Long-term intravenous epoetin-α / darbepoetin-α ratio in iron-replete hemodialysis patients

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ABSTRACT: ***Background:*** **Equivalence of intravenous (i.v.) and subcutaneous (s.c.) dosage requirements is a notable characteristic of darbepoetin-α (DPO), as opposed to other epoetins (EPOs). Currently in Europe, the EPOs/DPO conversion factor (200 IU EPOs = 1 μg DPO) does not take into account the route of drugs administration. To better define this ratio we have conducted a prospective, long-term trial in a group of hemodialysis patients.**

Subjects and methods: **At the start, we evaluated 40 iron-replete hemodialysis patients, but the final study was performed in the remaining 25 patients. During the first 6 months, patients were on i.v. epoetin-α (EPOα) maintenance therapy (phase 1: T-6 to T0). After conversion to i.v. DPO (initial 200:1 ratio) the observation was prolonged for a period of 12 months (phase 2: T0 to T12). DPO was administered at extended dose intervals and the EPOα/DPO rate was adjusted every month to maintain hemoglobin (Hgb) stability. Iron status and factors inhibiting erythropoiesis were continually checked to exclude unstable patients.**

Results: **Phase 1: EPOα weekly mean dose showed no significant variation. Phase 2: EPOα/DPO conversion factor progressively rose from 200 to 256.7 ± 86.9 IU/μg at T7 ($p<0.005$) and 336.8 ± 104.3 IU/μg at T12 ($p<0.0005$). DPO weekly mean dosage decreased from 40.0 ± 12.0 μg/week at T0 to 31.6 ± 3.7 μg/week at T7 ($p<0.005$) and 24.6 ± 7.0 μg/week at T12 ($p<0.0005$). Mean weekly/patient acquisition cost of EPOα was €70.6 ± 21.3 (T-6 to T0); after switching, the cost of DPO was €72.4 ± 22.7 (T0) and fell to €53.1 ± 11.2 during T6 to T12.**

Conclusions: **The progressive increase of EPOα/DPO ratio demonstrated that i.v. DPO requires lower doses compared with i.v. EPOα. When drugs are administered i.v., the starting EPOα/DPO conversion factor should be increased over the 200:1 ratio, similar to recommendations outlined in the United States and Japan. DPO dose reduction translated to notable cost-savings.**

Key words: *Epoetin-α, Darbepoetin-α, Intravenous, Conversion factor, Hemoglobin, Stable iron-replete hemodialysis patients*

INTRODUCTION

Erythropoiesis-stimulating agents (ESAs) have revolutionized the management of renal anemia. Since about 1990, 2 forms of recombinant human erythropoietin, epoetin-alpha (EPOα) and epoetin-beta (EPOβ), have been available, and more recently darbepoetin-alfa (DPO), a novel erythropoiesis stimulating protein, has been introduced.

EPOα and EPOβ differ slightly in their glycosylation patterns and especially in their formulations (1, 2). These differences have effects not only on the pharmacokinetic and pharmacodynamic properties of EPOs, but also on their stability, solubility and immunogenicity (3-5). Because of this latter feature, in December 2002, health authorities in all European countries formally contraindicated subcutaneous (s.c.) administration of EPOα in renal patients, recommending exclusively the intravenous (i.v.) route. The route of administration of EPOs is important for immunogenic response and in relation to therapeutic efficacy, and as a result, current U.S. and European guidelines advocate more effectively using the s.c. rather than the i.v. route, although the immunogenicity of EPOs is particularly prominent when administered via the s.c. route (6, 7).

The amino acid sequence of DPO differs from that of the EPOs and is engineered to obtain increased num-

bers of sialic acid–containing carbohydrate chains (8). In vivo DPO potency appears superior, and the pharmacokinetic profile shows a much longer elimination half-life and slower clearance than EPOα, with prolonged erythropoietic effect (9). Therefore DPO can be administered less frequently to obtain the same biological response of EPOs (10). Another DPO peculiarity is the equivalence of i.v. and s.c. dosing requirements to achieve target levels of hemoglobin (Hgb) (11).

The conversion factor between EPOs and DPO was based on the formula equating the protein mass of the 2 molecules (200 IU EPOs = 1 μg DPO) (12). This ratio is recommended in the European DPO approved dosing schedule (Aranesp and Nespo Product Information), but several trials have shown that this ratio does not accurately predict the dosage needs for the conversion of all patients and conditions (13-16). The 200:1 equivalence ratio is applied to both EPOα and EPOβ. Moreover, the route of ESAs administration has not been taken into account. For these reasons, recent papers have outlined that this "approved" EPO/DPO dose ratio should be challenged in clinical practice (17-19).

To better define this conversion factor, we have conducted a long-term, prospective study on a group of stable, iron-replete hemodialysis patients. The trial began with i.v. EPOα treatment in maintenance phase and was continued for 6 months. At the end of this first period, using the initial 200:1 equivalence, all patients were switched to less frequent administration of DPO maintaining the same route. During the following 12 months, DPO dose was adjusted to maintain stable Hgb levels as recommended by European guidelines (7). The EPOα/DPO ratio was evaluated to establish eventual changes from the accepted value. Consequent pharmacoeconomic analysis was performed. Hematological markers of iron status and potential factors inhibiting erythropoiesis and response to ESAs were continually checked to exclude unstable patients.

Subjects and methods

The study was approved by the therapeutics commission of our institution. Informed consent was obtained from 40 hemodialysis patients on stable treatment with i.v. EPOα and with normal iron status. During the trial (before and after switching to DPO) 15 patients were excluded on the basis of malignancy (n=1), infection (n=2), evidence of blood loss (n=2), variability of Hgb level (n=4), kidney transplantation (n=2), transfer to other dialysis unit (n=1) or death (n=3). Demographics and etiology of end-stage renal disease of the remaining 25 subjects are shown in Table I. At the beginning, 4 patients showed relative erythropoietin resistance, as gauged by EPOα dosage requirement of >200 IU/kg per week (19); all of those completed the study. The management of uremic anemia included maintenance Hgb >11 g/dL, determined from a sample taken prior to the dialysis session (at the end of the longest interval in the weekly dialysis schedule). When Hgb level fell below 10.5 g/dL or exceeded 12.5 g/dL, a 25% stepwise adjustment was performed in the total weekly ESA dose (up or down) and/or dosing frequency, according to the type of ESA.

During the first period, patients were observed with i.v. EPOα in maintenance therapy for 6 months (phase 1: T-6 to T0). The second period began with conversion to i.v. DPO and lasted for 12 months (phase 2: T0 to T12).

DPO was administered at extended dosing intervals as follows: patients receiving EPOα into the venous line 2 (n=10) or 3 (n=13) times a week were switched to once-a-week administration; patients receiving EPOα once weekly (n=2) were switched to once every other week. Following the recommendations published in the current approved European Summary of Product Characteristics, the initial EPOα/DPO conversion factor was calculated using the 200 IU to 1 μg ratio. If needed, to maintain Hgb stability, this ratio was adjusted every month, during the following period of observation.

Iron status was assessed monthly by measuring ferritin levels and transferrin saturation (TSAT). An attempt to ensure adequate iron stores was made by aiming for a ferritin level of up 100 ng/mL and a TSAT up to 20%. To achieve these targets, a standardized i.v. iron gluconate dose (62.5 mg) was administered once a week. When ferritin levels fell to <200 ng/mL, i.v. iron

TABLE I - PATIENTS INCLUDED: DEMOGRAPHICS AND ETIOLOGY OF END-STAGE RENAL DISEASE

Demographics and etiology	
Age (years)	63.8 ± 15.8
Race: Caucasian (%)	100
Sex	
Male	21
Female	4
Weight (kg)	62.4 ± 10.6
Dialysis duration (months)	31.6 ± 28.9
Dialysis modality (%)	
Hemodialysis	56
Hemodiafiltration	44
Etiology (n)	
Glomerulonephritis	4
Polycystic kidney disease	3
Obstructive uropathy	3
Hypertension	3
Other/unknown	12

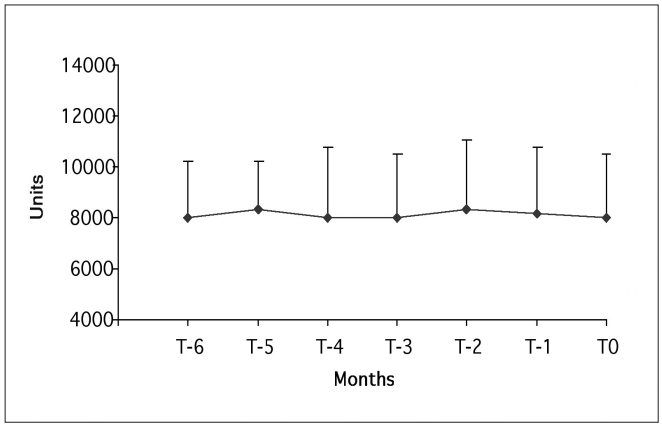


Fig. 1 - Phase 1: no variation of mean weekly EPOα doses.

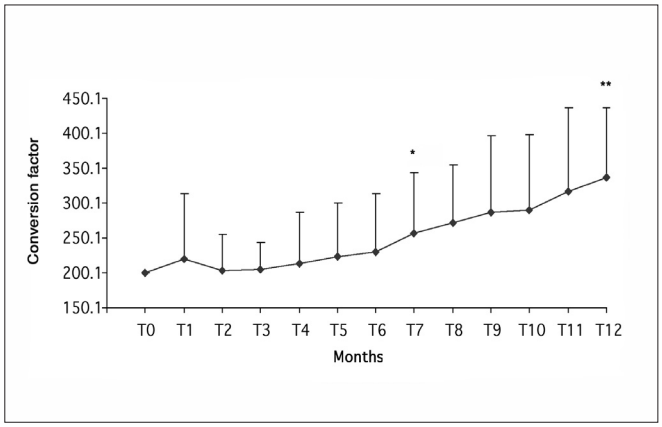


Fig. 2 - Progressive increase of EPOα/DPO conversion factor from switchover to 12th month (phase 2); *p<0.005, **p<0.0005, vs. baseline.

gluconate was increased to 3 times a week (187.5 mg/week).

To exclude other causes of deficiency anemias associated with hemodialysis, water-soluble, dialyzable vitamins such as folate and cobalamin were measured in the serum every 3 months. Folic acid and vitamin B_{12} supplementation was used: levofolinic acid (1.5 mg i.v. at the end of dialysis session) was administered in the case of low serum folate levels or macrocytosis; idroxicobalamin (1,000 µg i.v. at the end of dialysis session) was given for serum cobalamin deficiency or megalocytosis. Indices of nutritional status, inflammation and parathyroid activity were monitored by quarterly measure of serum albumin, C-reactive protein (CRP) and intact parathyroid hormone (i-PTH). A 3-monthly estimation of dialysis adequacy was performed by means of the urea Kt/V (20).

Acquisition costs of dosing ESAs were expressed in euros (€).

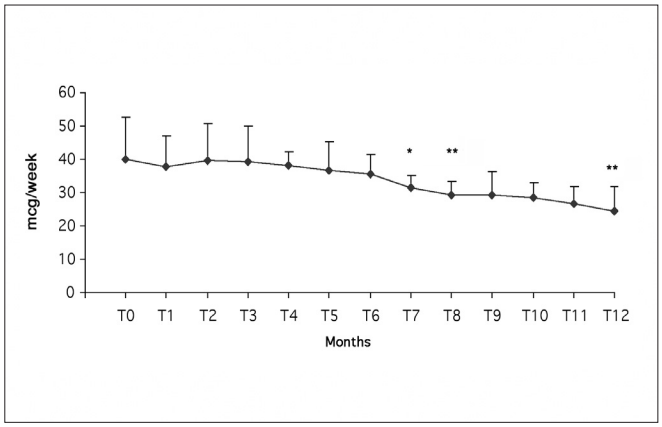


Fig. 3 - Decrease of DPO weekly mean dosage from switchover to 12th month (phase 2); *p<0.005, **p<0.0005.

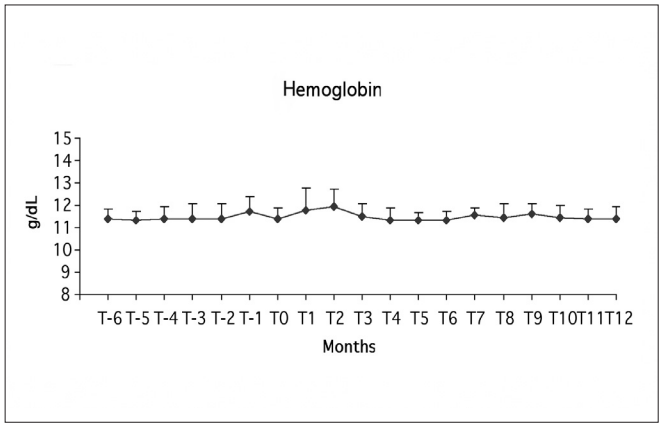
Statistical analysis

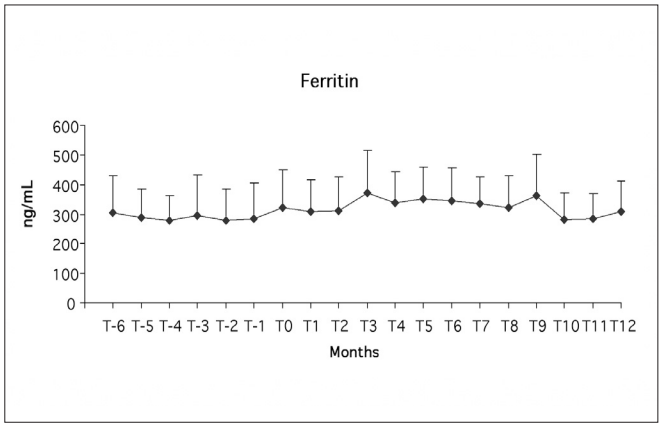
Collected data are presented as means ± SD. Statistical analyses were carried out using Student's paired *t*-test to explore the differences in means of the study variables measured during the two periods of ESAs treatment regimens. Statistical significance was set at a p value of <0.05.

Results

Phase 1: EPOα weekly mean doses did not show any significant variations (Fig. 1). Phase 2: the conversion factor, when switching from i.v. EPOα to i.v. DPO at T0, rose progressively from 200 to 256.7 ± 86.9 IU/µg at T7 (p<0.005) and 336.8 ± 104.3 IU/µg at T12 (p<0.0005) (Fig. 2). This increase started to be statistically significant at T8 (p<0.005), T9 (p<0.05), T10 (p<0.005), T11 and T12 (p<0.0005) with respect to the EPOα/DPO ratio at T7. No difference was found between patients with high EPOα dosage requirements (>200 IU/kg/week) and those with lower dosage requirements, in their relative EPOα/DPO conversion factor, and no variation of dose requirement was noted when the dosage interval of DPO was fixed once every other week in comparison with weekly administration (data not shown).

DPO weekly mean dosage demonstrated a decrease from 40.0 ± 12.0 µg/week at T0 to 31.6 ± 3.7 µg/week at T7 (p<0.005), 29.4 ± 1.6 µg/week at T8 (p<0.0005) and 24.6 ± 7.0 µg/week at T12 (p<0.0005) (Fig. 3).





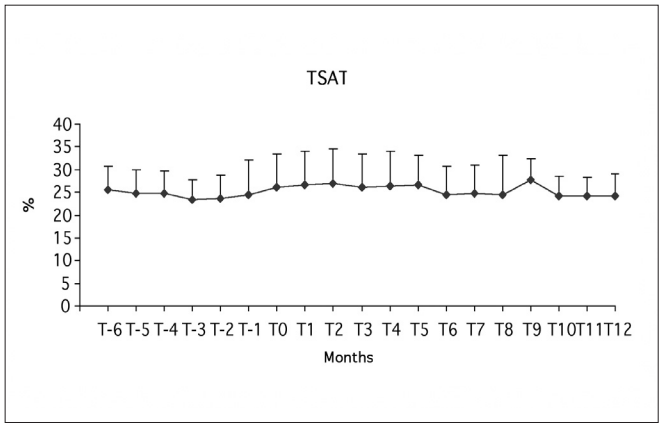


Fig. 4 - No variation of hemoglobin, ferritin and TSAT mean values during long-term observation period (phase 1 and phase 2). TSAT = transferrin saturation.

Hemoglobin, iron stores, vitamins, indices of nutritional status, inflammation, parathyroid activity and dialysis adequacy

Mean Hgb concentration was 11.38 ± 0.46 g/dL at T-6, 11.4 ± 0.47 g/dL at T0, 11.31 ± 0.42 g/dL at T6 and 11.38 ± 0.54 at T12. Monthly Hgb, serum ferritin and TSAT mean values are shown in Table II and in Figure 4. No significant variation of Hgb, serum ferritin and TSAT mean levels during the long-term observation period (phase 1 and phase 2) was observed.
Measures of serum folate and cobalamin, serum albumin, PCR, i-PTH and urea Kt/V, performed every 3 months, did not show any significant change during the present study (Tab. III).

TABLE II - HEMOGLOBIN AND MARKERS OF IRON STATUS

	T-6	T-5	T-4	T-3	T-2	T-1	T0
Hgb (g/dL)	11.38 ± 0.46	11.32 ± 0.41	11.37 ± 0.59	11.41 ± 0.62	11.4 ± 0.63	11.7 ± 0.70	11.4 ± 0.47
Ferritin (ng/mL)	305.8 ± 123.3	288 ± 98.5	278.1 ± 85.3	295.1 ± 136.2	277 ± 108.8	284.2 ± 119.9	321.5 ± 128.1
TSAT (%)	25.5 ± 6.6	24.7 ± 5.2	24.8 ± 5.2	23.6 ± 4.8	23.6 ± 4.2	24.4 ± 5.2	26.0 ± 7.8

	T1	T2	T3	T4	T5	T6
Hgb (g/dL)	11.8 ± 0.97	11.97 ± 0.73	11.52 ± 0.52	11.34 ± 0.54	11.32 ± 0.35	11.31 ± 0.42
Ferritin (ng/mL)	309.5 ± 105.5	313.1 ± 114.2	371.2 ± 145.3	338.5 ± 102.9	351.3 ± 108.8	344.4 ± 111.3
TSAT (%)	26.6 ± 7.6	26.9 ± 7.4	26.2 ± 7.7	26.5 ± 7.6	26.7 ± 7.5	24.4 ± 6.4

	T7	T8	T9	T10	T11	T12	
Hgb (g/dL)	11.5 ± 0.34	11.45 ± 0.61	11.6 ± 0.5	11.42 ± 0.60	11.41 ± 0.42	11.38 ± 0.54	NS
Ferritin (ng/mL)	336.8 ± 90.1	321.6 ± 106.5	361.8 ± 140.5	281.3 ± 92.1	285.6 ± 84.9	308.8 ± 103.8	NS
TSAT (%)	24.7 ± 6.3	24.6 ± 6.3	27.8 ± 8.5	24.2 ± 4.5	24.2 ± 4.3	24.3 ± 4.9	NS

Hgb = hemoglobin; TSAT = transferrin saturation.

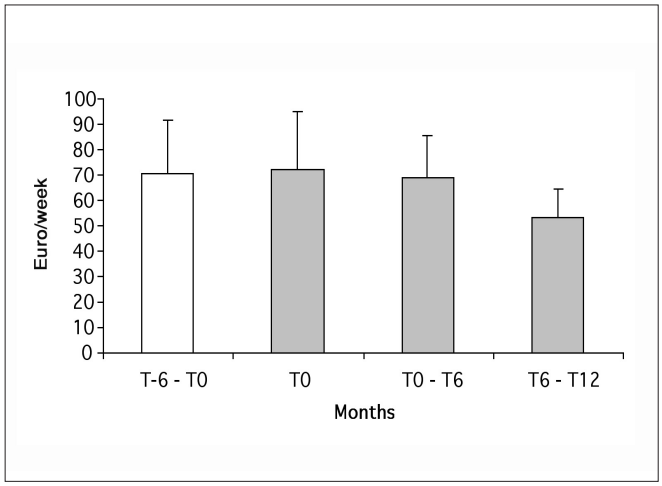


Fig. 5 - Mean weekly patient cost of ESAs (open column, EPOα; shaded columns, DPO).

Cost of ESAs

Our analysis was based on a local institutional contract price of €1.74/200 IU of EPOα and €1.81/µg of DPO. Mean weekly patient cost of EPOα during phase 1 (T-6 to T0) was €70.6 ± 21.3. At the switching to DPO, the cost increased to €72.4 ± 22.7, due to the different prices of ESAs. During the first 6 months of phase 2 (T0 to T6), mean weekly patient cost of DPO was €69.0 ± 16.8 and in the second 6-month period (T6 to T12), it fell to €53.1 ± 11.2, in consequence of the marked reduction of dosage requirements (Fig. 5).

Discussion

Our study confirms the objective difficulties in maintaining hemodialysis patients for long-term observation when the stability of clinical and laboratory parameters is needed to validate the behavior of the primary end point. This fact is particularly evident during the studies regarding uremic anemia, influenced as they are by variability of hematological data, in consequence of different factors. In patients with end-stage renal disease, Hgb levels fluctuate much more compared with the general population. This individual variability caused a significant portion of dialysis patients (29%) to move both above and below the target Hgb level range during a relatively short period of follow-up (21). We used a long period of averaging, which has been suggested as a method to provide more stable measurement of anemia correction outcomes; however, we lost 30% of patients to follow-up, because of biological and comorbid conditions influencing their response to ESAs therapy and individual Hgb level variability caused by other factors (i.e., sampling methods, laboratory assays and dialytic variations of body weight) (6, 22, 23).

For these reasons, our study population includes a relatively small number of patients; nevertheless, it assures a valid evaluation of the ratio between EPOα and DPO during a long period of monitoring free of limits linked to the fluctuation of the data compared before and after ESA change.

The EPOα/DPO conversion factor progressively increased to a statistically significant change at the beginning of the second 6-month period. In the following

TABLE III - VITAMINS AND INDICES OF NUTRITIONAL STATUS, INFLAMMATION, PARATHYROID ACTIVITY AND DIALYSIS ADEQUACY

	T-6	T-3	T0	T3	T6	T9	T12	p Value
Folate (n.v. >5.38 ng/mL)	20.5 ± 7.4	20.2 ± 7.5	21.7 ± 6.6	24.1 ± 3.6	24.1 ± 3.3	24.7 ± 6.6	24.4 ± 3.0	NS
Cobalamin (n.v. 211-911 pg/mL)	727.2 ± 602.4	794.2 ± 636.5	775.2 ± 670.1	850.2 ± 580.7	859.8 ± 554.7	856.4 ± 450.5	827.8 ± 413.9	NS
Albumin (n.v. 3.4-4.7 g/dL)	4.0 ± 0.4	3.9 ± 0.4	3.9 ± 0.5	3.8 ± 0.5	4.1 ± 0.6	4.1 ± 0.6	4.0 ± 0.6	NS
CRP (n.v. 0-5.0 mg/L)	5.6 ± 5.6	5.9 ± 6.0	7.8 ± 7.7	7.6 ± 7.5	6.1 ± 6.2	6.7 ± 6.7	5.3 ± 5.2	NS
i-PTH (pg/mL)	224.8 ± 157.0	155.5 ± 131.5	234.2 ± 182.3	245.3 ± 212.4	164.7 ± 109.3	182.0 ± 141.2	134.7 ± 90.6	NS
Kt/V (Daurgirdas)	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.3	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	NS

CRP = C-reactive protein; i-PTH = intact parathyroid hormone; NS = not significant; n.v. = normal value.

months, the increase was even more evident and was highest at the end of the period of study. In line with this result, average weekly dose of DPO requirements showed a reduction from the time of the switchover, becoming statistically significant at T7 and even more noticeable.

Higher EPOs/DPO ratios than commonly admitted (200:1) were previously reported (13, 14, 19); nevertheless, we found low conversion rates referred to by other authors (15, 16). Most studies examining ESAs with regard to EPOs and DPO have not specified the forms of recombinant human erythropoietin administered or whether via the i.v. or s.c. route.

It is now well known that a reduction in dosage requirement is usually needed when switching from i.v. to s.c. administration of EPOs (24, 25). Pharmacokinetic studies demonstrate that EPOα has lower bioavailability but a longer half-life after s.c. than after i.v. administration (26). A more rapid fall in circulating erythropoietin with i.v. dosing may affect erythropoiesis through shortened survival of red blood cells, resulting in neocytolysis, the process by which young erythrocytes are destroyed (27, 28). Changing of EPOα from s.c. to i.v. route, in compliance with the resolution of the European Medical Agency, results in an increase in mean dose for maintenance of Hgb levels in hemodialysis patients (29, 30). In contrast, some AA find no differences between the dose of s.c. and i.v. EPOs needed (31, 32). However, studies showing that administration route does not interact with the efficacy of EPOs have had a smaller number of patients and have been observational, mostly in an unselected population.

Longer DPO terminal half-life means that the serum concentration of the drug remains above the threshold value longer, and therefore the efficacy is equal for i.v. or s.c.. DPO has a 3-fold longer half-life than EPOs following i.v. administration and approximately 2-fold longer than EPOs by the s.c. route (9).

The above-mentioned reports support our results. Lower doses of i.v. DPO were able to maintain target Hgb levels than those of i.v. EPOα. Consequently, when ESAs are administered i.v., the initial EPOα/DPO conversion factor should be increased over the conventional ratio based on the formula equating the protein mass of the 2 molecules. Indeed, Japanese Approved Product Information suggests that patients be switched to i.v. DPO based on the ratio of 240 IU EPOs = 1 μg DPO.

In our dialysis population, the EPOα/DPO conversion rate was not different between patients with relative erythropoietin resistance and those with lower dosage. When the dosage interval of DPO was fixed once every other week no variation of dose requirement was noted in comparison with patients treated with weekly administration. However, these observations are limited by the restricted number of patients enrolled in the study. We can conclude that i.v. DPO administered once weekly was more efficacious than twice- or thrice-weekly i.v. EPOα, in keeping with the findings of other authors and confirming our previous reports (33, 34). The increase of EPOα/DPO conversion factor was progressive, but became noticeable and significant some months after switching. This late result may reflect the frequency in changing ESAs dosage; in our dialysis unit it may take up to 4 weeks for adjustment of the dosage given to patients in the maintenance phase. Therefore a long-term observation period was appropriate to obtain the data. The fact that only "selected" patients were included in the analysis could allow a better response to DPO treatment; however, we emphasize that the dose of EPOα required was stable in the maintenance period, while in the same patients DPO dose decreased progressively after the switchover.

Medication acquisition costs are influenced by institutional contract pricing and dosing. The progressive decrease of DPO weekly mean dose translated to appreciable cost-savings compared with those for EPOα. This result was much more significant, if we took into account the higher price of DPO than that of EPOα, on the basis of the contract pricing of our institution.

In conclusion, the starting EPOs/DPO conversion factor set by the European schedule is probably not appropriate for the i.v. route. It is desirable that the fixed ratio be replaced by an aggregate of conversion factors, similar to recommendations outlined in the United States (35). In these prescribing notes, dose conversion between EPOs and DPO is not always linear across the dosing spectrum and is mostly higher than 200 IU EPOs =1 μg DPO. However, further clinical trials will still be required to investigate the effects of route of ESAs administration and others factors that influence erythropoietic response, to provide conclusive evidence regarding the switching of treatments.

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