ORIGINAL RESEARCH

Comparable pharmacokinetics and pharmacodynamics of two epoetin alfa formulations Eporon® and Eprex® following a single subcutaneous administration in healthy male volunteers

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Purpose: This study aimed to assess and compare the pharmacokinetic (PK) and pharmacodynamic (PD) properties following a single subcutaneous injection of epoetin alfa (Eporon®) with those of the comparator (Eprex®) in healthy male subjects.

Subjects and methods: A randomized, double-blind, two-sequence, crossover study was conducted. Subjects were randomly assigned to receive a single dose, that is, 4,000 IU, of the test or comparator epoetin alfa. After 4 weeks, all subjects received the alternative formulation. The primary PK parameters, maximum observed concentration (C_{max}) and area under the curve extrapolated to infinity (AUC_{inf}), were calculated with the serum erythropoietin (EPO) concentrations from blood samples collected for 144 h after dosing. The reticulocyte, hematocrit, hemoglobin and red blood cell counts were measured up to 312 h as PD markers. The primary PD parameters, maximum observed effect (E_{max}) and area under the effect curve (AUEC), were obtained from the baseline-corrected reticulocyte count. The serum EPO concentration and the reticulocyte count were used to assess the concentration–response relationship. The tolerability and immunogenicity profiles were assessed together.

Results: Forty-two subjects completed the study. The mean EPO concentration–time profiles were comparable between the two formulations. The geometric mean ratios (90% CI) of the C_{max} and AUC_{inf} were 0.908 (0.843–0.978) and 1.049 (0.999–1.101), respectively, both of which were within the regulatory range of 0.80–1.25. Additionally, the PD and tolerability profiles were similar between the two formulations. The time-matched serum EPO concentration and PD markers presented a counterclockwise hysteresis, suggesting a time delay between the measured concentration and the response. Both formulations were well tolerated, and production of anti-drug antibodies was not observed.

Conclusion: The two epoetin alfa formulations had similar PK, PD and tolerability profiles. Furthermore, both formulations had a similar time-matched serum EPO concentration and erythropoietic response profile. Thus, the two formulations are expected to be used interchangeably in clinical settings.

Keywords: epoetin alfa, erythropoietin, anemia, pharmacokinetics, pharmacodynamics

Introduction

Erythropoietin (EPO) is a glycoprotein hormone which has a pivotal role in red blood cell (RBC) production. In adult humans, EPO is mainly produced in the peritubular

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cells of the kidney and secreted into the systemic circulation. EPO binds to the EPO receptor expressed on the erythroid progenitor cells of the bone marrow, and this binding triggers RBC production.[1] In patients with chronic kidney disease, EPO production is commonly reduced, which eventually leads to normocytic and normochromic anemia.[2] An erythropoiesis stimulating agent, such as recombinant human EPO (rHuEPO), is one of the key medications for chronic kidney disease-related anemia, which reduces the need for blood transfusions and increases the quality of life.[3–5]

rHuEPO has been developed by the aid of revolutionary recombinant DNA technology. The first rHuEPO which was approved by the regulatory authorities was epoetin alfa (Epogen®; Amgen Inc., Thousand Oaks, CA, USA).[6] Epoetin alfa is synthesized in genetically engineered Chinese hamster ovary cells. Epoetin beta follows next, which differs in the glycosylation site.[7] While epoetin alfa and beta have the same amino acid sequence with human EPO, the second-generation rHuEPO, darbepoetin alfa, has a different amino acid sequence and two additional glycosylation sites. Darbepoetin alfa has a longer elimination half-life than that of the previously developed rHuEPO, thereby enabling therapy with an administered dose only once every 1 or 2 weeks.[8] A number of generic formulations have been developed for the aforementioned rHuEPO, and they are widely prescribed up to the present day.

Eporon® is another epoetin alfa formulation which is produced from an EPO high-yield Chinese hamster ovary cell line. The safety and effectiveness of Eporon were evaluated in a previously conducted Phase III study in anemic patients with end-stage chronic failure.[9] The effectiveness of the drug was defined as having a statistically equal response rate of 90%, while the response was defined as an increase in hemoglobin (HB) by at least 2 g/dL or reaching 10 g/dL. As a result, the safety and effectiveness with a response rate of 87.5% (42/48 patients) were established. Accordingly, Eporon got its marketing approval with an indication for the treatment of anemia associated with chronic kidney disease. Eporon is currently being marketed internationally, including in the Republic of Korea, Thailand and Turkey.

The general pharmacokinetic (PK) properties of epoetin alfa have already been reported in previous studies.[10–12] Subcutaneously injected epoetin alfa has a slow absorption and reaches its peak concentration at 5–24 h after dosing.[10] The volume of distribution is close to the human plasma volume at 3–7 L. Epoetin alfa has a nonlinear clearance at a high dose, while a linear clearance is observed at a lower dose.[11] Its elimination half-life is prolonged by ~20% in chronic kidney disease patients.[12] On the other hand, the PK

properties of Eporon have not been assessed and compared with the original epoetin alfa formulation. In addition, due to the complex nature and heterogeneity of biologic products, the concentration–response relationship between formulations may differ. Thus, a pharmacodynamic (PD) assessment is recommended for a similarity assessment of the two biologic products.[13]

Based on this understanding, this study primarily assessed the PK and PD properties of a single subcutaneous injection of the test epoetin alfa (Eporon) and compared those properties with the properties of the comparator epoetin alfa (Eprex®) in healthy male subjects. Furthermore, the concentration–response relationships of the two formulations were assessed and compared.

Subjects and methods
Study design
A randomized, double-blind, single-dose, two-sequence, crossover study was conducted in healthy Korean volunteers. This study was conducted at the Clinical Trials Center of Seoul National University Hospital, Seoul, Republic of Korea (ClinicalTrials.gov identifier: NCT02580006), in accordance with the principles of the Declaration of Helsinki and the Guideline for Good Clinical Practice of the International Conference on Harmonization.[14,15] The study protocol and informed consent form were approved by the Institutional Review Board of Seoul National University Hospital (Institutional Review Board No 1508-094-695). Subjects were provided detailed information on the study, and they confirmed their voluntary participation in the study by signing the informed consent form.

Healthy male volunteers aged 19–50 years and weighing 55.0–90.0 kg with a body mass index of 18.0–27.0 kg/m^2 were eligible to participate in the study. Subjects who showed at least one of the following clinical laboratory lab results were excluded: HB level <12 g/dL or >17 g/dL, vitamin B12 level <200 pg/mL, ferritin level <21.8 ng/mL, transferrin level <190 mg/dL and any abnormal range for the reticulocyte (RET) count, erythrocytes, platelets or serum potassium levels. The number of subjects was determined based on the results of a previous clinical study on a single subcutaneous injection of epoetin alfa in healthy subjects.[16] Assuming that the intraindividual variability of the area under the curve from time zero to the time of the last observation (AUC$_{last}$) was 28%, a 20% difference in the log-transformed area under the curve for the rHuEPO could be detected with a 90% test power at an alpha of 0.05 with a sample size of 35. Considering an approximate drop-out rate of 20%, the total number of subjects was 42.

The enrolled subjects were randomly allocated to one of the two sequences and received a single subcutaneous injection of 4,000 IU of either the test drug (Eporon injectable solution in a prefilled syringe [4,000 IU/0.4 mL rHuEPO; Dong-A ST Co., Ltd., Seoul, Republic of Korea]) or the comparator drug (Eprex injectable solution in a prefilled syringe [4,000 IU/0.4 mL rHuEPO; Janssen-Cilag Pty Ltd., Beerse, Belgium]) in the abdomen, according to the allocated sequences with a 28-day washout period: sequence A, given the test drug in period 1 followed by the comparator drug in period 2; sequence B, given the comparator drug in period 1 followed by the test drug in period 2. During the study period, a single iron tablet (Ferroba-U SR tablet®, dry ferrous sulfate; Bukwang Pharm. Co., Ltd., Seoul, Republic of Korea) per day was provided to each subject as a concomitant drug from the day following the drug administration to the last visit of each period to supplement iron. Blood samples for the PK assessment were obtained at predose and 1, 2, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48, 72, 96, 120 and 144 h postdose. For the PD assessment, the RET count (%), hematocrit (HCT; %), HB (g/L) and RBC count ($10^6/mm^3$) were measured at predose and 12, 24, 48, 72, 96, 120, 144, 216 and 312 h postdose.

Bioanalytical methods

Serum EPO concentrations were quantified by a validated enzyme-linked immunosorbent assay method. Quantikine® IVD® ELISA, a human EPO immunoassay kit (R&D Systems Inc., Minneapolis, MN, USA), was used to measure the serum EPO concentrations. Exogenous EPO from rHuEPO and endogenous EPO were quantified together without distinction. The calibration curve was constructed with calibration standard samples using seven different concentrations (excluding the blank sample). For the quality control, samples of low, medium and high concentration (15.031, 82.531 and 147.531 mIU/mL, respectively) were prepared. Calibration curves of the test and comparator drugs showed linearity within a concentration range of 5.000–400.000 mIU/mL ($r^2 > 0.99$ for both test and comparator). The inter- and intra-assay precision was $< 5.9\%$ and $< 3.0\%$, respectively, for the test and $< 6.9\%$ and $< 2.4\%$, respectively, for the comparator epoetin alfa. The inter- and intra-assay accuracy was -6.1% to -2.0% and -6.2% to -2.1%, respectively, for the test and -7.8% to 1.3% and -5.0% to 5.6%, respectively, for the comparator epoetin alfa. The analyses of the hematologic parameters for PD assessment (RET, HCT, HB and RBC count) were carried out in the Department of Laboratory Medicine, Seoul National University Hospital, which is accredited by the College of American Pathologists. The RET count, HCT, HB and RBC count were determined by the flow cytometry method with the Sysmex XE-2100 Hematology Autoanalyzer (Sysmex Corporation, Kobe, Japan).

PK and PD analyses

The PK parameters were calculated by noncompartmental analysis using Phoenix® WinNonlin® (Version 6.4; Certara, L.P., Princeton, NJ, USA). The maximum observed serum EPO concentration (C_{max}) and the time of C_{max} (T_{max}) were directly obtained from the data. The AUC_{last} was calculated by the linear trapezoidal method up to T_{max} and by the log trapezoidal method after T_{max}. The area under the curve extrapolated to infinity (AUC_{inf}) was obtained with the following formula: $AUC_{inf} = AUC_{last} + C_{last}/\lambda_z$, where C_{last} is the last observed serum EPO concentration and λ_z is an estimated terminal elimination rate constant. The terminal half-life ($t_{1/2}$) was calculated by dividing natural-log 2 by λ_z. The total clearance (CL/F) was calculated with the following formula: $CL/F = dose/AUC_{last}$, where F denotes the bioavailability. The mean residence time (MRT_{last}) was calculated by dividing the area under the first moment curve by the AUC_{last}.

The time courses of the RET count, HB, HCT and RBC count were investigated and compared between the test and comparator drugs as PD markers. Among the PD markers, the RET count was considered as the primary PD marker for the erythropoietic response. As PD parameters, maximum effect change (ΔE_{max}) and the area under the baseline-adjusted effect curve ($\Delta AUEC$) were calculated by the linear trapezoidal method for the RET count, HB, HCT and RBC count using the baseline-adjusted values. In addition, the time-matched PK/PD data (ie, serum EPO concentration and each PD marker) were visualized on a scatter plot to investigate the time delay between the PK and PD.

Safety and tolerability analysis

Safety and tolerability profiles of the drug were assessed with subjects who received at least a single dose of the study drug. Safety and tolerability assessments were based on the reports of adverse events (AEs), results of vital sign assessment, electrocardiogram and clinical laboratory tests. Local reaction of the drug was evaluated 1, 24 and 48 h after the injection. To evaluate the immunogenicity of the study drug, anti-drug antibody (ADA) formation was assessed at the predose of each period and the post-study visit.

Statistical analysis

SAS (Version 9.4; SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. The PK comparison was performed with the primary PK parameters C_{max} and AUC_{inf}. For the log-transformed C_{max} and AUC_{inf}, linear mixed-effect

analysis of variance was performed with a fixed effect for the formulation, period and sequence and a random effect for the subject nested for the sequence. The geometric mean ratio of the test to the comparator with its 90% CI for each PK parameter was calculated. The test drug was considered to demonstrate a PK equivalence with the comparator drug if the 90% CI for each PK parameter was within the range of 0.80–1.25. ΔE_{max} and $\Delta AUEC$ of the RET count, the primary PD parameters, were included in the PD comparison. With the linear mixed-effect analysis of variance, the mean difference between the test and the comparator drugs was calculated with its 90% CI and the P-value. The PD similarity was confirmed by a P-value above 0.05 for each PD parameter.[13] A P-value <0.05 was considered to be statistically significant.

Results
Demographics
A total of 43 subjects were enrolled in this study. Except for one subject who dropped out before receiving the treatment, all the enrolled subjects completed the study. The mean ± SD (min–max) for age, height, weight and body mass index of all the randomized subjects were 29.9±6.3 years (19–44 years), 173.8±4.6 cm (163.4–185 cm), 70.2±6.3 kg (58.3–81.7 kg) and 23.2±1.8 kg/m² (19.9–26.3 kg/m²), respectively. Demographic and other baseline characteristics were not significantly different between the two sequences.

PK results
The time courses of the serum EPO concentration were similar after a single subcutaneous injection of both formulations. For both formulations, EPO had a slow systemic absorption with a median T_{max} of 10–12 h and exhibited multiphasic behaviors in the elimination phase (Figure 1). The 90% CIs of the geometric mean ratio (test/comparator) for both the C_{max} and AUC_{inf} fell within the prespecified range of 0.80–1.25, demonstrating the PK equivalence of the two epoetin alfa formulations. The other PK parameters were also comparable between the two formulations (Table 1).

PD results
The mean RET counts gradually increased up to 144 h after the drug administration and decreased until the last observation time (312 h). The time courses for the RET count change were similar between the test and comparator epoetin alfa. The mean ΔE_{max} and $\Delta AUEC$ of the RET count, the primary PD parameters, were comparable between the test and the comparator (P=0.569 and 0.796, respectively). Moreover, the general time courses, ΔE_{max} and $\Delta AUEC$ for HB, HCT and RBC count changes were also similar between the two formulations (Table 2; Figure 2).

The RET count level did not directly correspond to the change in the serum EPO concentration, but showed a hysteretic relationship. The plot of the serum EPO concentration versus the RET count joined in the time sequence had a counterclockwise hysteresis loop. After the serum EPO concentration reached its maximum, the RET count level started to increase. The RET count was still in an increased state from the baseline until 144 h after the dosing. The relationship of the RET count and the serum EPO concentration was similar in both the test and comparator epoetin alfa. The HCT, HB and RBC count also showed a counterclockwise hysteresis loop. However, all PD marker values recovered
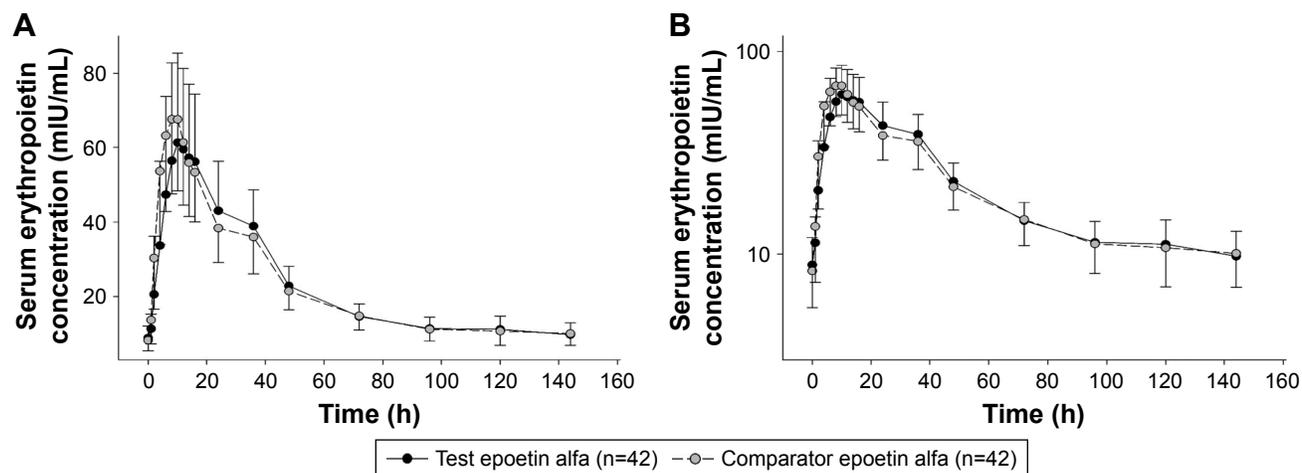
Figure 1 Mean serum concentration–time profile of serum erythropoietin following a single subcutaneous administration of the test (black circle) or the comparator (gray circle) epoetin alfa.
Note: (**A**) Linear scale and (**B**) semi-log scale.

Table 1 Pharmacokinetic parameters following a single subcutaneous administration of the test or the comparator epoetin alfa

Parameters	Test (n=42)	Comparator (n=42)	GMR (90% CI)[a]
T_{max} (h)[b]	12.0 (6.0–36.0)	10.0 (6.0–16.0)	–
C_{max} (mIU/mL)	65.1±25.5 (39.1)	70.4±20.6 (29.3)	0.908 (0.843–0.978)
$AUC_{0-144\,h}$ (h·mIU/mL)	3,256.2±690.1 (21.2)	3,246.7±654.2 (20.1)	1.003 (0.972–1.035)
AUC_{0-inf} (h·mIU/mL)	4,520.2±1,248.4 (27.6)	4,281.4±969.9 (22.7)	1.049 (0.999–1.101)
$t_{1/2}$ (h)	88.1±48.2 (54.7)	71.5±35.7 (49.9)	–
CL/F (mL/h)	939.4±216.2 (23.0)	982.6±226.5 (23.0)	–
MRT_{last} (h)	49.3±6.1 (12.4)	47.5±5.8 (12.2)	–

Notes: Data are presented as mean ± SD (coefficient of variation [%]). [a]GMR (90% CI) of the test to the comparator epoetin alfa. [b]Data are presented as median (minimum–maximum).
Abbreviations: $AUC_{0-144\,h}$, area under the curve from time zero to the time of the last observation; AUC_{0-inf}, area under the curve extrapolated to infinity; C_{max}, maximum observed serum EPO concentration; CL/F, total clearance; GMR, geometric mean ratio; CI, confidence interval; MRT_{last}, mean residence time; $t_{1/2}$, terminal half-life; T_{max}, time of C_{max}; SD, standard deviation.

to the baseline values at 144 h after the dosing. The relationship of the serum EPO concentration and the HCT, HB and RBC count was similar for both the test and the comparator epoetin alfa (Figure S1).

Safety and tolerability

After a single subcutaneous injection of 4,000 IU epoetin alfa into the healthy male subjects, 57 AEs were reported from 22 subjects. The number of subjects with AEs and the number of AEs were comparable between the two treatments (P=1.000 and 0.354, respectively). Among the 57 AEs, 11 cases from four subjects were considered to be treatment related (eight cases in the test drug group and three cases in the comparator drug group), which were considered mild and resolved without any treatment. The most commonly reported

treatment-related AEs were headache and vomiting (three cases for each AE), which are already known as common adverse drug reactions for the rHuEPO formulations.

No clinically significant changes were observed regarding clinical laboratory results, electrocardiogram results, vital signs and physical examinations. Local injection reactions were observed in four subjects (erythema in one subject and bruise in three subjects); however, all the reactions were mild in severity and resolved without any other treatment. The ADA reactivity was negative for all samples from both treatment groups.

Discussion and conclusion

In this study, the PK and PD properties of two epoetin alfa formulations were assessed and compared. A previous study

Table 2 Pharmacodynamic parameters for the reticulocyte count, hemoglobin, hematocrit and red blood cell count following a single subcutaneous administration of the test or the comparator epoetin alfa

Parameters	Test (n=42)	Comparator (n=42)	Mean difference (90% CI)[a]	P-value (ANOVA)
Reticulocyte count				
T_{max} (h)[b]	144.1 (0.0–216.9)	143.9 (96.0–312.6)	–	–
ΔE_{max} (%)	0.83±0.27 (33.15)	0.80±0.28 (35.71)	0.03 (−0.05–0.11)	0.569
$\Delta AUEC$ (h·%)	129.43±57.96 (44.78)	132.22±64.57 (48.84)	−2.79 (−20.88–15.31)	0.796
Hemoglobin				
T_{max} (h)[b]	96.0 (0.0–312.9)	96.0 (0.0–314.0)	–	–
ΔE_{max} (g/L)	8.6±4.8 (55.5)	8.8±5.9 (67.4)	−0.02 (−0.21–0.16)	0.846
$\Delta AUEC$ (h·g/L)	936.2±859.8 (91.8)	1,023.2±967.3 (94.5)	−8.70 (−43.17–25.76)	0.673
Hematocrit				
T_{max} (h)[b]	96.0 (0.0–312.8)	96.0 (0.0–314.0)	–	–
ΔE_{max} (%)	2.7±1.5 (53.6)	2.7±1.8 (64.4)	−0.01 (−0.58–0.57)	0.978
$\Delta AUEC$ (h·%)	328.7±267.8 (81.5)	306.0±265.2 (86.7)	22.76 (−80.46–125.99)	0.712
Red blood cell count				
T_{max} (h)[b]	96.0 (0.0–312.8)	96.0 (0.0–314.0)	–	–
ΔE_{max} (10^6/mm³)	0.29±0.17 (56.58)	0.30±0.20 (67.43)	0.00 (−0.07–0.06)	0.902
$\Delta AUEC$ (h·10^6/mm³)	33.01±28.81 (87.28)	33.68±32.02 (95.09)	−0.67 (−12.19–10.85)	0.922

Notes: Data are presented as mean ± SD (coefficient of variation [%]). [a]Mean difference (90% CI) between the test and the comparator epoetin alfa. [b]Data are presented as median (minimum–maximum).
Abbreviations: CI, confidence interval; ANOVA, analysis of variance; $\Delta AUEC$, area under the baseline-adjusted effect curve; ΔE_{max}, maximum effect change; T_{max}, time of E_{max}; SD, standard deviation.
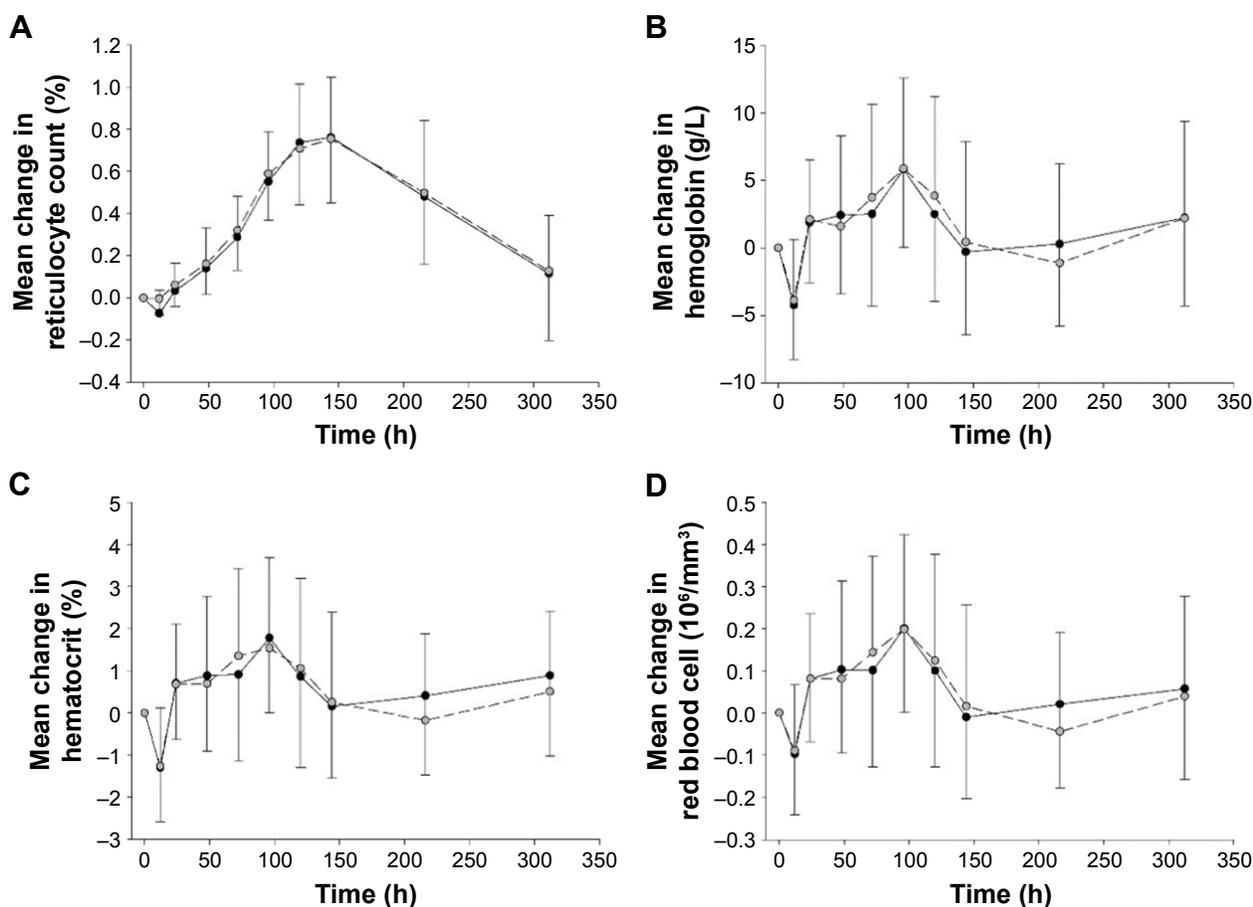
Figure 2 Mean change in hematologic parameter levels following a single subcutaneous administration of the test (black circle) or the comparator (gray circle) epoetin alfa.
Note: (**A**) Reticulocyte count; (**B**) hemoglobin; (**C**) hematocrit and (**D**) red blood cell count.

has reported that there was no significant difference between male and female subjects in serum EPO concentrations and hematologic response (RET, RBC and Hb) following the administration of epoetin alfa.[17] Thus, only male subjects were recruited for this study. As a result, the PK and PD profiles and parameters of the test epoetin alfa were similar to those of the comparator epoetin alfa in healthy male subjects.

EPO is eliminated from the systemic circulation by binding to its receptor in the bone marrow. The binding process has a low capacity and high affinity.[18] It has been reported that the PK of epoetin alfa may be affected by the aforementioned binding characteristics showing nonlinear disposition profiles.[19] Accordingly, a typical nonlinear behavior of elimination was observed for both formulations in this study. The characteristic elimination profiles have also been observed for other EPO receptor-binding drugs such as epoetin beta and darbepoetin alfa.[20,21]

In this study, the RET count was set as the primary marker for the PD assessment. The RET count has been reported to have high relevance for the change in erythropoiesis.[22]

In addition, the dose–response relationship is well established for the RET count with rHuEPO.[23] Moreover, regulatory authorities recommend the RET count as a PD marker. For example, the guidelines on the clinical development of rHuEPO products published by Europe and Korea recommend the RET count as a PD marker for single administration studies.[24,25]

After the subcutaneous injection of epoetin alfa, transient decreases in RET count, HB, HCT and RBC count were observed at 12 h postdose for both formulations. Among the nine PD measurement time points, 12th hour was the only time point for which the RET count, HB, HCT and RBC count were measured in the evening (around 9:00 PM). The circadian rhythm of hematologic parameters could be one possible explanation for these transient decreases. In a previous study, decreased hematologic parameter levels were observed in the evening when compared with those taken in the morning.[26] Furthermore, the decrement of the hematologic parameter levels in that study was comparable with the results of this study.

During the study period, subjects were instructed to take a single iron tablet daily, starting 1 day after the dosing until the last visit. Several studies, which have assessed the PD properties of epoetin alfa in healthy volunteers, have also provided daily oral iron supplementation.[27–29] Exogenous EPO in healthy volunteers increases the iron demand and eventually depletes the circulating iron, causing a relative iron deficiency state.[30] For this reason, the iron supplementation provided was expected to prevent a relative iron deficiency state and enable assessment of the net PD changes induced by the exogenous EPO.[16]

The time-matched serum EPO concentrations and PD marker levels were further assessed and counterclockwise hysteresis was observed for both treatments. A counterclockwise hysteresis implies that there is a time delay between the measured concentration and the PD response. Possible causes of this indirect relationship include the duration of the exogenous EPO moving from systemic circulation to its binding site in the bone marrow and the delayed observation of the response.[31,32] More specifically, for the latter, the maturation of normoblasts into RET takes 5–7 days, for which EPO plays a pivotal role.[33]

In this study, no ADA was developed during the study period for either formulation. It has been reported that ADA formation is rare with subcutaneous injection of epoetin alfa. Despite the low incidence, patients who develop ADAs from exogenous EPO may have a serious AE called pure red-cell aplasia (PRCA).[34] PRCA patients become severely anemic with a rapidly decreasing HB level and eventually become dependent on transfusions.[35] According to one retrospective study, reported cases of PRCA mostly occurred in hemodialysis patients who received subcutaneous epoetin alfa. Most PRCA cases recovered with the discontinuation of epoetin and immunosuppressive therapy.[36] Currently, antibody-mediated PRCA has been shown to be related to manufacturing problems, including uncoated rubber stoppers and formulations without human serum albumin. Today, PRCA infrequently occurs in hemodialysis patients who receive epoetin alfa.[35,37]

Conclusion

The test epoetin alfa demonstrated similarities with the comparator in terms of the PK and PD profiles. Tolerability, which included immunogenicity profiles, was similar between the two products. The hysteretic relationships between the serum EPO concentration and the erythropoietic response were comparable between the two products. The similarities between the formulations imply that the two epoetin alfa products can be used interchangeably in clinical settings.

Acknowledgment

Disclosure

Sun Ju Heo and Tae Young Oh are current employees of Dong-A ST Co., Ltd. The other authors report no conflicts of interest in this work.

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Supplementary material
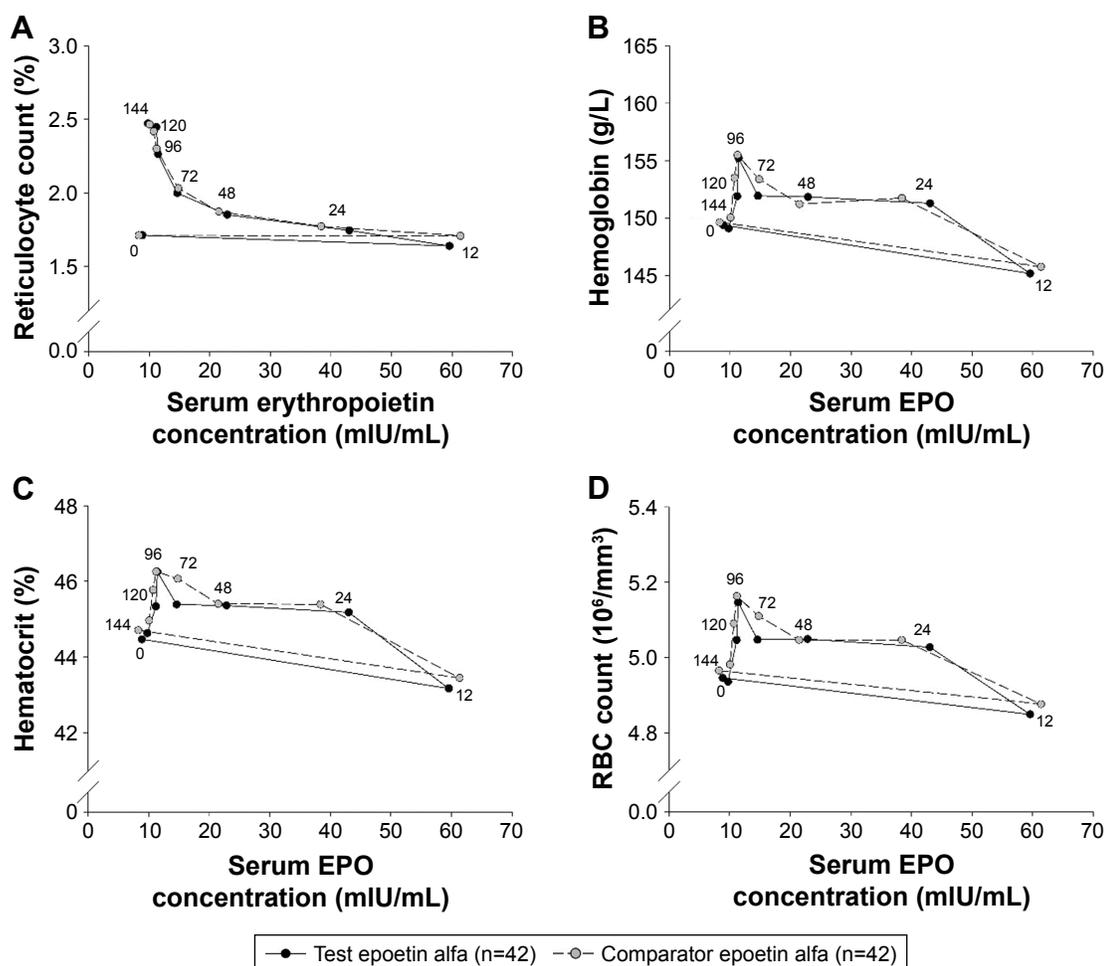
Figure S1 The time-matched serum EPO concentration and the hematologic parameter levels following a single subcutaneous administration of the test (black circle) or the comparator (gray circle) epoetin alfa.
Notes: (**A**) Reticulocyte count; (**B**) hemoglobin; (**C**) hematocrit and (**D**) red blood cell count. Number around the circle indicates the time point of the measurement.
Abbreviations: EPO, erythropoietin; RBC, red blood cell.