PHARMACOKINETICS AND DISPOSITION

Wing Cheung · Neil Minton · Kulasiri Gunawardena

Pharmacokinetics and pharmacodynamics of epoetin alfa once weekly and three times weekly

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Abstract Objective: To compare the pharmacokinetics, pharmacodynamics, and tolerance of epoetin alfa administered subcutaneously (s.c.) once weekly (q.w.) and three times weekly (t.i.w.).
Methods: An open-label, randomized, parallel-design study was conducted in 36 healthy adults with hemoglobin (Hb) levels of 11.7–14.0 g/dl for women and 13.0–14.8 g/dl for men. Subjects were randomized to receive epoetin alfa 150 IU/kg s.c. t.i.w. or 40,000 IU s.c. q.w. for 4 weeks. Serum erythropoietin concentrations were measured using a validated enzyme-linked immunosorbent assay (ELISA). Pharmacokinetic parameters [peak serum concentration (C_max), mean predose trough concentration (C_min), time to C_max (t_max), clearance after s.c. administration (CL/F), area under the plasma concentration–time curve (AUC), and terminal elimination half-life (t_1/2)] were calculated using model-independent methods. Mean changes from baseline and AUC of percentage reticulocytes, Hb, and total red blood cell (RBC) concentrations over the 1-month study period were calculated.
Results: The C_max values for serum epoetin alfa q.w. were six times and AUC_{(0–168)} values three times that of the t.i.w. regimen. Time profiles of changes in percentage reticulocytes, Hb, and total RBC over 1 month were similar between regimens. The rate of increase in Hb was similar for the two groups, and both groups exhibited a 3.1-g/dl increase in mean Hb levels from baseline through day 29. Changes in ferritin levels were generally similar between groups and reflected expected use of iron stores for Hb production. Epoetin alfa administered t.i.w. or q.w. was well tolerated and no serious adverse events occurred.
Conclusion: The pharmacodynamic responses were equivalent between groups despite expected differences in total erythropoietin exposure. These results indicate that the epoetin alfa 150 IU/kg t.i.w. and 40,000 IU q.w. regimens can be considered clinically equivalent.
Keywords Epoetin alfa · Pharmacokinetics · Pharmacodynamics

Introduction

Epoetin alfa administered in a multiple-dose weekly regimen has been shown to correct anemia in patients with cancer through increases in hemoglobin (Hb) and/or hematocrit and reductions in transfusion requirements, and to improve patient quality of life [1, 2, 3, 4, 5, 6, 7, 8]. Improvements in quality of life after epoetin alfa was administered three times weekly (t.i.w.) have been associated with increased Hb or hematocrit levels independent of response to chemotherapy [2, 3].

Recently, clinicians have moved toward a once-weekly (q.w.) fixed-dose administration of 40,000 IU epoetin alfa to reduce the inconvenience and time commitment necessary for t.i.w. treatment. Two clinical trials in healthy subjects have defined the pharmacokinetics and pharmacodynamics of various single and multiple subcutaneous (s.c.) doses of epoetin alfa [9], while two other clinical trials of the q.w. dosing regimen—one in patients who received chemotherapy alone [10] and the other in patients receiving radiotherapy concomitantly or sequentially with chemotherapy [11]—have demonstrated clinical efficacy similar to that seen with t.i.w. regimens [1, 2, 3, 4, 5, 6, 7, 8].

The study presented here was conducted to compare an epoetin alfa fixed-dose regimen of 40,000 IU q.w. with the epoetin alfa weight-adjusted regimen of 150 IU/kg t.i.w. The primary objective was to evaluate the pharmacokinetic profile of epoetin alfa t.i.w. and q.w.
and to demonstrate that both regimens are clinically equivalent. Secondary objectives included assessment of the pharmacodynamic profiles, clinical outcomes, tolerance, and safety parameters of the two regimens.

**Methods**

This open-label, randomized, parallel-design study enrolled 36 healthy volunteers. Eligible subjects were persons between 18 years old and 45 years old who had Hb levels between 12.0 g/dl and 14.0 g/dl inclusive for women, and between 13.0 g/dl and 14.0 g/dl inclusive for men. Women were required to be postmenopausal, incapable of childbearing, or practicing an acceptable method of birth control that had to be continued during the study. Subjects were to have ideal weight for height and body size (±15% of the Metropolitan height and weight table); a negative stool occult blood test; normal iron (Fe) parameters, serum folate, and vitamin B12 levels; to be nonsmoking; and to not drink alcohol during the treatment phase of the study. Iron deficiency was defined as ferritin less than 45 ng/ml or Fe/TIBC ratio (transferrin saturation) less than 20% or below the lower limit of normal values.

Subjects were ineligible if they had a significant history of a disease/dysfunction of a body system, including hemolytic anemia, gastrointestinal bleeding, or thrombosis and/or pulmonary embolism; a chronic medical condition requiring prescription medications; or androgen therapy within 2 months of randomization. Additional exclusion criteria were blood donation within the past 90 days, percentage reticulocytes 3.0% or greater, serum erythropoietin level 30 mIU/ml or greater, or previous exposure to recombinant human erythropoietin (r-HuEPO). Subjects received oral Fe supplementation on days 1–29 (2 Ferro-Grad® capsules containing elemental Fe 105 mg each daily). All other medications were restricted to the first 2 weeks prior to study drug through study completion, with the exception of acetylsalicylic, vitamins, or oral hormonal contraceptives. Screening was performed within 2 weeks prior to the initial administration of epoetin alfa.

The study was conducted at the Clinical Research Unit, Chiltern International, Stoke Poges, Buckinghamshire, U.K., in accordance with the Declaration of Helsinki and under the requirements outlined in current Good Clinical Practices. An independent ethics committee reviewed the protocol and amendments, and subjects provided their written consent.

Eligible subjects were randomized to one of two treatment groups:

1. Epoetin alfa 150 IU/kg s.c. t.i.w. for 4 weeks
2. A fixed-dose regimen of epoetin alfa 40,000 IU s.c. q.w. for 4 weeks

Subjects in the t.i.w. group received epoetin alfa on days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26; q.w. subjects received epoetin alfa on days 1, 8, 15, and 22. Epoetin alfa (EPREX®/ERYPO®, Ortho Biotech/Janssen-Cilag) was supplied as the commercial 10,000 IU/ml and 40,000 IU/ml formulations for the t.i.w. group and q.w. group, respectively. Subjects fasted for at least 10 h prior to dosing on day 1, but received water as needed.

Sample analyses for clinical laboratory tests were performed at Havenhurn Laboratories, Stoke Poges, Buckinghamshire, U.K. Subjects were considered to have completed the study if they had participated for the full duration (29 days) of the study and had taken all required doses of the study drug, were compliant with the blood sampling procedures, and had completed day-29 evaluations and procedures.

**Blood sampling**

Blood samples (3 ml) for Hb, percentage reticulocytes, and red blood cells (RBCs) were drawn during screening; on day 1 at 30 min and 10 min prior to the initial dose of study medication; and on days 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26, and 29 between 0800 hours and 1000 hours if possible. Venous blood samples (2.5 ml) were collected for the determination of serum erythropoietin concentration at the following schedules for the two groups. For the t.i.w. group, collection was on day 1 at 30, 20, and 10 min prior to the initial dose of study medication, on day 8 and day 15 immediately prior to dosing, on day 22 and day 24 immediately prior to dosing and at 0.5, 3, 6, 9, 12, 15, 18, 24, 30, and 36 h postdose, and on day 26 immediately prior to dosing and at 0.5, 3, 6, 9, 12, 15, 18, 24, 30, 36, 48, and 72 h postdose. For the q.w. group, collections occurred on day 1 at 30, 20, and 10 min prior to the initial dose of study medication, on day 8 and day 15 immediately prior to dosing, and on day 22 immediately prior to dosing and at 0.5, 3, 6, 9, 12, 15, 18, 24, 30, and 36 h postdose, and on day 26 immediately prior to dosing and at 0.5, 3, 6, 9, 12, 15, 18, 24, 30, 36, 48, and 72 h postdose. The total amount of blood withdrawn was the same for both groups.

If the Hb level at any time during the treatment phase equaled or exceeded 18.0 g/dl, a second sample was drawn and Hb was measured again to confirm the finding. If confirmed, phlebotomy was performed to reduce the Hb. Initially, 1.0 unit of blood was removed and if the Hb was still 18.0 g/dl or higher, another 0.5–1.0 unit of blood was removed and Hb again measured. Epoetin alfa was discontinued for any phlebotomized subject, and the subject completed the required evaluations and procedures.

**Erythropoietin assay**

Serum erythropoietin concentrations were measured using a validated enzyme-linked immunosorbent assay (ELISA) kit procedure (manufactured by R&D Systems, Inc., Minneapolis, Minn.). The kit was modified at the RW Johnson Pharmaceutical Research Institute (Karuitan, N.J.) to use in-house r-HuEPO in standards and spiked quality control samples. Standard concentrations used in the assay were 7.8, 15.6, 31.3, 50, 62.5, 100, 125, and 250 mIU/ml. Sensitivity, defined as the lowest standard giving acceptable precision, was 7.8 mIU/ml and the assay range was extended to 5000 mIU/ml via quality control dilutions. The quality controls of the standard concentrations were used in the validation of the ELISA method. Accuracy was established from 86.6% to 116.1%, and the intra-assay coefficient of variation (% CV) was 12.9% or less.

**Pharmacokinetic analyses**

Pharmacokinetic parameters were calculated using serum erythropoietin concentrations corrected for predose endogenous erythropoietin levels. Postdose serum concentration values were corrected for predose baseline erythropoietin concentrations by subtracting the mean baseline erythropoietin concentration, determined from the average values of the samples collected at 30, 20, and 10 min before dosing, from each of the values. Predose serum erythropoietin concentrations were not included in the calculation of mean value if they were below the quantification limit of the assay. If the concentration values of all three of a subject’s predose samples were below the quantification limit of the assay, then the quantification limit of the assay, 7.8 mIU/ml, was assigned as the mean baseline erythropoietin concentration for that subject. Actual blood draw times (in hours relative to the time of the first dose) were used in the calculation of pharmacokinetic parameters. The following pharmacokinetic parameters were calculated with model-independent methods using the WinNonlin software, Version 1.1 (Scientific Consulting, Incorporation, Apex, N.C.):

- Peak serum concentration (Cmax): the observed maximum serum concentration during the fourth week of the dosing period.
- Time to Cmax (tmax): the time at which Cmax occurs. The tmax value was not reported for the t.i.w. group because Cmax occurred randomly at any one of the three doses during the fourth dosing week.