Evaluation of a biosimilar recombinant alpha epoetin in the management of anemia in hemodialysis patients

Fatemeh Beiraghdar a, Yunes Panahi b,*, Behzad Einollahi a, Eghlim Nemati a, Amirhossein Sahebkar c,d,*, Arash Hassanzadeh a, Hamid T. Khosroshahi e, Sima A. Azar e, Javid Safa e, Sadroddin R. Hashemi e, Jalal Etemadi e, Eisa T. Marzony a, Hamid Noshad e

a Nephrology and Urology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
b Research Center of Chemical Injuries, Baqiyatallah University of Medical Sciences, Tehran, Iran
c Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
d Neurogenic Inflammation Research Center, Department of Medical Biotechnology, Mashhad University of Medical Sciences, Mashhad, Iran
e Department of Nephrology, Tabriz University of Medical Sciences, Tabriz, Iran

Received 9 January 2015; accepted 20 February 2015
Available online 28 February 2015

Abstract Background: The efficacy of human recombinant erythropoietins (rHuEPOs) in the treatment of anemia with different etiologies is proven. Development of biosimilar rHuEPO products with lower cost and wider availability is important for the care of anemic patients. Objective: The aim of the present study was to determine the bioequivalence and safety of a biosimilar rHuEPO (Pastopoitin®) and compare it with the innovator product Eprex®, as a standard rHuEPO. Methods: One hundred and seven anemic patients on stable hemodialysis were recruited to this randomized double-blind comparative trial and assigned to either subcutaneous Pastopoitin (n = 50) or Eprex (n = 57). Each study group received rHuEPO at a dose of 80–120 IU/kg/week in 2–3 divided doses for a period of 3 months. Hematologic parameters including Hemoglobin, hematocrit, RBC, EBC, platelet, MCV, MCH and MCHC were checked every 2 weeks. Blood iron, ferritin, TIBC, creatinine, BUN and electrolytes (Na, K, Ca and P) were evaluated monthly over the 3 months.
1. Introduction

Anemia is a common and serious complication of chronic renal failure (CRF) (Nurko, 2006), and is responsible for considerable morbidity and mortality as well as severe impairment to the quality of life in both pre-dialysis and hemodialysis patients (Goch et al., 1992; Levin et al., 1999; Locatelli et al., 2004; O’Riordan and Foley, 2000). Anemia in CRF patients may either stem from defective erythropoietin production by kidneys or iron deficiency, and has been reported to be correlated with the severity of disease (Howard et al., 1989; Nurko, 2006). Correction of anemia by increasing blood hemoglobin (Hb) or hematocrit (Hct) values is essential for the survival of renal transplant patients as well as for those who are on hemodialysis (Locatelli et al., 2004; Port et al., 1998). Hence, much attempt has been made to introduce safe and effective treatments that can correct hematological abnormalities in anemic patients.

The major therapeutic advance for the management of anemia has been the introduction of recombinant human erythropoietin (rHuEPO). Owing to the efficacy of rHuEPO, the use of blood transfusion or steroid therapy in CRF patients is now obsolete. rHuEPO is indicated for both prevention and treatment of anemia after surgery or hemodialysis (Smith et al., 2003), and has been shown to improve the quality of life of hemodialysis patients at both cognitive and activity levels (Moreno et al., 2000).

Among the several types of rHuEPOs that have been produced, alpha epoetins are the most widely used class. The innovator product of alpha epoetins is Eprex®, which is a standard drug with confirmed efficacy and well-tolerability. Nevertheless, alpha epoetins are not widely available and their high cost limits their use in target patients. Since the patent of Eprex® as the proprietary drug has expired, there is a need to develop biosimilar rHuEPO products with comparable efficacy and safety that could be used with higher availability and at a lower cost (MacLaren and Sullivan, 2005). The present study aimed to evaluate the efficacy and safety of Pastopoitin®, a biosimilar epoetin alpha, in comparison with the innovator product Eprex®, in patients with CRF on stable hemodialysis.

2. Material and methods

The study was a randomized double-blind parallel-group trial on patients referring to the nephrology clinics of the Madani, Ghiyasi, Sina, Fayazbaklsh, Imam Reza and Artesh hospitals. Inclusion criteria were male and female patients with end stage renal disease (GFR < 14 mL/min/1.73 m² body area) who were receiving hemodialysis for the first time or not longer than three months, hematocrit (Hct) < 30% or Hb < 10 g/dL, serum ferritin > 100 ng/mL, iron saturation > 20% and a negative history of erythropoietin therapy. Patients with pregnancy or breastfeeding, CRP > 10 mg/L and a history of uncontrolled hypertension, symptomatic ischemic heart disease, cardiovascular or cerebrovascular events, acute infection, elevated hepatic transaminases, graft rejection, polycystic kidney disease and malignancy were excluded from the trial. The study protocol was approved by the institutional Ethics Committee and written informed consent was obtained from all participants.

One-hundred and seven subjects met the inclusion criteria and were randomized to receive Pastopoitin (Pasteur Institute; n = 50) or Eprex (Cilag Inc., Switzerland; n = 57). Each rHuEPO product was administered at a subcutaneous dose of 80–120 IU/kg/week, in 2–3 divided doses (after each dialysis session) until blood Hb and Hct values reached normal range with a maximum duration of 3 months. The values of hematologic factors such as Hb, Hct, red blood cells (RBC), white blood cells (WBC), platelets (PLT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and RBC distribution width (RDW) were checked every 2 weeks. Blood iron, ferritin, total iron binding capacity (TIBC), creatinine, blood urea nitrogen (BUN) and electrolytes (Na, K, Ca and P) were evaluated monthly over the 3-month duration of study. Incidence of adverse events such as headache, nausea, vomiting, dizziness, fatigue, weakness, arthralgia, edema, chest pain, diarrhea, rashes, myocardial infarction, transient ischemic attack or stroke, hypertension and hypersensitivity reactions was also recorded throughout the study.

Statistical analyses were performed using SPSS software version 16. Data were expressed as means ± SD or number (%). Comparisons were made using ANOVA with Bonferroni adjustment for multiple comparisons. A two-sided p-value of less than 0.05 was considered as significant.

3. Results

Demographic characteristics of the study groups are summarized in Table 1. There was no statistically significant difference between the groups regarding any of the basic characteristics including age, gender, marital status, predialysis weight, and systolic and diastolic blood pressures (p > 0.05). Systolic and diastolic blood pressures remained unchanged by the end of trial (p > 0.05). Changes in hematologic parameters during the course of study are shown in Table 2. Mean Hb, Hct and RBC values...
were significantly increased by the end of trial in both groups ($p < 0.001$). There was no statistically significant difference between the Eprex and Pastopoitin groups regarding Hb, Hct, RBC, PLT, MCV, MCH, MCHC, WBC, RDW and reticulocyte count, neither at baseline nor at the end of study ($p > 0.05$) (Table 2).

Serum values of iron status biomarkers i.e., iron, ferritin and TIBC, as well as biomarkers of renal function i.e., BUN and creatinine did not significantly change in any of the study groups ($p > 0.05$). Likewise, between-group comparisons did not reveal any difference between Pastopoitin and Eprex groups in any of the abovementioned parameters, neither at baseline nor at the end of study ($p > 0.05$) (Table 3).

Mean baseline and endpoint values for serum electrolytes including K, Na, Ca and P in the study groups are shown in Table 4. No significant change in any of the electrolytes was observed in the study groups by the end of trial. The groups were also comparable regarding serum levels of the assessed electrolytes at baseline and at the end of study.

Table 5 shows the frequency of adverse events reported in the Pastopoitin and Eprex groups during the course of study. The most common adverse events in the study groups were weakness, arthralgia, headache and nausea. The frequency of adverse events was not significantly different between the study groups (Table 5).

### Table 1 Demographic characteristics of the study groups.

| Parameters       | Eprex   | Pastopoitin | p-Value |
|------------------|---------|-------------|---------|
| Mean age (years) | 52.51 ± 15.12 | 55.60 ± 14.74 | 0.898   |
| Marriage statues | Single (n) | 51 | 47 | – |
|                  | Marriage (n) | 6 | 3 | – |
| Sex (no)         | Male | 33 | 36 | 0.256 |
|                  | Female | 22 | 17 | – |
| Weight before dialysis (kg) | 64.0 ± 12.1 | 68.0 ± 11.2 | 0.147 |
| SBP (mmHg)       | Baseline | 139.42 ± 21.54 | 141.19 ± 22.31 | 0.65 |
|                  | Endpoint | 138.39 ± 20.78 | 139.49 ± 21.42 | 0.48 |
| DBP (mmHg)       | Baseline | 93.27 ± 15.03 | 94.06 ± 12.75 | 0.12 |
|                  | Endpoint | 93.22 ± 13.32 | 92.45 ± 13.97 | 0.12 |

SBP: systolic blood pressure; DBP: diastolic blood pressure.

### Table 2 Changes in hematologic parameters in the study groups.

| Parameters       | Eprex   | Pastopoitin | p-Value |
|------------------|---------|-------------|---------|
| Hb (g/dL)        | Baseline | 8.48 ± 1.14 | 8.47 ± 0.94 | 0.11 |
|                  | Endpoint | 9.81 ± 1.21 | 9.5 ± 1.25 | 0.25 |
| Hct (%)          | Baseline | 27.41 ± 2.96 | 27.44 ± 2.86 | 0.64 |
|                  | Endpoint | 31.82 ± 4.19 | 31.89 ± 3.11 | 0.06 |
| RBC (million/mm³) | Baseline | 3.12 ± 0.45 | 3.13 ± 0.38 | 0.38 |
|                  | Endpoint | 3.77 ± 0.68 | 3.71 ± 0.43 | 0.17 |
| Platelet (10⁰/mL) | Baseline | 197.03 ± 88.28 | 203.86 ± 77.9 | 0.53 |
|                  | Endpoint | 186.18 ± 66.63 | 228.33 ± 71.78 | 0.18 |
| MCV (fL)         | Baseline | 87.3 ± 7.41 | 86.61 ± 7.71 | 0.3 |
|                  | Endpoint | 86.16 ± 10.61 | 86.98 ± 7.23 | 0.65 |
| MCH (pg)         | Baseline | 27.16 ± 3.01 | 26.72 ± 2.63 | 0.19 |
|                  | Endpoint | 27.76 ± 10.35 | 26.04 ± 2.48 | 0.1 |
| MCHC (pg)        | Baseline | 30.83 ± 2.06 | 30.81 ± 1.99 | 0.06 |
|                  | Endpoint | 30.70 ± 2.11 | 29.98 ± 1.71 | 0.38 |
| WBC (10³/mm³)    | Baseline | 6.1 ± 2.45 | 6.52 ± 1.84 | 0.23 |
|                  | Endpoint | 5.99 ± 1.55 | 6.81 ± 1.72 | 0.45 |
| RDW (%)          | Baseline | 14.39 ± 2.18 | 14.4 ± 1.7 | 0.1 |
|                  | Endpoint | 14.03 ± 1.88 | 14.46 ± 1.74 | 0.34 |
| Reticulocyte (%) | Baseline | 1.18 ± 0.46 | 1.35 ± 0.67 | 0.04 |
|                  | Endpoint | 1.18 ± 0.55 | 1.32 ± 0.61 | 0.37 |

* Significant difference versus baseline value ($p < 0.05$). Hb: hemoglobin; Hct: hematocrit; RBC: red blood cell; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; WBC: white blood cell; RDW: red blood cell distribution width.

### Table 3 Changes in iron status and renal function biomarkers in the study groups.

| Parameters       | Eprex   | Pastopoitin | p-Value |
|------------------|---------|-------------|---------|
| Iron (µg/dL)     | Baseline | 110.72 ± 119.11 | 101.73 ± 59.73 | 0.31 |
|                  | Endpoint | 85.22 ± 17.7 | 90.66 ± 34.82 | 0.06 |
| Ferritin (ng/mL) | Baseline | 443.53 ± 283.61 | 430.66 ± 275.63 | 0.53 |
|                  | Endpoint | 472.96 ± 284.54 | 426.61 ± 282.29 | 0.84 |
| TIBC (µg/dL)     | Baseline | 280.69 ± 57.18 | 300.84 ± 75.66 | 0.08 |
|                  | Endpoint | 290.04 ± 41.96 | 302.06 ± 74.13 | 0.07 |
| BUN (mg/dL)      | Baseline | 63.31 ± 27.59 | 57.9 ± 22.8 | 0.16 |
|                  | Endpoint | 65.56 ± 23.89 | 57.74 ± 18.52 | 0.9 |
| Creatinine (mg/dL) | Baseline | 9.20 ± 3.24 | 8.92 ± 2.79 | 0.4 |
|                  | Endpoint | 10.09 ± 3.23 | 9.63 ± 2.93 | 0.95 |

TIBC: total iron binding capacity; BUN: blood urea nitrogen.

### Table 4 Changes in serum trace element levels in the study groups.

| Parameters       | Eprex   | Pastopoitin | p-Value |
|------------------|---------|-------------|---------|
| K (mg/dL)        | Baseline | 5.23 ± 1.80 | 5.42 ± 1.68 | 0.15 |
|                  | Endpoint | 5.43 ± 0.99 | 5.32 ± 2.12 | 0.8 |
| Na (meq/L)       | Baseline | 139.63 ± 3.26 | 138.83 ± 3.29 | 0.07 |
|                  | Endpoint | 139.73 ± 3.28 | 139.73 ± 3.07 | 0.18 |
| Ca (meq/L)       | Baseline | 8.59 ± 0.94 | 8.75 ± 0.98 | 0.73 |
|                  | Endpoint | 8.66 ± 0.86 | 8.77 ± 1.11 | 0.57 |
| P (meq/L)        | Baseline | 5.05 ± 1.63 | 5.07 ± 1.51 | 0.69 |
|                  | Endpoint | 5.21 ± 1.7 | 5.01 ± 1.62 | 0.8 |
et al. reported restoration of Hb following administration of transplant patients with a Hb value of <12.5 g/dL, Biesen 2012a,b; Grzeszczak et al., 2005; Weiss et al., 2000). In renal the normal range (Biesen et al., 2005; Beiraghdar et al., week has been shown to maintain Hb and Hct values within neous injection of rHuEPO with a frequency of 2–3 times per subcuta- rHuEPOs in the management of anemia in CRF patients has been shown by several studies. In most of the studies, subcuta- nal dose of 150 U/kg/week followed by weekly increments et al. showed that rHuEPO, administered at a starting subcuta- of patients reached normal Hb and Hct values after 3 months study, mean Hb level significantly increased and at least 20% of patients reached target levels of Hb (11 g/dL) and Hct (35%) after 4 months of treatment (Baltar et al., 2007). In the present study, mean Hb level significantly increased and at least 20% of patients reached normal Hb and Hct values after 3 months of erythropoietin therapy. Mean Hct value significantly increased at least 8 weeks after erythropoietin therapy, and this was accompanied by an elevation of RBC count. These results are consistent with previous reports (Baltar et al., 2007; Beiraghdar et al., 2012a,b; Biesen et al., 2005; Tsiara et al., 2007; Van Loo et al., 1996) and indicate the comparable effi- cacy of Pastopoitin with other rHuEPOs in correcting CRF- associated anemia in hemodialysis patients. In the current study, no significant difference in other hematological parameters such as PLT, WBC and reticulocyte count as well as MCH, MCV, MCHC, RDW, iron, TIBC and ferritin was observed between the study groups. Van Loo et al. also showed that PLT and WBC values were not significantly changed following rHuEPO therapy (Van Loo et al., 1996). In the study by Baltar et al. mean serum creatinine, a determinant of kidney function, was reported to remain constant during treatment with rHuEPO (Baltar et al., 2007). This is consistent with the present findings on the stable renal function during therapy, reflected by the unaltered levels of creatinine and BUN. Moreover, there was no significant alteration in serum electrolytes (Na and K) during the course of treatment.

Adverse effects observed in this study were generally mild and included headache, hypertension, nausea, weakness and arthralgia. These adverse events were not clinically serious and their frequencies did not significantly differ between Pastopoitin and Eprex groups. The safety of rHuEPO has also been shown in previous studies, as reported by Beisen et al. (2005) and Beiraghdar et al. (2012a,b) in renal transplant and hemodialysis patients.

The present data clearly indicate bioequivalence of the biosimilar product Pastopoitin with the innovator product Eprex in correcting CRF-associated anemia in hemodialysis patients. In addition, Pastopoitin had a similar safety profile compared with Eprex. Hence, Pastopoitin may be considered as an effective and safe biosimilar rHuEPO preparation with a wide availability and lower cost compared to Eprex. Future investigations are required to confirm the efficacy and safety of this biosimilar alpha epoetin product in patients with other types of anemia e.g. post-transplant patients and patients undergoing chemotherapy.

Acknowledgment

This study was financially supported by the Clinical Trial Research Center, Tehran, Iran.

References

Baltar, J., Moran, N., Ortega, F., et al., 2007. Erythropoietin safety and efficacy in chronic allograft nephropathy. Transpl. Proc. 39, 2245–2247.

Beiraghdar, F., Panahi, Y., Einollahi, B., et al., 2012a. Investigation of the efficacy of a biogenic recombinant human erythropoietin alfa in the correction of post-transplantation anemia: a randomized comparative trial with Eprex. Clin. Lab. 58, 1179–1185.

Beiraghdar, F., Panahi, Y., Einollahi, B., et al., 2012b. Investigation of the efficacy of a biogenic recombinant human erythropoietin Alfa in the management of renal anemia in patients on hemodialysis: a multi-center clinical trial. Clin. Lab. 58, 737–745.

Biesen, W.V., Vanholder, R., Veyes, N., et al., 2005. Efficacy of erythropoietin administration in the treatment of anemia immediately after renal transplantation. Transplantation 79, 367–368.

Goch, J., Birgegard, G., Wikstrum, B., et al., 1992. Serum erythropoietin levels in the immediate kidney-post transplant period. Nephron 60, 30–34.

Grzeszczak, W., Sulowicz, W., Rutkowski, B., et al., 2005. The efficacy and safety of once-weekly and once fortnightly subcuta- neous epoetin beta in peritoneal dialysis patients with chronic renal anaemia. Nephrol. Dial. Transplant. 20, 936–944.

Howard, A.D., Moore Jr., J., Welch, P.G., et al., 1989. Analysis of the quantitative relationship between anemia and chronic renal failure. Am. J. Med. Sci. 297, 309–313.

| Parameters          | Eprex (n) | Pastopoitin (n) |
|---------------------|-----------|-----------------|
| Headache            | 13        | 29              |
| Hypertension        | –         | 1               |
| Nausea              | 11        | 6               |
| Weakness            | 51        | 49              |
| Arthralgia          | 44        | 23              |
| Edema               | –         | –               |
| Vomiting            | –         | 1               |
| Dizziness           | 3         | –               |
| Fatigue             | 8         | 5               |
| Chest Pain          | 5         | –               |
| Thrombosis          | –         | –               |
| Hypersensitivity reactions | –   | –               |
| Rash                | –         | –               |
| Diarrhea            | 2         | 2               |
| MI                  | –         | –               |
| TIA/stroke          | –         | –               |

TIA: transient ischemic stroke.

4. Discussion

Effective management of anemia is integral to the care of patients with CRF, particularly those on stable hemodialysis. The use of rHuEpo has completely obviated the need for blood transfusion and steroid therapy in CRF patients, thereby reducing the adverse events commonly associated with such conventional therapies (Locatelli et al., 2004; Schmid and Schiíff, 2010; Shahani et al., 2009).

Since the pioneer trials in the 1980s, the efficacy of rHuEPOs in the management of anemia in CRF patients has been shown by several studies. In most of the studies, subcuta- neous injection of rHuEPO with a frequency of 2–3 times per week has been shown to maintain Hb and Hct values within the normal range (Biesen et al., 2005; Beiraghdar et al., 2012a,b; Grzeszczak et al., 2005; Weiss et al., 2000). In renal transplant patients with a Hb value of <12.5 g/dL, Biesen et al. reported restoration of Hb following administration of rHuEPO at a dose of 100 IU/kg, 3 times per week (Biesen et al., 2005). In a randomized prospective trial, Van Loo et al. showed that rHuEPO, administered at a starting subcuta- neous dose of 150 U/kg/week followed by weekly increments of 30 U/kg, is beneficial in correcting Hct values in the early post-surgical period in renal transplant patients (Van Loo et al., 1996). Baltar et al. administered rHuEpo to patients with chronic allograft nephropathy at a subcutaneous dose of 2000 IU/kg once a week. Approximately 48% of patients were reported to reach target levels of Hb (11 g/dL) and Hct (35%) after 4 months of treatment (Baltar et al., 2007). In the present study, mean Hb level significantly increased and at least 20% of patients reached normal Hb and Hct values after 3 months of erythropoietin therapy. Mean Hct value significantly increased at least 8 weeks after erythropoietin therapy, and this was accompanied by an elevation of RBC count. These results are consistent with previous reports (Baltar et al., 2007; Beiraghdar et al., 2012a,b; Biesen et al., 2005; Tsiara et al., 2007; Van Loo et al., 1996) and indicate the comparable effi- cacy of Pastopoitin with other rHuEPOs in correcting CRF- associated anemia in hemodialysis patients. In the current study, no significant difference in other hematological parameters such as PLT, WBC and reticulocyte count as well as MCH, MCV, MCHC, RDW, iron, TIBC and ferritin was observed between the study groups. Van Loo et al. also showed that PLT and WBC values were not significantly changed following rHuEPO therapy (Van Loo et al., 1996). In the study by Baltar et al. mean serum creatinine, a determinant of kidney function, was reported to remain constant during treatment with rHuEPO (Baltar et al., 2007). This is consistent with the present findings on the stable renal function during therapy, reflected by the unaltered levels of creatinine and BUN. Moreover, there was no significant alteration in serum electrolytes (Na and K) during the course of treatment.

Adverse effects observed in this study were generally mild and included headache, hypertension, nausea, weakness and arthralgia. These adverse events were not clinically serious and their frequencies did not significantly differ between Pastopoitin and Eprex groups. The safety of rHuEPO has also been shown in previous studies, as reported by Beisen et al. (2005) and Beiraghdar et al. (2012a,b) in renal transplant and hemodialysis patients.

The present data clearly indicate bioequivalence of the biosimilar product Pastopoitin with the innovator product Eprex in correcting CRF-associated anemia in hemodialysis patients. In addition, Pastopoitin had a similar safety profile compared with Eprex. Hence, Pastopoitin may be considered as an effective and safe biosimilar rHuEPO preparation with a wide availability and lower cost compared to Eprex. Future investigations are required to confirm the efficacy and safety of this biosimilar alpha epoetin product in patients with other types of anemia e.g. post-transplant patients and patients undergoing chemotherapy.

Acknowledgment

This study was financially supported by the Clinical Trial Research Center, Tehran, Iran.
Levin, A. et al., 1999. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. Am. J. Kidney Dis. 34, 125–134.
Locatelli, F., Pisoni, R.L., Combe, C., et al., 2004. Anemia in haemodialysis patients of five European countries: association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol. Dial. Transplant. 19, 121–132.
MacLaren, R., Sullivan, P.W., 2005. Cost-effectiveness of recombinant human erythropoietin for reducing red blood cells transfusions in critically ill patients. Value Health 8, 105–116.
Moreno, F., Sanz-Guajardo, D., Lopez-Gomez, J.M., et al., 2000. Increasing the hematocrit has a beneficial effect on quality of life and is safe in selected hemodialysis patients. J. Am. Soc. Nephrol. 11, 335–342.
Nurko, S., 2006. Anemia in chronic kidney disease: causes, diagnosis, treatment. Cleve. Clin. J. Med. 73, 289–297.
O’Riordan, E., Foley, R.N., 2000. Effects of anaemia on cardiovascular status. Nephrol. Dial. Transplant. 15, 19–22.
Port, F.K., Orzol, S.M., Held, P.J., et al., 1998. Trends in treatment and survival for hemodialysis patients in the United States. Am. J. Kidney Dis. 31, S34–S38.
Schmid, H., Schiff, H., 2010. Erythropoiesis stimulating agents and anaemia of end-stage renal disease. Cardiovasc. Hematol. Agents Med. Chem. 8, 164–172.
Shahani, S., Braga-Basaria, M., Maggio, M., et al., 2009. Androgens and erythropoiesis, past and present. J. Endocrinol. Invest. 32, 704–716.
Smith, K.J., Bleyer, A.J., Little, W.C., et al., 2003. The cardiovascular effects of erythropoietin. Cardiovasc. Res. 59, 538–548.
Tsiara, S.N., Chaidos, A., Bourantas, L.K., et al., 2007. Recombinant human erythropoietin for the treatment of anaemia in patients with chronic idiopathic myelofibrosis. Acta Haematol. 117, 156–161.
Van Loo, A., Vanholder, R., Bernaert, P., et al., 1996. Recombinant human erythropoietin corrects anaemia during the first weeks after renal transplantation: a randomized prospective study. Nephrol. Dial. Transplant. 11, 1815–1821.
Weiss, L.G., Clyne, N., Divino Fihlho, J., et al., 2000. The efficacy of once weekly compared with two or three times weekly subcutaneous epoetin b: results from a randomized controlled multicentre trial. Swedish Study Group. Nephrol. Dial. Transpl. 15, 2014–2019.