<100 CFU/mL and <10 µg/L, respectively).[27,28] Also, we did not observe any trend toward improvement in inflammatory parameters (CRP and ferritin levels).

In our population, the conversion rate was higher in patients with relative erythropoietin resistance. These results differ from an Italian study that found the same rate irrespective of the previous dosage of epoetin alfa.[32] However, these results are similar to those reported by Bock et al: from a conversion factor of around 200:1 in patients using lower doses (<5,000 IU/week) to more than 300:1 at doses of >10,000 IU/week.[23] In that study, only 49% of patients used IV epoetin alfa. An explanation for the differences between the conversion factors at different doses was proposed by Nissenson,[17] who suggested that epoetin loses some efficacy at high doses. This effect would be related to the use of epoetin in weekly or less frequent schedules.[33]

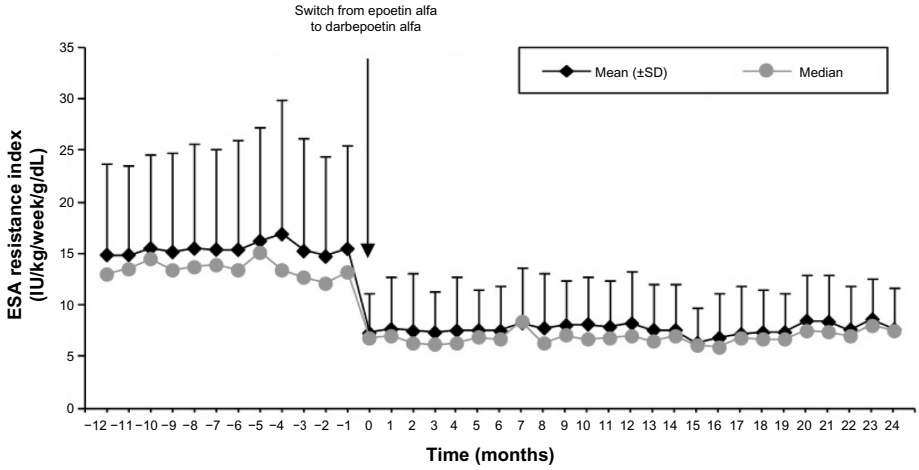

Figure 3 Changes in erythropoiesis-stimulating agent (ESA) resistance index over time.
Abbreviation: SD, standard deviation.

Our study design did not allow for the detailed analysis of within-subject variability. The monthly stability of Hb levels was comparable, and achieved a mean of 8 months during the 2 years of treatment with darbepoetin alfa. This also raises the possibility of reducing the frequency of Hb checks. Hb stability was accompanied by an increased ESA dose stability.

Regarding between-subject variability, we did not find any difference in the coefficient of variation of Hb levels between epoetin alfa and darbepoetin alfa, in line with prior publications that suggest that this type of variability is due to intrinsic factors associated with the disease and its comorbidities.[34]

The main limitation of the study is the fact that data were retrospectively collected. We excluded from the present analysis around 50% of all prevalent hemodialysis patients.[25] Although there is a possible bias due to the inclusion of survivors, the exclusion of 30% of the more stable patients due to transplantation should compensate for this. Thus, we think that our cohort can be regarded as representative of hemodialysis patients receiving ESAs.

Conclusion

In patients on hemodialysis receiving ESAs, conversion from epoetin alfa to darbepoetin alfa was associated with an approximate and persistent 65% reduction of the required dose. To maintain Hb stability, a conversion rate of 300:1 seems to be appropriate for most patients receiving low doses of epoetin alfa (≤200 IU/kg/week), while 350:1 would be better for patients on higher doses.

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Disclosure

The conclusions, interpretations, and opinions expressed herein are those of the authors. This study was financially supported by Amgen. The authors report no other conflicts of interest in this work.

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