Treatment of Renal Anemia in Saudi Dialysis Patients: Between Darbepoetin Alfa and Recombinant Human Erythropoietin (rHuEPO)

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Abstract

Background: Darbepoetin alfa is an erythropoietic agent with a 3-fold longer elimination half-life than recombinant human erythropoietin (rHuEPO), which allows less frequent dosing, and hence it maintains an effective hemoglobin control at extended dose intervals compared with rHuEPO. This study assessed the efficacy and safety of unit doses of darbepoetin alfa for the treatment of renal anemia in hemodialysis (HD) and peritoneal dialysis (PD) patients.

Methods: In this prospective study, 143 dialysis patients (68 HD and 75 PD patients) maintained on stable rHuEpo treatment were switched to darbepoetin alfa at extended dose intervals by the same route of administration as previous rHuEpo therapy [intravenous (i.v.), n=78 or subcutaneous (s.c.), n= 65]. Patients receiving rHuEpo two or three times a week were switched to darbepoetin alfa once a week and those receiving rHuEpo once a week were switched to darbepoetin alfa once every two weeks. The unit doses of darbepoetin alfa (10-150 ug) were titrated to maintain hemoglobin concentrations of 10-12 g/dl for 24 weeks.

Results: Hemoglobin (Hgb) concentrations were maintained effectively in our patients regardless of the dose interval of darbepoetin alfa. The overall mean change in Hgb concentration from baseline to evaluation period was an increase of 0.18 g/dl (95% CI ± 0.16). Regardless of route of administration, darbepoetin alfa effectively maintained mean Hgb concentration above 11 g/dl throughout the entire study period. Darbepoetin alfa administered by both the i.v. and s.c. routes resulted in stable mean Hgb concentrations during the evaluation period. Subjects with baseline Hgb concentrations < 11 g/dl experienced significant mean increase in Hgb concentration from baseline to evaluation, which was more pronounced following i.v. than s.c. administration (0.79 vs 0.55 g/dl respectively). Relative to baseline, i.v. and s.c. darbepoetin alfa dosage requirements decreased in subjects with baseline Hgb ≥11 g/dl (21.64 to 15.86 ug/week and 21.95 to 18.52 ug/week respectively p=0.0214), while there was a little increase in darbepoetin alfa dosage in subjects with baseline Hgb < 11 g/dl (25.22 to 26.76 ug/week and 22.74 to 24.81 ug/week in the i.v. and s.c. groups respectively p=0.0581). The percentage change in dose requirements from baseline to evaluation period in all patients, regardless of route of administration was not significant (2.28%, 95% CI -3.64, 7.89). Hemoglobin concentrations were also effectively maintained in patients who received darbepoetin alfa once weekly and once every other week. Darbepoetin alfa was well tolerated in all HD and PD patients, and the safety profile was consistent with previous trials with darbepoetin alfa in dialysis patients.

Conclusion: The treatment of renal anemia in dialysis patients (both HD and PD) with unit doses of darbepoetin alfa is both effective and well tolerated. Moreover, administration of darbepoetin alfa by both i.v. and s.c. route is associated with stable Hgb concentration. Darbepoetin alfa administered i.v. or s.c once weekly or once every other week is an effective and safe treatment regimen for hemodialysis and peritoneal dialysis patients with renal anemia.

Keywords: ESRD; Dialysis; Anemia; Hemoglobin; Darbepoetin alfa; rHuEpo

Introduction

Erythropoiesis-stimulating agents have been credited with a reduced need for red cell transfusion and improved quality of life for patients with end-stage renal disease (ESRD) who have severe anemia [1]. Trials comparing lower and higher hemoglobin (Hgb) targets have been interpreted to suggest that targeting of a lower Hgb range would be a safer approach in these patients [2-4]. Darbepoetin alfa is a unique erythropoietic protein that by virtue of its longer elimination half-life [5] and greater in vivo biological activity [6] can be administered less frequently than rHuEpo. Several studies have confirmed that darbepoetin alfa can be administered less frequently than rHuEpo to correct and maintain Hgb in subjects with chronic kidney disease both on dialysis and not on dialysis [7-16]. Moreover it has been shown that, in contrast to rHuEpo, there is no difference in intravenous (i.v.) and subcutaneous (s.c.) dose requirements for darbepoetin alfa [12,16]. For the route of Erythropoiesis-stimulating agents, subcutaneous administration is more convenient than the i.v. administration in patients on peritoneal dialysis or those with chronic kidney disease without arterio-venous fistula [17]. The s.c. route improved the efficacy of therapy resulting in a reduced dosing requirements of Erythropoiesis-stimulating agents to maintain the target hemoglobin level [18]. However many patients on hemodialysis still continue to be treated via the i.v. route. The primary reason is probably the discomfort with s.c. injections. The s.c. administration of two or three times weekly causes pain at every injection. Once-weekly therapy using high dose of rHuEpo with an enlarged administration interval has been attempted since the 1990s, the results, however, were not encouraging [19]. Recent studies have demonstrated that darbepoetin alfa i.v. and s.c. dose
requirements are comparable [11,20]. The implication of this finding is clinically relevant, as it enables clinicians to base their decision on the most suitable route of administration of the erythropoietic-stimulating agents’ therapy on clinical and not economic reasons. Moreover, it has been shown recently that i.v. darbepoetin alfa administered at extended dose intervals is as effective as i.v. rHuEpo in achieving and maintaining Hgb concentrations [9,12,21]. Our study was conducted in order to confirm further the efficacy and safety of unit doses of darbepoetin alfa given at extended dose intervals for maintaining Hgb concentrations within a defined target range in dialysis patients.

Subjects and Methods

Subjects

One-hundred and forty-three dialysis patients (68 on HD and 75 on PD) were enrolled in this prospective study. Of the PD population, forty-eight (64%) were on CAPD (continuous ambulatory peritoneal dialysis) and 27 (36%) were on APD (automated peritoneal dialysis). Clinically stable subjects (>18 years of age) with mean Hgb concentration between 10-12 g/dl, receiving HD or PD for at least 6 months were recruited. The study protocol required that patients were receiving a stable dose of rHuEpo, given once, twice or three times weekly (i.v. or s.c.) for at least 12 weeks prior to the study. To ensure adequate iron stores for supporting Erythropoiesis, entry criteria specified that transferrin saturation had to be >20%, or ferritin >100 ug/l. Patients with severe congestive heart failure (New York Heart Association class III or IV), uncontrolled hypertension (pre-dialysis diastolic blood pressure >100 mmHg), recent or recurrent bleeding episodes, H.I.V., chronic inflammations (2 patients with bronchiectasis and 1 with pulmonary T.B.) or evidence of uncontrolled hyperparathyroidism were excluded from the study, as were those scheduled for a living-related kidney transplantation. Neither red blood cell transfusions nor major surgery were permitted within 12 weeks before the screening period. The study was conducted in accordance with the revised Declaration of Helsinki, and the study protocol was approved by our Institution’s Research Ethics Committee and the patients were requested to give written informed consents before participation.

Study drug

The darbepoetin alfa (Aranesp TM, Amgen Inc., Thousand Oaks, California) used in the study is produced by recombinant DNA technology and is expressed by cultured mammalian cells. Darbepoetin alfa was supplied in vials as a clear, colorless, sterile protein solution. The study drug was administered according to our intravenous iron protocol (Table 3) to maintain iron levels above this minimum. Adverse events and blood pressure were monitored throughout the study. Blood samples were drawn every 4 weeks for serum albumin, creatinine, blood urea nitrogen, calcium, phosphorus, AST, ALT and intact parathyroid hormone, ferritin levels and to screen for antibodies to erythropoietic proteins. A radio immune precipitation (RIP) screening assay was used to detect seroreactivity to darbepoetin alfa. In addition Residual kidney function (RKF) was assessed by measuring the Kt/V and estimating the patient’s glomerular filtration rate (GFR) by calculating the mean of weekly creatinine clearance.

Statistical analysis

We compared the mean change in Hgb concentration between the baseline (mean of four values) and evaluation period (mean of

| Hgb level (g/dl) | rHuEpo dosage | Darbepoetin alfa dosage |
|-----------------|---------------|-------------------------|
| Hgb 10.5 or less | 6000 IU, once/week | 90 ug, once/week |
| Hgb > 10.5 - 11.0 | 6000 IU, 2 times/week | 60 ug, once/week |
| Hgb 11 - 12.0 | 6000 IU, once/week | 30 ug, once every 2 weeks |
| Hgb > 12.0 | Discontinued | Discontinued |

*Hgb* = hemoglobin

Table 2: Titration protocol of darbepoetin alfa according to Hgb concentrations.

| Ferritin level (ng/dl) | Transferrin saturation % | I.V. iron dosage |
|------------------------|---------------------------|----------------|
| Ferritin < 100 | 100-200 mg 2 X/week |
| 100 < Ferritin < 200 | < 20 | 200 mg 1 X/week |
| 200 < Ferritin < 400 | < 25 | 200 mg 1 X/2 weeks |
| Ferritin > 600 | > 50 | Discontinued |

Table 3: Intravenous iron protocol.

| Darbepoetin alfa (n=143) | s.c. (n=65) |
|--------------------------|-------------|
| L.v. (n=78) | s.c. (n=65) |
| Sex, n (%) | |
| Male | 57 (73.1) | 40 (61.5) |
| Female | 21 (26.9) | 25 (38.5) |
| Age (years) (Mean±SD) | 57.6±13.6 | 59.2±14.5 |
| Weight (Kg) (Mean±SD) | 71.4±12.4 | 73.1±13.8 |
| D.M., n (%) | 33 (42.3) | 30 (46.2) |
| H.P.N., n (%) | 60 (76.9) | 51 (78.5) |
| CRP (mg/L) (Mean±SD) | 2.8±1.3 | 2.7±1.7 |
| Dialysis modality | ||
| HD, n (%) | 38 (48.7) | 30 (46.2) |
| PD, n (%) | 40 (51.3) | 35 (53.8) |
| Frequency of darbepoetin alfa | ||
| Once per week, n (%) | 14 (17.9) | 16 (24.6) |
| Once every 2 weeks, n (%) | 64 (82.1) | 49 (75.4) |

D.M. = diabetes mellitus, H.P.N. = hypertension, CRP = C-Reactive protein, HD= hemodialysis, PD= peritoneal dialysis

Table 3: Patients’ characteristics.
four values). Based on a previous darbepoetin alfa study [11], where a SD of 0.8 g/dl was observed for change in Hgb, it was estimated that detection of a change in Hgb concentration of 0.7 g/dl or more between baseline and the evaluation period (weeks 21-24) is significant. The number and percentage of evaluable patients who successfully maintained Hgb concentration (mean Hgb concentration >10.0 g/dl during the evaluation period and the exact 95% confidence intervals (CIs) are presented. The mean change in Hgb (95% CI) from baseline to evaluation period for patients who successfully maintained Hgb is presented, along with the median change (95% CI) in average dose of darbepoetin alfa. Summary statistics (mean or geometric mean, median, SD and range for continuous variables, and number and percentage of subjects in each category (for categorical variable) are presented for baseline, efficacy and safety. Change in Hgb and dose is summarized with means (geometric means for dose) and 95% CI. All statistical analyses were performed with the SAS System Version 8.2.

Results

A total of 143 subjects were enrolled in the study. Subjects’ baseline characteristics were similar regardless of the route of administration of darbepoetin alfa, and were representative of dialysis population (Table 3). Seventy-five (52.4%) patients were on PD and 68 (47.6%) were on HD. Seventy-eight (54.5%) subjects received darbepoetin alfa i.V. and 65 (45.5%) subjects received s.c. darbepoetin alfa. Forty-one (out of 78, 52.6%) of the i.V. group were on PD and 37 (out of 78, 47.4%) were on HD. Of the 65 s.c. group, 34 (out of 65, 52.3%) patients were on PD and 31 (out of 65, 47.7%) patients were on HD. The mean age was similar in both groups (57.6 vs 59.2). The most common cause of ESRD was diabetes mellitus in both the i.v. and s.c. groups (42.3% and 46.2% respectively). Baseline serum albumin and other biochemical parameters before and after darbepoetin alfa use were also similar (Table 4). The mean Hgb concentration at baseline was 11.21 g/dl (range 10.5-12.0 g/dl). All subjects completed both the 20-week dose titration period and the subsequent 4-week evaluation period. The overall mean concentration >11 g/dl. All subjects completed both the 20-week dose titration period and the subsequent 4-week evaluation period. The overall mean change in Hgb concentration from baseline to evaluation period was 0.18 g/dl (95% CI + 0.16) (Table 5). Regardless of route of administration, darbepoetin alfa effectively maintained mean Hgb concentration above 11 g/dl throughout the entire study period (Figure 1). Mean Hgb concentration increased most markedly over the first 10 weeks of darbepoetin alfa treatment (Figure 1). Darbepoetin alfa administered by both the i.v. and s.c. routes resulted in stable mean Hgb concentrations during the evaluation period (Figure 2). Subjects with a baseline Hgb concentration <11 g/dl (n=42) experienced a clinically significant mean increase in Hgb concentration of 0.62 g/dl (95% CI 0.52+0.71) at evaluation. Subjects with a baseline Hgb concentration >11 g/dl (n=101) experienced a mean decrease of 0.11 g/dl (95% CI -0.17 to -0.06). Subjects with baseline Hgb concentrations <11 g/dl experienced significant mean increase in Hgb concentration from baseline to evaluation, which was more pronounced following i.v. than s.c. administration (0.79 vs. 0.55 g/dl respectively) (Table 5).

Table 5: Mean (95% CI) change in Hgb* from baseline to evaluation (weeks 21-24).

| Route of administration | Mean baseline Hgb | Mean change in Hgb |
|-------------------------|-------------------|-------------------|
| I.v. (n=78)             |                   |                   |
| Hgb < 11 g/dl (n=22)    | 10.56 (10.52 to 10.61) | 0.79 (-0.64 to 0.95) |
| Hgb ≥ 11 g/dl (n=56)    | 11.83 (11.78 to 11.87) | -0.05 (-0.15 to 0.04) |
| S.c. (n=65)             |                   |                   |
| Hgb < 11 g/dl (n=20)    | 10.54 (10.49 to 10.61) | 0.55 (0.38 to 0.67) |
| Hgb ≥ 11 g/dl (n=45)    | 11.86 (11.82 to 11.92) | 0.18 (-0.33 to 0.14) |

*Hgb: hemoglobin

![Figure 1](image_url) Mean hemoglobin concentrations (95% CI) over time by route of administration.
Safety

Out of the 143 study subjects, 12 (8.4%) patients experienced at least one adverse event that was considered by the investigator to be treatment related. These included injection site pain, diarrhea and hypertension. Analyses of the adverse event profile by age, sex, dialysis modality and administration route revealed no notable differences in the incidence rates for any of these subgroups. There were no cases of antibody-mediated pure red cell aplasia associated with darbepoetin alfa treatment. Over the study period, no relevant changes were observed in the mean systolic and diastolic blood pressure values, and there was no clinically relevant change in the use of anti-hypertensive medications. There were no changes in laboratory or biochemical variables associated with darbepoetin alfa treatment. Mean serum ferritin concentration was 532.5 μg/l at baseline and 541.7 at evaluation. In addition the mean transferring saturation remained above 20% throughout the study (29.8% at baseline and 27.7% at evaluation).

Discussion

Previous studies have shown that darbepoetin alfa can effectively maintain the Hgb concentration when given at extended dose intervals relative to rHuEpo in dialysis patients [9-13]. The results of our study further confirms the results of these earlier trials and indicate that unit dosing with darbepoetin alfa can effectively and safely maintain Hgb concentration within a target range after switching from rHuEpo at extended dose intervals. Mean Hgb concentrations were maintained above 11 g/dl throughout the evaluation period, regardless of route and frequency of administration. We noticed that i.v. darbepoetin alfa administration was associated with a higher increase in Hgb concentration compared with s.c. darbepoetin alfa. Following i.v. administration, there was an increase of Hgb of 0.78 g/dl relative to baseline, which was moreover associated with a decrease of i.v. weekly dose requirements of over 20%. While overall s.c. weekly dose requirements increase over the study period, this appears to be due to the fact that patients with baseline Hgb concentrations < 11 g/dl were sub optimally controlled while being treated with rHuEpo. The dose of s.c. darbepoetin alfa was subsequently increased in these patients over the course of the study, and this was associated with a Hgb increase of almost 0.6 g/dl. Moreover, regardless of Hgb category at baseline (< 11.0 or > 11.0 g/dl), following i.v. administration, there was an increase in Hgb concentration that was associated with a decrease in weekly requirements of darbepoetin alfa. The observation that i.v. and s.c. darbepoetin alfa dose requirements were not significantly different at evaluation, results mainly from the decrease in i.v. dose requirements during the course of the study. This contrasts markedly with the previous decade of experience with rHuEpo. Despite reducing the frequency of administration of darbepoetin alfa, there was no change in mean Hgb concentration from baseline to the evaluation period in the overall study population. Indeed, mean Hgb concentrations were maintained above the European Best Practice Guidelines recommendation of 11.0 g/dl throughout the entire study period [24]. The Hgb concentrations increased over the initial 10-week period of the study, which was accompanied by a stabilization period over weeks 10-24. The slight decline in Hgb concentrations after the week 10 is probably reflective of subjects achieving the target Hgb concentration of > 11.0 g/dl and therefore required by the study protocol to have a dose reduction (data not shown). Of these subjects who met the threshold of > 11.0 g/dl, 62% did so during weeks 1-10 and the remaining 38% met the threshold during weeks 10-24. Approximately 31.5% of patients (45/143 subjects) had a baseline Hgb concentration < 11.0 g/dl suggesting that they were sub optimally controlled while being treated with rHuEpo. In keeping with the observations of a previous study [12], these patients experienced a significant mean increase in Hgb of almost 0.7 g/dl after switching to darbepoetin alfa. The increase in this study population was even more pronounced in the subgroup receiving i.v. darbepoetin alfa (+0.79 g/dl), although there was also clinically significant (+0.55 g/dl) increase in patients who received s.c. darbepoetin alfa. These data suggest that patients will be able to maintain target Hgb concentrations recommended for European patients with renal anemia [24] when switched from rHuEpo to darbepoetin alfa at extended dose intervals. Current treatment guidelines recommend that, given its pharmacokinetic profile, rHuEpo should be administered two or three times weekly for the treatment of anemia in dialysis patients [24,25]. Although rHuEpo...
has been evaluated using a once weekly schedule for maintaining Hgb concentrations [26,27], this was undertaken in a limited number of stable and highly selected HD patients. In addition, our study showed that there was no significant difference between i.v. and s.c. darbepoetin alfa administration in maintaining Hgb concentrations to the target level in contrast with erythropoiesis where dose requirements for i.v. dosing were approximately one-third higher than for s.c. dosing [9,11,14]. The effectiveness and safety profile in patients receiving darbepoetin alfa once every two weeks was very similar to that observed in patients on the once-weekly regimen and both regimens were consistent with results reported previously [9,11,28]. In addition, the similar levels of Kt/V, weekly creatinine clearance, serum albumin and other biochemical parameters indicate the stable condition of our patients throughout the study period. Furthermore, the ability to dose patients less frequently with darbepoetin alfa may have economic implications for healthcare providers, especially in relation to reduced nursing time, and notwithstanding the improved convenience for the patients. It is anticipated that future studies will address these issues.

Conclusion

This study indicates that renal anemia treatment with unit doses of darbepoetin alfa in dialysis patients can effectively and safely maintain hemoglobin concentrations with either once weekly or once every other week administration. In common with a previous darbepoetin alfa trial in dialysis patients, i.v. and s.c. dose requirements were not different. Clinically, i.v. darbepoetin alfa may provide improved outcomes over i.v. rHuEpo, at a reduced frequency of administration, and with the advantages of sparing patients the discomfort of repetitive s.c. injections. The results of this study suggest that the use of darbepoetin alfa in dialysis patients can optimize anemia management for patients with ESRD and for healthcare providers.

Acknowledgment

The authors express their deep thanks and appreciation for all the hemodialysis and peritoneal dialysis staff and technicians at King Fahd University Hospital, Dammam University.

References

1. Eschbach JW, Abdulhadi MH, Browne JK, Delano BG, Downing MR, et al. (1998) Recombinant human erythropoietin in anemic patients with end-stage renal disease: results of a phase III multicenter clinical trial. Ann Intern Med 111: 992-1000.
2. Singh AK, Szczczes L, Tang KL, Barnhart H, Sapp S, et al. (2006) Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 355: 2085-2098.
3. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, et al. (1996) The effect of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 339: 584-590.
4. Szczczes LA, Barnhart HK, Sapp S, Feilker GM, Hernandez A, et al. (2010) A secondary analysis of the CHOIR trial shows that comorbid conditions differentially affect outcomes during anemia treatment. Kidney Int 77: 239-246.
5. Macdougall IC, Gray SJ, Elston O, Breen C, Jenkins B, et al. (1999) Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients. J Am Soc Nephrol 10: 2392-2395.
6. Egrie JC, Browne JK (2001) Development and characterization of novel erythropoiesis stimulating protein (ESP). Nephrol Dial Transplant 16: 3-13.
7. Coyne D, Ling BN, Toto R, McDermott-Vitak AD, Trotman ML, et al. (2000) Novel erythropoiesis stimulating protein (NESP) corrects anemia in dialysis patients when administered at reduced dose frequency compared with recombinant human erythropoietin (rHuEpo). J Am Soc Nephrol 11: A1380.
8. Graf H, Lacombe JL, Braun J, Gomes da Costa AA (2000) Novel Erythropoiesis stimulating protein (NESP) effectively maintains Hemoglobin (Hgb) when administered at a reduced dose frequency compared with recombinant human erythropoietin (r-HuEpo) in end-stage renal disease patients. J Am Soc Nephrol 11: A1317.
9. Nissenson AR, Swan SK, Lindberg JS, Soroka SD, Beatey RN, et al. (2002) Randomized controlled trial of darbepoetin alfa for the treatment of anemia in hemodialysis patients. Am J Kidney Dis 40: 110-118.
10. Vanrenterghem Y, Jadoul M, Foret M, Walker R (2001) Novel erythropoiesis stimulating protein (NESP) administered once every 3 weeks by the intravenous or subcutaneous route maintains hemoglobin (Hb) in dialysis patients. J Am Soc Nephrol 365: A1878.
11. Vanrenterghem Y, Barany P, Mann JEF, Kerr PG, Wilson J, et al. (2002) Randomized trial of darbepoetin alfa for treatment of renal anemia at a reduced dosing frequency compared with rHuEpo in dialysis patients. Kidney Int 62: 2167-2175.
12. Locatelli F, Canaud B, Giacardi F, Martin-Malo A, Baker N, et al. (2003) Treatment of anemia in dialysis patients with unit dosing of darbepoetin alfa at a reduced frequency relative to recombinant human erythropoietin (rHuEpo). Nephrol Dial Transplant 18: 362-369.
13. Braun J (2002) Darbepoetin alfa administered once every 4 weeks maintains Hb levels in patients with chronic kidney disease (CKD) receiving dialysis. [abstract M317]. Nephrol Dial Transplant 17: 136.
14. Locatelli F, Oliveses J, Walker R, Wilkie M, Jenkins B, et al. (2001) Novel erythropoiesis stimulating protein for treatment of anemia in chronic renal insufficiency. Kidney Int 60: 741-747.
15. Suranyi MG, Lindberg JS, Navarro J, Elias J, Brenner RM, et al. (2003) Treatment of anemia with darbepoetin alfa administered de novo once every other week in chronic kidney disease. Am J Nephrol 23: 106-111.
16. Walczyk M, Agawal A, Ling B (2003) Aranesp™ (darbepoetin alfa) administered once monthly maintains hemoglobin levels in patients with chronic kidney disease (CKD). National Kidney Foundation Clinical Nephrology Meeting. Spring 2003. Dallas.
17. Lee YK, Kim SG, Seo JW, Oh JE, Yoon JW, et al. (2008) A comparison between once-weekly and twice- or thrice-weekly subcutaneous injection of epoetin alfa: results from a randomized controlled multicenter study. Nephrol Dial Transplant 23: 3240-3246.
18. Besrab A, Reyes CM, Homberger J (2002) Meta-analysis of subcutaneous versus intravenous epoetin in maintenance treatment of anemia in hemodialysis patients. Am J Kidney Dis 40: 439-446.
19. Macdougall IC (2002) Once weekly erythropoietic therapy: is there a difference between the available preparations?. Nephrol Dial Transplant 17: 2047-2051.
20. Canaud B (2002) Darbepoetin alfa dose requirements for i.v. and s.c. administration are equivalent in anemic dialysis patients [Abstract M319]. Nephrol Dial Transplant 17: 137.
21. Hofl WH (2002) IV darbepoetin alfa is more effective than IV rHuEpo in maintaining target Hb concentrations in patients with renal anemia [abstract O77]. Nephrol Dial Transplant 17: 24.
22. Aljama P, Bommer J, Canaud B, Carrera F, Eckardt KU, et al. (2001) Practical guidelines for the use of NESP in treating renal anemia. Nephrol Dial Transplant 16: 22-28.
23. Uehlinger DE, Gotch FA, Sheiner LB (1992) A pharmacodynamic model of erythropoietin therapy for uremic anemia. Clin Pharmacol Ther 51: 76-89.
24. Cameron JS (1999) European Best Practice Guidelines for the management of anemia in patients with chronic renal failure. Nephrol Dial Transplant 14: 1-50.
25. (1997) NKF-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. National Kidney Foundation Dialysis Outcomes Quality Initiative. Am J Kidney Dis 30: 192-240.
26. Weiss LG, Clyne N, Divino Fihilo J, Frisenette-Fich C, Kurkus J, et al. (2000) The efficacy of once weekly compared with two or three times-weekly subcutaneous epoetin beta: results from a randomized controlled multicenter trial. Swedish Study Group. Nephrol Dial Transplant 15: 2014-2019.
27. Locatelli F, Baldamus CA, Villa G, Ganea A, Martin de Francisco AL (2002) A secondary analysis of the CHOIR trial shows that comorbid conditions differentially affect outcomes during anemia treatment. Kidney Int 77: 239-246.
28. Nissenson AR (2001) Novel erythropoiesis stimulating protein for managing the anemia of chronic kidney disease. Am J Kidney Dis 38: 1390-1397.