

Structured Conversion from Thrice Weekly to Weekly Erythropoietic Regimens Using a Computerized Decision-Support System: A Randomized Clinical Study

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In view of the recent interest in weekly erythropoietic regimens and the lack of studies directly comparing the available agents, the clinical effectiveness of darbepoetin- α (DA) and epoetin- β (EB), when administered via the subcutaneous route on a weekly basis, after conversion from thrice-weekly subcutaneous EB, was studied. In this 9-mo, single-center, randomized study of an unselected hemodialysis population, anemia was managed with a computerized decision-support system. Per-protocol analysis of the 81 patients in each arm who completed the study showed similar hemoglobin outcomes between treatment arms, both at randomization and at the end of the study. After conversion from thrice-weekly EB to DA (at a ratio of 200 IU:1 μ g, at which products are cost-neutral in the European Union), a significant fall in dose from a mean of 0.59 μ g/kg per wk after randomization to 0.46 μ g/kg per wk in the last month ($P = 0.002$) was observed; in the comparator arm, the reduction in frequency of administration of EB was associated with a significant dose increase from a mean of 107.5 to 133.2 IU/kg per wk ($P = 0.002$) during the same period. At hemoglobin stability, mean EB dose was found to be 44% higher than DA dose (when multiplied by 200). Similar significant dose differences were apparent in a modified intention-to-treat analysis. The study demonstrated that, under a decision-support system, both products were capable of adequately maintaining hemoglobin outcome when administered on a weekly basis but with significant dose differences at 9 mo.

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The anemia of chronic kidney disease is associated with increased mortality, cardiovascular disease, sleep abnormalities, loss of cognitive function, and impaired quality of life (1–5). The partial correction of anemia through the administration of recombinant human erythropoietin (EPO) products has been shown to improve survival (6) and cardiovascular status (7) and to alleviate other symptoms. In view of the half-life of the agents, these studies have been undertaken typically through the administration of EPO several times per week.

The interest in weekly erythropoietic regimens was stimulated by the development and licensing of darbepoetin- α (DA), a hyperglycosylated (and hypersialated) isoform of EPO with a prolonged half-life, whether administered via the subcutaneous (48.8 h) or intravenous (25.3 h) route (8). Results from recent randomized studies support the efficacy of weekly subcutaneous epoetin- β (EB) in maintaining hemoglobin (Hb), when compared with more frequent dosing in highly selected patient populations (9,10). These findings have not been substantiated outside the confines of a clinical trial (11,12).

Two recent randomized studies compared weekly DA with

more frequent EPO dosing, during maintenance-phase treatment (13,14), demonstrating similar efficacy between regimens. No randomized studies have compared the effectiveness of weekly subcutaneous EB and DA, despite the growing need for such a study (15).

The evolution of a computerized decision-support system to manage anemia within our unit has been described previously (16–18). The system acts as an Hb “clamp,” serving to fix population Hb outcomes to a predictable distribution. In the context of thrice-weekly subcutaneous administration of EB, UK Renal Association Standards (19) have been consistently achieved for several years and the system has been used in a previous, large, randomized study (20).

Materials and Methods

Study Population and Randomization

This open-label, single-center, prospective, randomized study (of a predefined 9-mo period) was designed to compare the clinical effectiveness of two subcutaneous weekly erythropoietic regimens, DA and EB, on conversion from thrice-weekly subcutaneous EB, in a prevalent, unselected, iron-replete, outpatient hemodialysis population. Written, informed consent was obtained from patients before the study, which was performed in accordance with the Declaration of Helsinki and subsequent modifications. The Local Research Ethics Committee approved the protocol; no deviations were necessary during the course of the study.

All adult (18 yr or older), prevalent hemodialysis patients (receiving hemodialysis >90 d) were invited to participate, regardless of individual iron status, transfusion burden, Hb at randomization, or comor-

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bidities. Exclusion criteria were inability to give informed consent, receiving home hemodialysis, unsuitability for intravenous iron or erythropoietic agents, and uncontrolled hypertension at randomization (defined as a diastolic BP ≥ 100 mmHg). Consenting patients were randomized on a 1:1 basis, either to conversion from thrice-weekly subcutaneous EB to weekly subcutaneous DA (converted at a ratio of 200 IU:1 μg , in accordance with the manufacturer's recommendations within the European Union), or to continue subcutaneous EB, receiving their total thrice-weekly dose in one weekly injection.

Study Drugs and Anemia Management System

As the nature of the computerized system is one of frequent dose titration to maintain a stable population outcome, there was no run-in period before conversion. The dialysis population as a whole had been managed by the same system for >1 yr before the study, on a thrice-weekly EB regimen, with a stable mean dose of 7800 IU/wk, a mean population Hb outcome of 11.8 ± 1.7 g/dl, and stable population ferritin and hypochromic red blood cell (HRC) values that met revised European Best Practice Guideline (21) minima.

EB (NeoRecormon; Hoffman-LaRoche, Basel, Switzerland) was administered from 100,000-IU multidose vials (20,000 IU/ml). Total weekly EB doses were derived for each step of an existing thrice-weekly, EB dose escalation ladder, each step of which then was divided by 200 and rounded up or down to the nearest and most convenient DA total dose (Aranesp; Amgen, Thousand Oaks, CA), available in pre-filled syringes of 10, 15, 20, 30, 40, 50, 60, 80, 100, and 150 μg . Several DA dose intervals were achieved through a combination of two pre-filled syringes. All injections were administered by nursing staff during dialysis via the subcutaneous route, into thigh, arm, or abdomen, according to patient preference.

Patients' monthly blood samples were taken before and after the second dialysis session of the week. Data were also collected on mean predialysis BP and postdialysis body weight (during the preceding 2-wk period); transfusion burden; and weekly doses of EB, DA, and iron for each month of the study period.

On a monthly basis, the computerized decision-support system analyzed Hb concentrations, Hb trends (during the preceding 30 d), and transfusion burden to advise unit dose increments until the lower Hb threshold of 11 g/dl was achieved (unless Hb had risen by >1 g/dl in the previous 30 d, when no dose change was recommended). Predialysis Hb concentrations greater than the ceiling of 12 g/dl brought about a unit dose decrement (unless Hb had fallen by >0.5 g/dl, when dose remained unchanged). When Hb concentrations lay between the threshold and ceiling, unit dose increments were advised when Hb had fallen by >0.5 g/dl and dose decrements if Hb had risen by >1 g/dl. Hb concentrations >15.5 g/dl brought about a recommendation for a halving of the weekly dose. These computer-generated recommendations were reviewed and actioned by one clinician (C.T.). Treatment failure was defined as inability to sustain an Hb ≥ 10 g/dl despite 3 mo of maximal erythropoietic stimulation (EB dose of 300 IU/kg per wk or DA dose of 1.5 $\mu\text{g}/\text{kg}$ per wk), despite usual investigation and collateral treatment. Elective (nonemergency) blood transfusions were sanctioned at a threshold of 8 g/dl for symptom relief. Patients who received blood transfusion were not excluded from statistical analysis.

A combination of regular, low-dose parenteral iron sucrose (Venofer; Vifor France SA, Cedex, France) replacement therapy and incremental dosing was used for iron-deficient and iron-replete patients, respectively. When serum ferritin values fell below 100 $\mu\text{g}/\text{L}$, 50 mg iron was administered thrice-weekly. For ferritin values between 100 and 500 $\mu\text{g}/\text{L}$, the percentage of HRC determined prescribed iron dose: $<2\%$, 50 mg weekly; 2 to 5%, 50 mg twice-weekly; $>5\%$, 50 mg thrice-weekly.

Iron administration was withheld when serum ferritin values exceeded 500 $\mu\text{g}/\text{L}$.

To ensure uniformity of management, all other aspects of patients' care were undertaken by two supervising consultants (not directly connected with the study) through a monthly clinical review meeting.

Statistical Analyses

As population Hb outcome was stabilized by the computerized system, study drug doses at 9 mo were chosen as the primary end point. A sample size of 150 at 9 mo (with 1:1 randomization) was based on a significance level (α , two-sided) of 0.05, β error of 0.1, and power ($1 - \beta$) of 0.9; predicted significant difference between treatment arms was equivalent to 37 IU/kg per wk (SD for EB dose of 75 IU/kg per wk, standardized difference of 0.49).

We performed a per protocol (pP) analysis (of patients who completed follow-up and received at least one dose of the study drugs) and a modified intention-to-treat (mITT) analysis of all patients who received at least one dose of the study drugs and completed at least 3 mo of follow-up (to minimize carryover effect from thrice-weekly EB therapy), with last available results or last dose carried forward (analyses used in other randomized studies comparing DA and thrice-weekly EB [13,14]). Statistical analysis was performed using Minitab 13.1. Continuous, parametric data were analyzed using two-sample or paired *t* test, where appropriate; nonparametric data were analyzed with Mann Whitney *U* or Wilcoxon signed rank analysis. Categorical data were analyzed by χ^2 analysis. Data are presented as mean \pm SD (if parametric) or median and interquartile range (where nonparametric).

Results

Patient Characteristics

Informed consent to undergo randomization was given by 217 patients (see Figure 1 for flow of patients through study). No case stratification was attempted. Of the 112 patients who were randomized to treatment with DA, 87 completed the study (six of whom, while managed through the computerized system, maintained Hb concentrations >12 g/dl independent of exogenous erythropoietic stimulation before and during the study period). Of the 107 patients who were assigned to continue EB therapy, 82 completed the study (one requiring no erythropoietic treatment). As a result, 81 patients in each arm were suitable for pP analysis. Failures to complete the study (for reasons of renal transplantation, transfer of dialysis modality, or death) were not statistically different between groups (see Figure 1). Four patients were withdrawn from the EB arm: Two treatment failures (individuals who had diabetes and a heavy burden of chronic sepsis, converted to thrice-weekly EB therapy); one patient received a diagnosis of anti-EPO antibody-associated pure red cell aplasia before conversion (reported in detail elsewhere [22]); and another developed pseudoporphyria, possibly related to iron repletion. One patient withdrew consent from the DA arm, complaining of discomfort at injection sites.

pP Analyses

Baseline data of the pP population are shown in Table 1. Although there was a trend toward more women in the DA arm, there were no statistically significant differences in gender distribution between groups or differences in age, time on dialysis, ethnicity, weight, cause of renal failure (by EDTA

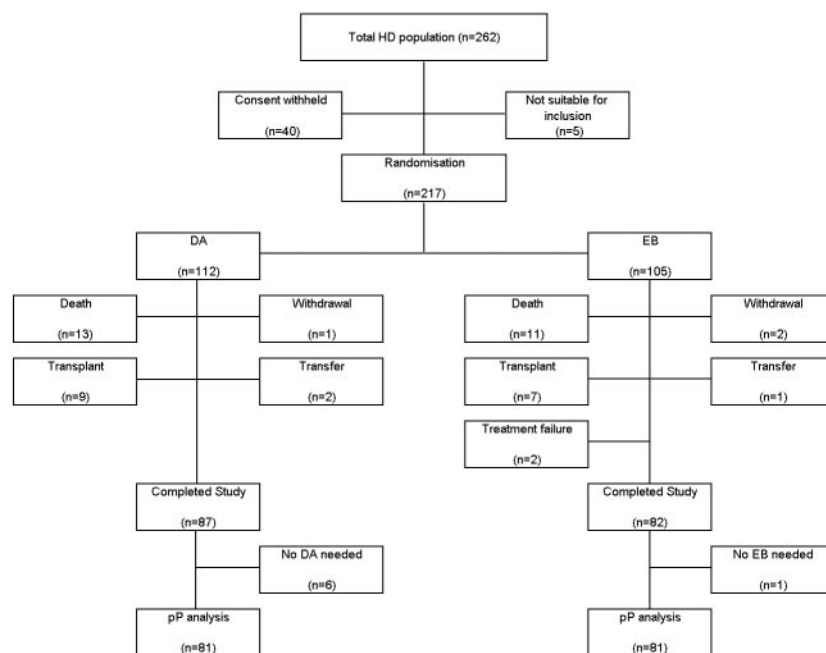


Figure 1. Flow of patients.

Table 1. Baseline data of pP population^a

Variable	DA (n = 81)	EB (n = 81)	P Value
Age (yr)	64 (51 to 73)	63 (46 to 72)	0.36 ^b
Time on dialysis (d)	945 (426 to 1901)	818 (385 to 2020)	0.23 ^b
Male:female	40:41	52:29	0.07 ^c
White:black:Asian	62:8:11	69:6:6	0.35 ^c
Diabetes	7	8	0.79 ^c
APKD	7	4	0.35 ^c
Previous transplants	10	14	0.38 ^c
CRP (mg/L)	8 (5 to 16)	8 (5 to 19)	0.38 ^b
Albumin (g/L)	38 (36 to 41)	39 (36 to 42)	0.41 ^b
eKt/V	1.35 (1.21 to 1.55)	1.34 (1.05 to 1.48)	0.16 ^b
PTH (ng/L)	110 (52 to 243)	124 (54 to 242)	0.84 ^b
Weight (kg)	65.8 (56.5 to 79)	67.8 (59.6 to 80.1)	0.11 ^b
Hb (g/dl)	11.86 ± 1.4	11.73 ± 1.7	0.65 ^d
Weekly EB dose (IU/kg per wk)	91 (60 to 157)	79 (47 to 143)	0.27 ^b
Serum ferritin (μg/L)	478 (363 to 571)	499 (407 to 610)	0.25 ^b
HRC (%)	2 (2 to 5)	2 (2 to 4.2)	0.75 ^b

^apP, per protocol; DA, darbepoetin-α; EB, epoetin-β; APKD, adult polycystic kidney disease; CRP, C-reactive protein; PTH, parathyroid hormone; Hb, hemoglobin; HRC, hypochromic red blood cell.

^bMann-Whitney *U* analysis.

^cχ² analysis.

^dTwo-sample *t* test.

coding), prevalence of previous transplantation, or any biochemical parameters believed to influence the management of renal anemia.

Figure 2 shows that both pP groups had similar Hb concentrations at baseline (month 0). Mean baseline Hb in those who were randomized to DA was 11.86 ± 1.4 and 11.73 ± 1.7 g/dl in the EB arm. There were no significant differences in Hb

between the beginning and the end of the study (months 0 and 9) in either group (95% confidence interval [CI] for change through study in DA arm, −0.4 to 0.3 g/dl; EB, −0.5 to 0.4 g/dl).

Among the 81 patients per arm, 22 units of blood were transfused to 8 of those who were treated with DA; 32 units were given to 11 of the EB arm. There were no statistically

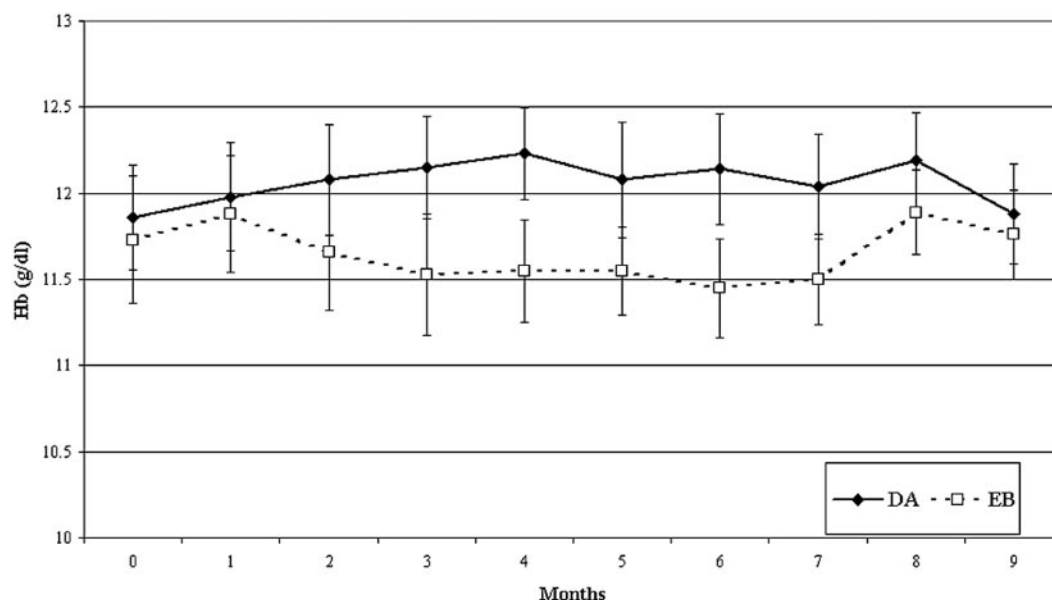


Figure 2. Mean hemoglobin (Hb; 95% confidence interval [CI]) of per-protocol (pP) study populations.

significant differences in the numbers who received transfusions or the number of units given to these patients.

Baseline weekly EB doses (administered in three divided doses) were similar in both groups. Those who were randomized to DA were receiving a median EB dose of 91 (60 to 157) IU/kg per wk (total weekly dose, 6000 [3226 to 10,775] IU/wk) before randomization; those who were randomized to EB were receiving a median EB dose of 79 (47 to 143) IU/kg per wk (6000 [3048 to 9000] IU/wk). 95% CI of EB dose difference at baseline was -9 to 31 IU/kg per wk.

When study drug doses during the first and last months were compared, there was a significant fall in median DA dose from 0.44 (0.25 to 0.85) $\mu\text{g/kg}$ per wk to 0.37 (0.23 to 0.62) $\mu\text{g/kg}$ per wk (95% CI, 0.032 to 0.178 $\mu\text{g/kg}$ per wk; $P = 0.006$), whereas

median dose in the EB arm rose from 92 (51 to 135) IU/kg per wk to 116 (67 to 189) IU/kg per wk (95% CI, 10.6 to 42 IU/kg per wk; $P = 0.002$). Figure 3 graphically demonstrates a period of dose titration followed by dose stability. During the study period, mean DA dose fell by 20%, from 0.59 to 0.46 $\mu\text{g/kg}$ per wk, whereas mean EB dose increased by 24% from 107 to 133 IU/kg per wk.

To allow direct comparison of doses required to achieve similar Hb outcomes, we multiplied DA doses at 9 mo by 200 (a ratio at which products are cost-neutral under European licensing); this DA “equivalent” dose of 74 (45 to 123) IU/kg per wk was significantly lower than the EB dose at 9 mo by Mann Whitney U analysis (95% CI, 17 to 61 IU/kg per wk; $P < 0.001$). Mean EB dose at 9 mo was 44% higher than the

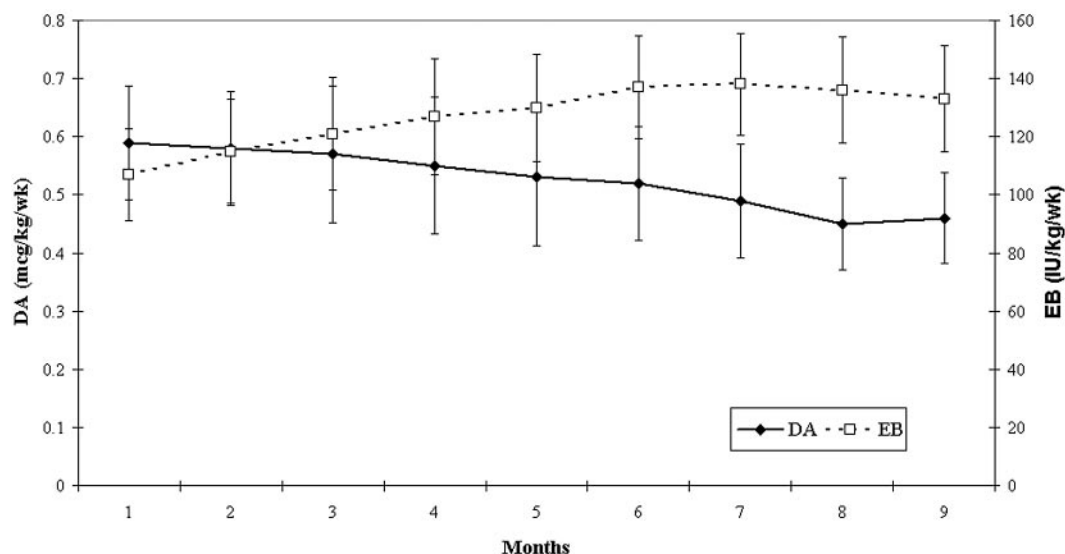


Figure 3. Mean (95% CI) darbepoetin- α (DA) and epoetin- β (EB) doses in pP populations through study period.

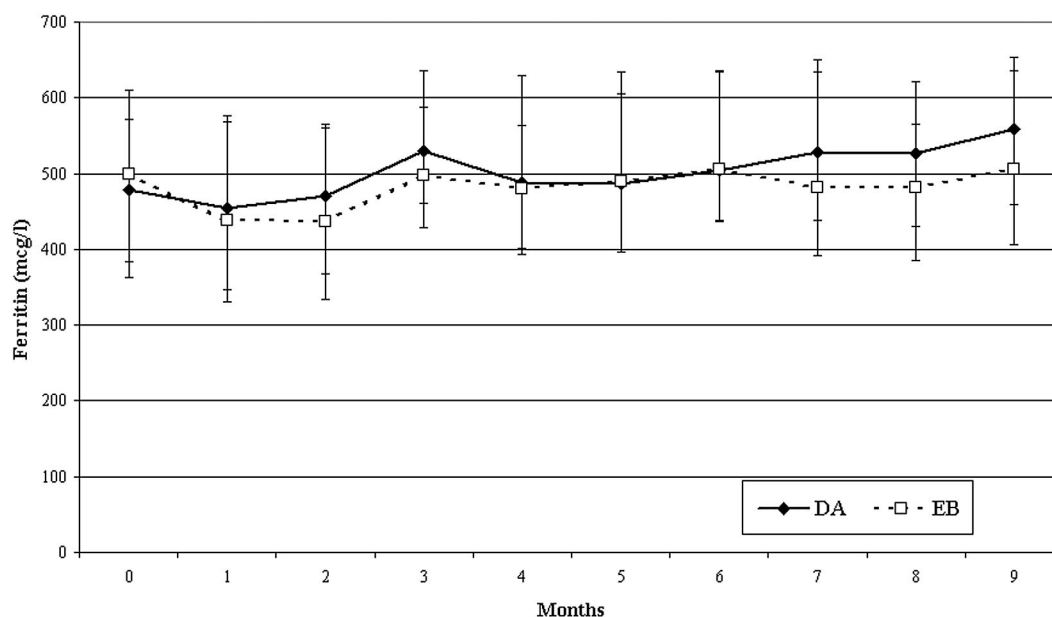


Figure 4. Median (interquartile range) serum ferritin values through study in pP populations.

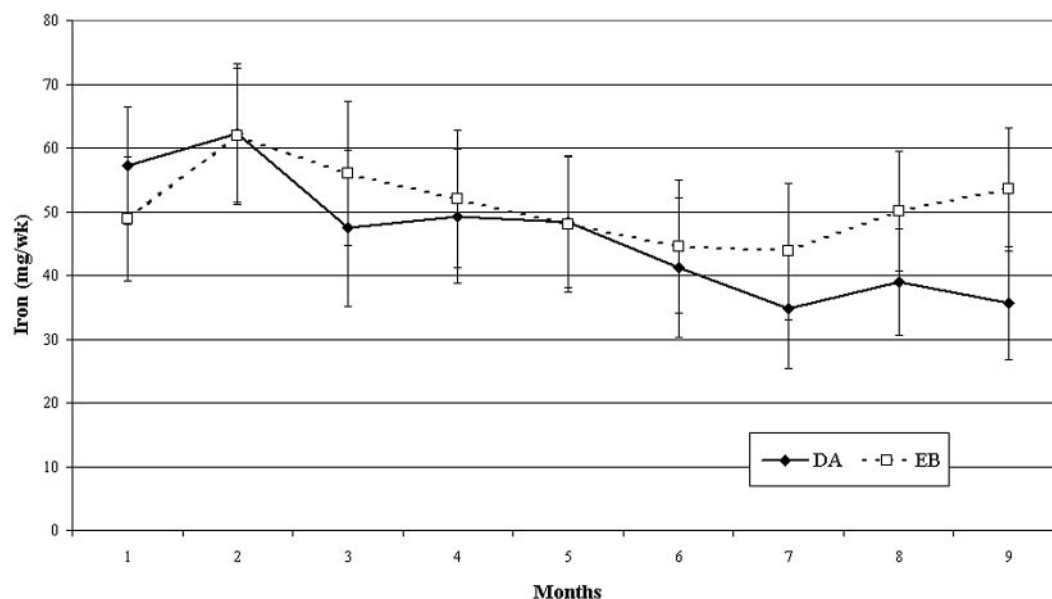


Figure 5. Mean weekly iron doses in each arm through study in pP populations.

DA dose at 133 IU/kg per wk compared with 92 IU/kg per wk.

At randomization, there were no significant differences in markers of iron stores or weekly iron dose between groups. Median serum ferritin in those who were randomized to DA was 478 (363 to 571) $\mu\text{g/L}$ and 499 (407 to 610) $\mu\text{g/L}$ in those who were randomized to continue EB. Although no significant change in ferritin was seen through the study in the EB arm, a significant rise was observed in those who were randomized to DA: 95% CI for increase of 57 to 170 $\mu\text{g/L}$ (see Figure 4), although difference in ferritin between groups at 9 mo remained nonsignificant. The sustained rise in serum ferritin in

the DA arm during the latter months of the study was associated with a significant fall in prescribed iron during this period (mean dose of 57 mg/wk fell to 36 mg/wk; see Figure 5); in contrast, there was no significant change in iron dosing in the EB arm through the study.

Median (interquartile range) HRC values at randomization were 2% (2 to 5%) in the DA arm and 2% (2 to 4.2%) in the EB arm. Although HRC increased significantly ($P < 0.01$) in each arm (to a median of 3% [1 to 8] in both arms), the lack of difference between treatment arms persisted. In both arms, >80% achieved the revised European Best Practice Guideline (21) minimum of <10% HRC throughout the study.

Table 2. Concurrent events during study period in pP population

Event	DA	EB	P
Septicemia	2	2	1.0
Pneumonia	5	3	0.47
Access surgery	9	4	0.15
Other surgery	4	9	0.15
Parathyroidectomy	1	2	0.56
Tunneled line procedure	8	6	0.58

BP was similar in both groups at randomization. Mean values in the DA arm were $146 \pm 23/77 \pm 11$ mmHg and $144 \pm 24/76 \pm 11$ mmHg in those who continued EB. There were no significant changes in BP values throughout the study in either treatment arm. Intercurrent hypertension precluded a recommended dose escalation at some juncture in six patients in the DA arm and seven in the EB arm (nonsignificant by χ^2 analysis), with recommendations on dose changes followed in all other circumstances. There was no difference in the incidence of significant intercurrent events (*i.e.*, surgical, infective, and access related events) between groups by χ^2 analysis (see Table 2).

mITT Analyses

Of those who were randomized to DA, 99 were suitable for mITT analysis, as were 97 of those who were randomized to EB. There were no differences between groups in terms of the demographic variables listed in Table 1. Examination of Hb concentrations and doses through the study period revealed Hb stability and dose changes of a similar scale and statistical significance to pP analysis (see Tables 3 and 4 for results of statistical analyses). When the final doses of study drugs were compared directly (as above, by multiplying DA dose by 200), EB doses were significantly higher than DA (95% CI of dose difference at 9 mo, 23 to 73 IU/kg per wk).

Discussion

This is the first randomized study to compare the clinical effectiveness of EB and DA therapy when both are administered via the subcutaneous route on a weekly basis after dose conversion; it may be seen as a test of the general application of previous efficacy studies. The challenge of a sustaining large, unselected, dialysis patient group over long time intervals is

considerable, which is perhaps why it is not attempted more frequently.

The study was run according to a declared protocol, with no necessary changes. The groups, drawn from an unselected patient population, were balanced according to all relevant criteria, reflective of normal hemodialysis populations. The decision-support system served to restore Hb outcomes after a period of dose stabilization, allowing direct comparison of doses required to achieve comparable Hb ranges at 9 mo of study.

In contrast with the published studies of Weiss *et al.* (9) and Locatelli *et al.* (10), we observed a significant (24%) dose increase associated with the conversion of this population from thrice-weekly to weekly subcutaneous EB: A falling trend in Hb outcome was correctable but at a price of an average EB dose increase of nearly 2000 IU/patient per wk. In the absence of a thrice-weekly control group, this dose increment cannot be taken as evidence of an increased requirement as a result of weekly treatment, although the population Hb outcomes and EB doses had been stable in the preceding 12 mo.

We observed significant (20%) dose reductions on conversion to DA, as the system responded to a rising Hb trend. Vanrenterghem *et al.* (14) found no change in Hb outcome or dose on analyzing the results of 224 dialysis patients 32 wk after conversion to (intravenous and subcutaneous) DA, concluding equivalence to thrice-weekly EPO. Nissenson *et al.* (13) found a nonsignificant fall in (intravenous) DA dose and a rise in Hb of 0.24 g/dl 28 wk after converting 169 randomly selected patients from intravenous EPO. The statistically significant dose reductions in our study partly reflect the conversion from thrice-weekly EB to weekly DA at a ratio of 200:1 (as advocated by the manufacturer within the European Union) and the degree of control of Hb outcome. It is apparent that had conversion been at the ratio of 260:1 (recommended by the Centers for Medicare and Medicaid Services [23]), the fall in DA dose would have been less marked.

It is important to note that there were no differences in either ferritin or HRC between treatment arms at the beginning or the end of study to indicate the development of functional iron deficiency. The parameters eKt/V, parathyroid hormone, and C-reactive protein did not change significantly during the study (data on file; not reported here for reasons of space).

Both pP and mITT analyses gave results of a similar nature. pP analyses serve to increase treatment differences by reducing uninformative “noise” (24), whereas mITT analyses include

Table 3. Mean Hb concentrations of mITT populations at baseline and end of study (*P* values for differences between treatment arms and change through study included)

	DA (<i>n</i> = 99)	EB (<i>n</i> = 97)	<i>P</i> Value (between Arms)
Baseline	11.9 ± 1.5	11.7 ± 1.8	0.23
Final	11.9 ± 1.5	11.5 ± 1.4	0.08
<i>P</i> value (Δ during study)	0.83	0.49	

mITT, modified intention to treat.

Table 4. Median (interquartile range) study drug doses among mITT populations

	DA (n = 99)	EB (n = 97)
Baseline	0.44 (0.23 to 0.86)	99 (51 to 167)
Final	0.38 (0.23 to 0.62)	122 (70 to 220)
P value	0.02	0.01

patients whose data through the course of the study minimize any differences. We chose pP as our primary analysis to ensure similarity of Hb distribution between groups, allowing us to compare doses directly, because the computerized system ensures predictable Hb outcome only for contemporaneous populations.

It is relevant to note that although the many published, randomized studies have compared erythropoietic regimens over a 24-wk period, we failed to observe complete dose and Hb stabilization (in both arms) until at least 28 wk after conversion in our unselected population, and iron status might yet have equilibrated further. It seems that the minimum follow-up period for randomized studies under similar conditions needs re-examination, especially where the effectiveness in unselected populations is concerned.

In conclusion, we have found that both DA and EB are capable of maintaining Hb when given by the subcutaneous route weekly in a large, unselected hemodialysis population, under the guidance of a computerized support system. Conversion to subcutaneous DA from thrice-weekly subcutaneous EB (at a ratio of 200:1) was associated with significant dose reductions, particularly in the prevalence of higher doses. In a parallel, randomized patient group, administration of subcutaneous EB at a reduced frequency was associated with significant dose increments to maintain Hb outcome, which contributed to the dose differences that had developed after 9 mo of observation.

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