Timing of the Administration of Intravenous Darbepoetin Alfa During the Dialysis Session: Does It Impact Efficacy?

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BACKGROUND: Darbepoetin alfa (DA) is an erythropoietin-stimulating agent (ESA) preferably administered through intravenous (IV) route in hemodialysis (HD) patients. Although some in vitro studies suggest the possibility of partial adsorption of ESAs in dialysis membranes (Mb) and lines, these data are not clinically confirmed.

METHODS: This 12-month, prospective, single-center cross-over study assessed the impact of the time of IV DA injection during HD on hemoglobin (Hgb) level and ESA dosing. A total of 90 HD patients received IV DA once every other week (Q2W), delivered at 2 possible time points: the middle or end of the HD session. After 6 months, the injection time point was crossed over to the other timing modality for another 6 months.

RESULTS: Demographics for both groups of patients were similar. Mean Hgb level remained stable from baseline to month 6 (not significant) for both timing modality groups. The same was observed for DA dose. Hemodialysis session parameters, nutritional status, and Kt/V were similar and stable during the study. Mean transferrin saturation was 44% and serum ferritin was ≥100 μg/L in more than 92% of patients. Iron supplementation remained unchanged and there were no blood transfusions during the study.

CONCLUSIONS: Q2W DA maintained target Hgb concentrations. The lack of difference in Hgb levels and DA dosing between the 2 injection timings suggests a lack of clinically significant adsorption/interaction between DA and dialysis Mb/lines. Therefore, timing of IV DA administration can be flexible and adapted to the routine practice of each local dialysis unit.

Anemia is a common complication of end-stage renal disease and these patients, including those undergoing hemodialysis (HD), are successfully treated with erythropoietin-stimulating agents (ESAs). Several in vitro studies[1,2] have shown recombinant human erythropoietin (rhEPO) could be partly eliminated by membrane adsorption with some dialysis membranes (Mb). A more recent study suggested this might be the case only with high-flux membranes.[3]

Darbepoetin alfa (DA) is an engineered rhEPO analogue. Compared with standard rhEPO, it has a longer in vivo activity and can therefore be administered less frequently.[4,5] Intravenous (IV) or subcutaneous (SC) routes are possible. The SC route is preferably used when patients are not on dialysis, due to lack of vascular access.[6] Darbepoetin alfa is generally well tolerated, and clinical trials of 20–52 weeks duration have demonstrated the efficacy of SC and IV administration in the treatment of anemia associated with chronic kidney disease both in dialysis and pre-dialysis patients.[4] Other studies have demonstrated that IV DA, administered once every other week (Q2W) in dialysis patients, can maintain hemoglobin (Hgb) concentrations at targeted levels with no increase in dosing.[7,8]

The present study aimed to assess whether the timing of DA injection during dialysis sessions induced clinical differences; this is the experience from our center.

Subjects and Methods

This prospective, open-label, single-center cross-over study was conducted over a 12-month period, to assess the impact of the timing of IV DA injection during HD on Hgb levels and DA dose. All patients treated in our center were included in the study for 12 months (from February 1, 2006 to January 31, 2007). They were prescribed regular HD on Integra-Hospal generators for 3.5 to 4 hours thrice weekly: Monday-Wednesday-Friday (group M), or Tuesday-Thursday-Saturday (group T). For each patient, the first day for dialysis remained the same throughout the study. Upon inclusion, patients received IV DA, administered either in the middle or at the end of the HD session. Vascular access was insured ➲

DOI: 10.1002/dat.20397

Timing of Darbepoetin Administration

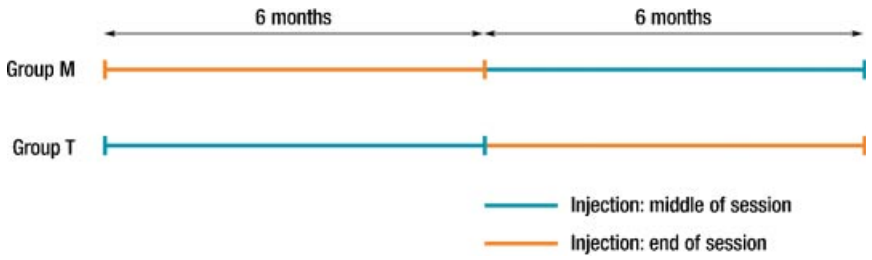

FIGURE 1. *Study design.*

TABLE I. Baseline characteristics of the study patients.

	Group M (n = 38)	Group T (n = 38)
Demographics		
Male, *n* (%)	25 (65%)	28 (73%)
Age, yrs, mean (SD)	59 (17.1)	56 (16.9)
Height, cm, mean (SD)	171 (7.7)	169 (6.9)
BMI, kg/m^2, mean (SD)	23.0 (4.6)	21.5 (4.1)
Systolic BP, mmHg, mean (SD)	130 (21.3)	137 (22.8)
Diastolic BP, mmHg, mean (SD)	78 (14.8)	81 (14.3)
Diabetes	7 (18%)	8 (20%)
Hypertension/nephroangiosclerosis	7 (18%)	5 (13%)
Glomerulonephritis	11 (29%)	16 (41%)
Others	13 (34%)	10 (26%)
Dialysis parameters		
Dialysis duration, yrs, mean (SD)	3.2 (2.7)	3.5 (4.5)
Creatinine, µmol/L, mean (SD)	870 (252.7)	850 (211.1)
URR, mean (SD)	0.70 (0.06)	0.69 (0.06)
Kt/V, mean (SD)	1.34 (0.22)	1.36 (0.24)
Calcium (Ca), Phosphorus (P) parameters		
PTH, pg/mL, median	269	284
Corrected calcium, mmol/L, mean (SD)	2.34 (0.18)	2.34 (0.15)
Phosphorus, mmol/L, mean (SD)	1.8 (0.6)	1.7 (0.5)
Ca × P product, mmol^2/L^2, mean (SD)	3.8 (1.2)	3.9 (1.1)
Nutritional parameters		
Albumin (g/L)	38.8 (3.96)	39.2 (3.67)
nPCR (g/kg/d)	0.88 (0.21)	0.92 (0.24)
Anemia work up (baseline)		
Hemoglobin, g/dL, mean (SD)	11.5 (1.01)	11.6 (1.34)
Transferrin saturation, %, mean (SD)	31 (11.8)	31 (11.4)
Ferritin, µg/L, mean (SD)	552 (292.9)	597 (261.1)
Ferritin ≥100 µg/L, %	97	100

Group M = Monday start; Group T = Tuesday start. PTH = parathyroid hormone

by double punction arteriovenous fistula in all patients. Darbepoetin alfa injection was scheduled for the first day of the weekly 3-day dialysis session (Monday: group M, or Tuesday: group T) every other week. After 6 months, the injection time point was crossed over to the other timing modality for another 6 months. The end of session injection was performed in the first 6-month period for group M and the second 6-month period for group T, and the middle of session injection was performed in the first 6-month period for group T and the second 6-month period for group M (*Figure 1*).

At the start of the dialysis session, each patient received a 0.2 to 0.6 mL injection of nadroparin, a low molecular weight heparin. High and medium permeability membranes were used throughout the study and were unchanged for each patient: cellulose triacetate (n = 33), polyamide (n = 30), polyethersulfone (n = 22), and polyacrylonitrile (n = 5) equally distributed and maintained in each group. Darbepoetin alfa injections were performed in the venous injection site before the drip chamber on the venous line (Pivipol Hospal, Gambro Dasco, S.p.A.).

The follow-up conditions were those of daily practice, and the protocol ensured that no complementary visits or biological assessments would be performed outside the usual HD follow-up. Hemoglobin levels, as well as other parameters were collected every other week on the mid-week session, and DA injections were performed on the first dialysis day of the following week. Descriptive statistics were applied for demographics at baseline, defined as the last known value before inclusion, and assessed variables. The main combined criterion was the variation of Hgb level and DA dosage throughout the treatment period, and was defined as the mean change in Hgb level and DA dose from baseline to month 6 (M6) for each timing modality. The target Hgb level was between 11.5 and 12 g/dL. Secondary criteria comprised the variation of Hgb level and DA dosage from baseline to M12 for each treatment group (M and T). Clinical, biological, and nutritional parameters were also assessed. Iron supplementations were quantified.

Statistical analysis of the data was performed using SAS version 9.1. Comparisons were done by Wilcoxon signed rank test for quantitative variables. Calculation of the sample size was made and as each patient was compared to himself/herself, the number of patients appeared to be adequate. Variance analyses for Hgb level and DA dosage were performed according to injection time point and time of follow up. Also, tests were performed to detect any carry-over effect. The complete analysis set (CAS) population consisted of all included patients who had a value for Hgb at M1 and M6 of either period 1 or 2. Tolerance population was defined as all patients who received at least 1 dose of IV DA. ➲

TABLE II. Mean Hgb and DA dose according to time of injection—CAS population.

	Parameter	Baseline	Month 6	*p*-Value*
End of session (n = 76)	Hgb (g/dL) (SD)	11.8 (1.1)	11.7 (1.1)	.42
	DA dose (μg/kg/wk)			
	Mean (SD)	0.47 (0.33)	0.51 (0.38)	.08
	Median	0.39	0.41	
Middle of session (n = 76)	Hgb (g/dL) (SD)	11.8 (1.2)	11.6 (1.0)	.23
	DA dose (μg/kg/wk)			
	Mean (SD)	0.50 (0.32)	0.52 (0.40)	.97
	Median	0.46	0.43	

**Wilcoxon signed rank test.*

TABLE III. Evolution of Hgb and DA dose in both dialysis groups.*

	Hemoglobin (g/dL) Mean (SD)		DA (μg/wk) Mean (SD)	
	Group M	Group T	Group M	Group T
Baseline	11.5 (1.0)	11.6 (1.3)	31.9 (19.7)	28.6 (17.0)
M3	11.5 (1.0)	11.5 (1.2)	31.3 (18.9)	30.8 (23.9)
M6	11.5 (1.0)	11.6 (1.1)	36.4 (20.5)	29.8 (22.1)
M9	11.9 (1.1)	11.7 (1.0)	34.9 (18.5)	30.3 (20.8)
M12	11.6 (0.9)	12.0 (1.0)	35.6 (21.4)	27.4 (21.8)

**Group M received DA from baseline to M6 at the end of the session and from M7 to M12 at the middle of the session. Group T received DA from baseline to M6 at the middle of the session and from M7 to M12 at the end of the session.*

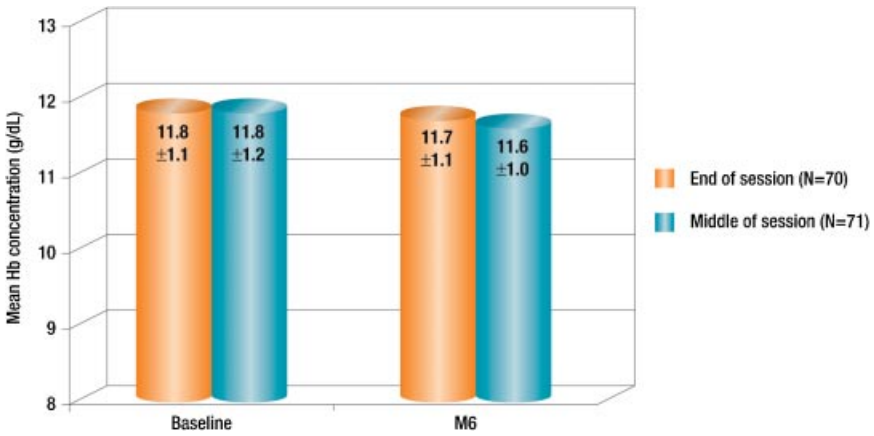

FIGURE 2. *Mean concentration of Hgb baseline and at M6 in both groups. Carry-over effect was not significant.*

Results

Out of 90 patients treated in our center and included, 14 discontinued the study (8 died, 3 had kidney transplantation, and 3 changed residence). The CAS population included 76 patients in the end of session group and 76 patients in the middle of session group. At the beginning of the study, patients in the M and T dialysis groups were comparable, and their baseline characteristics are presented in *Table I*. For all patients, the mean (±SD) duration of HD was 11 hours and 40 minutes (±20 min) per week. The mean blood flow was 285 ± 30 mL/min.

Hemoglobin

The mean level in Hgb from baseline to month 6 (M6) for each timing modality remained stable, and there was no difference between groups (*Table II*). Also, in the M or T dialysis group, levels of Hgb did not show any significant changes throughout the study, whether DA was injected in the middle or at the end of the dialysis session (*Table III* and *Figure 2*). For individual patients without any missing data for both study periods (n = 76), mean (SD) Hgb change from baseline to M6 was −0.15 (1.56) g/dL and −0.13 (1.49) g/dL for end and middle of session respectively (p = .68). Tests for the effect of the order of administration timing showed no detectable carry-over effect.

DA Dose

The same was observed for DA weekly dose, whether it was injected in the middle or at the end of the dialysis session (*Table II*), and the dose also remained stable for patients in the M or T dialysis group whatever time the compound was injected (*Table III*). No detectable carry-over effect was shown.

Membrane Effect

No particular effect on Hgb and DA dose could be attributed to the different membranes: cellulose triacetate (n = 33), polyamide (n = 30), or polyethersulfone (n = 22). The number of patients under polyacrylonitrile membrane was too small to make any conclusion.

Other Parameters

Hemodialysis session parameters (creatinine, URR, and Kt/V) were similar in both the M and T groups at baseline, and remained stable throughout the study. Nutritional status and calcium and phosphorus evaluations also remained stable (*Table IV*) and similar in the M and T dialysis groups. Mean transferrin saturation was 40% and ➲

TABLE IV. Biological parameters—Median values.*

	Group M (*n* = 38)			Group T (*n* = 38)		
	Baseline	**M6 End of Session**	**M12 Middle of Session**	**Baseline**	**M6 Middle of Session**	**M12 End of Session**
Dialysis parameters						
Creatinine (μmol/L)	886	945	942	856	903	943
URR	0.71	0.71	0.71	0.71	0.72	0.69
Kt/V	1.30	1.40	1.40	1.40	1.40	1.30
Ca and P parameters						
PTH (pg/mL)	269	257	241	284	205	211
Corrected calcium (mmol/L)	2.34	2.25	2.33	2.33	2.19	2.28
Phosphorus (mmol/L)	1.8	1.8	1.9	1.6	1.7	1.7
Ca × P product ($mmol^2/L^2$)	3.7	4.0	3.9	3.7	3.5	3.6
Nutritional parameters						
Albumin (g/L)	39.1	38.9	38.8	39.7	40.3	41.0
nPCR (g/kg/d)	0.90	0.90	0.90	0.90	0.90	0.80

* *There was no statistical difference for any value at any time of the study.*

50% respectively and remained at this level throughout the treatment period. Serum ferritin was ≥100 μg/L in more than 92% of patients at baseline, and remained so during the 12-month follow-up. IV iron administration remained unchanged, and there were no blood transfusions during the study.

Adverse Events

A total of 8 deaths were reported (4 patients: cardiac diseases; 2 patients: malnutrition and infection; 1 patient: dementia; 1 patient: complication on vascular access), and 14 patients (18%) underwent at least 1 hospitalization, including 3 for kidney transplant. The mean hospitalization duration was 7 days. None of these serious adverse events was drug-related.

A total of 34 adverse events (AEs) occurred in 26 patients, and did not result in hospitalization. The most frequent AEs were arteriovenous fistulas thromboses with 8 episodes in 5 patients. Also, 5 patients required treatment for hepatitis C. Both events are well-known in patients undergoing HD.

Discussion

Guidelines recommend the use of ESAs for the management of anemia in patients with chronic renal failure after ensuring adequate iron stores.[6] In the present article, we used a Q2W dosing regimen of IV DA. In a combined analysis of 8 multicenter trials in which 1,101 dialysis patients were switched from once-weekly rhEPO alfa or beta to Q2W DA, Mann demonstrated that Q2W DA was effective in maintaining target Hgb levels, regardless of the route of administration and with no notable increase in the weekly equivalent dose.[7] In another trial, 90 stable HD patients, who had received Q2W IV DA for a period of 6 months, were switched to Q2W IV DA for a further period of 6 months.[8] The Q2W dosing effectively and safely maintained Hgb concentrations and dose requirements were not different.

Guidelines also mention that the dialysis schedule should not be altered during ESA therapy.[9] In addition, dialysis should be optimized to ensure the effective treatment of renal anemia: that is, to maximize the effects of ESA therapy, the Kt/V should be >1.2 in a 3 times weekly HD program. We offered such schedule with a Kt/V between 1.34 and 1.36.

In vitro studies have shown differences in the adsorption of rhEPO on dialysis membranes. Cheung demonstrated that membranes made from copolymer of polyacrylonitrile and methallyl sulfonate bound rhEPO 30 times more than did cuprophan.[1] Similar results were presented by Mori and colleagues, who found a significant adsorption by polymethyl metacrylate and polyacrylonitrile membranes, but not by cuprophan, ethylene vinyl alcohol, or polysulfone membranes.[2] These studies were performed in the early 1990s. More recently, in a study performed on 211 patients undergoing dialysis using epoetin beta to correct anemia, Richardson and colleagues could not identify a significant difference in need for epoetin through the use of a polysulfone/high-flux membrane over a modified cellulose triacetate/midflux membrane, provided the patients were adequately dialyzed.[10] McMahon and colleagues came to the same conclusion in a study assessing pre-dialyzer and post-dialyzer serum concentrations of epoetin alfa, iron sucrose, and enoxaparin.[3] Apart from the latter, for which high-flux membranes required greater doses, no noteworthy difference among membranes was defined for the other compounds.

Despite these findings, the Summary of Product Characteristics of epoetin beta mentions that the compound should be injected at the end of dialysis session.[11] Other ESAs, and DA in particular, do not recommend a definite time for injection.[12] Because of the discrepancies in the findings resulting in some uncertainty, it is a common habit among nephrologists to inject

ESAs at the end of the HD sessions.[13,14] When the intravenous way is chosen for injection, ESAs are mostly injected at the end of the session either for routine practice,[15] recommendations of guidelines,[9,13] summary of product characteristics,[11] and pharmacodynamic considerations.[16,17] It can be noted, however that the end of a dialysis session can be somewhat hectic (hypotension, cramps, vomiting for the patient, preparation to disconnection for the nurse) and the injection can be forgotten. The possibility of injecting DA at another time during the dialysis session is somewhat preferable for the nurses in charge of the injection procedure.

Locatelli and colleagues point out that the biocompatibility of dialysis membranes and flux seem to have a smaller effect on anemia than expected, provided the patients are adequately dialyzed and do not have an iron or vitamin depletion.[18] In a study involving 68 patients, Movilli and colleagues emphasize that adequate dialysis in iron-replete patients contributes to optimize rhEPO responsiveness independent of the use of biocompatible synthetic membranes.[19]

The results of the present study are in agreement with these statements: no difference in Hgb and DA dose could be found using 3 different membranes (the number of patients using polyacrylonitrile is too small). We observed that, with an adequate dialysis ensuring stable biological parameters, the use of 3 different membranes and different times of injections during the HD session did not result in a clinical difference in the management of anemia with DA.

Conclusion

In this experience at our center, the lack of difference between the 2 injection timings suggests there is no significant adsorption or interaction between DA and dialysis membranes and/or lines. These findings tend to prove that timing can be flexible and adapted to local dialysis unit practices. More studies, however, will be needed to confirm these results.

Disclosure

Marie-Danielle Bernard, MD (Anticipsanté, Marly le Roi, France) assisted in writing the manuscript. Her assistance was funded by Amgen S.A.S. (France). D&T

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