ORIGINAL ARTICLE

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

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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.

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Results: A significant increase in hemoglobin, hematocrit and RBC was observed by the end of study in both Pastopoitin and Eprex groups ($p < 0.001$). However, these factors were not significantly different between the groups, neither at baseline nor at the end of study ($p > 0.05$). Likewise, the groups were comparable regarding MCV, MCH, MCHC, iron, ferritin, TIBC, creatinine, BUN and electrolytes at baseline as well as at the end of trial. Adverse events were not serious and occurred with the same frequency in the study groups. *Conclusion:* Pastopoitin showed comparable efficacy and safety profile with Eprex in anemic patients on hemodialysis. Hence, Pastopoitin may be considered as a rHuEPO with a lower cost and wider availability compared with the innovator product Eprex.

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, Fayazbakhsh, 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