Pharmacokinetic and Pharmacodynamic Profiles of Extended Dosing of Epoetin Alfa in Anemic Patients Who Have Chronic Kidney Disease and Are Not on Dialysis

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Background and objectives: Emerging evidence suggests that epoetin alfa can be administered at extended intervals of up to 4 wk. This open-label, randomized study was performed to characterize the pharmacokinetic and pharmacodynamic profiles of four dosing regimens of epoetin alfa administered subcutaneously in anemic patients who had chronic kidney disease and were not on dialysis.

Design, setting, participants, & measurements: Thirty-eight patients, enrolled from nine centers in the United States, were ≥18 yr of age and had hemoglobin <11.0 g/dl and GFR 12 to 60 ml/min per 1.73 m^2. Patients received one of four epoetin alfa dosing regimens: 50 IU/kg three times per week, 10,000 IU once weekly, or 20,000 IU every 2 wk for 36 d or 40,000 IU every 4 wk for 64 d. Each regimen provided a similar dosage of epoetin alfa over 4 wk. Dosage adjustments were not permitted.

Results: Drug exposure to epoetin alfa over 4 wk, based on area under the curve, was somewhat higher with the extended interval regimens compared with the three-times-weekly regimen. Mean change in hemoglobin during the study period was similar for all regimens. No patients were transfused. Three patients experienced five serious adverse events, none of which was considered treatment related.

Conclusions: Extended dosing interval regimens of epoetin alfa yielded modest pharmacokinetic differences but a similar pharmacodynamic response, suggesting that less frequent, higher dosages of epoetin alfa may be as effective as the current three-times-weekly regimen in anemic patients who have chronic kidney disease and are not on dialysis.

Clin J Am Soc Nephrol 3: 1006–1014, 2008. doi: 10.2215/CJN.05671207

Chronic kidney disease (CKD) is associated with the development of anemia, as a result of the reduction of erythropoietin levels as kidney disease progresses (1). Correction of anemia with epoetin alfa in patients with CKD has been shown to improve exercise tolerance and patient-reported physical functioning (2). Epoetin alfa is a recombinant form of erythropoietin with an amino acid sequence identical to human erythropoietin.

The current recommended initiation dosage of epoetin alfa in adult, anemic patients with CKD is 50 to 100 IU/kg three times weekly (2); however, several studies reported that despite its relatively short half-life, epoetin alfa can be given subcutaneously up to every 4 wk in patients with CKD and still achieve and maintain hemoglobin Hb levels within a specified target range (3–10). The objective of this study was to describe the pharmacokinetics, pharmacodynamics, and safety of the following dosing regimens of epoetin alfa in patients who had CKD and were not on dialysis: 50 IU/kg three times weekly, 10,000 IU once weekly, 20,000 IU every 2 wk, and 40,000 IU every 4 wk.

Received December 21, 2007. Accepted March 17, 2008.

Published online ahead of print. Publication date available at www.cjasn.org.

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Materials and Methods

This was a open-label, randomized, multicenter study of adult patients with anemia secondary to CKD. The study was reviewed by a central institutional review board and conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. All patients provided written informed consent to participate in the study.

Selection Criteria

Key inclusion criteria were age ≥18 yr, GFR 15 to 60 ml/min per 1.73 m^2 with a stable creatinine over the past 6 mo, and transferrin saturation ≥20% and/or ferritin ≥50 ng/ml. Key exclusion criteria were the following: anemia from causes other than CKD, liver function tests two times the upper limit of normal or more, history of thrombotic vascular events, systolic BP >150 mmHg, diastolic BP >100 mmHg, dialysis, iron saturation >70% or ferritin >1000 ng/ml, blood transfusion within 30 d before study treatment, and any erythropoiesis-stimulating agent within 6 wk before study treatment.

Interventions

Patients were assigned in a 1:1:1:1 ratio using a centralized, computer-generated randomization list to one of four treatment groups: 50 IU/kg three times weekly for 12 doses, 10,000 IU once weekly for four doses, 20,000 IU every 2 wk for two doses, or 40,000 IU every 4 wk for two doses. Epoetin alfa (PROCRIT®; Ortho Biotech Products, L.P., Raritan, NJ) was to be administered by subcutaneous injection. Dosage adjustment was not allowed. If at any time the hemoglobin was ≥13

ISSN: 1555-9041/304–1006

g/dl or increased by >1 g/dl in any 2-wk period, then no further epoetin alfa was given. The patient continued in the study, completing all required evaluations and procedures.

Patients were to receive oral elemental iron at a dosage of 200 to 400 mg/d. The use of commercially available erythropoietin products was not permitted. Transfusions of red blood cells (RBC) could be administered as necessary.

Pharmacokinetics

Venous blood samples (2.5 ml) were collected by direct venipuncture or indwelling catheter for determination of erythropoietin levels. All patients had serum pharmacokinetic (PK) samples drawn 30, 20, and 10 min before the first study drug administration of epoetin alfa. For each patient, the mean of these three samples was used as the baseline erythropoietin concentration for PK analysis. In the three-times-weekly group, additional samples were collected at 2, 4, and 6 h after dose on day 1; before dose on day 3 and on day 5; and at 3, 6, 9, 12, 24, 27, 36, 48, and 72 h after dose on day 5. In the other three treatment groups, additional samples were collected at 3, 6, 9, 12, 24, 27, 36, 48, 72, 96, 120, 144, and 168 h after dose on day 1. Samples were also obtained once weekly through day 29 in the three-times-weekly, once-weekly, and every-2-wk groups and through day 57 in the every-4-wk group.

Serum erythropoietin concentrations were measured using a validated ELISA method. The standard curve range for the assay is from the lower limit of quantification (7.8 mU/ml) to 250 mU/ml. Endogenous erythropoietin and serum levels of erythropoietin after administration of epoetin alfa were indistinguishable by the analytical method used. Baseline for PK analysis was defined as the average of the predose erythropoietin concentrations measured on day 1. PK parameters were determined using noncompartmental methods (WinNonlin Enterprise, version 5.1; Pharsight Corp., Mountain View, CA) including maximum observed serum erythropoietin concentration (C_{max}), area under the serum concentration-time curve (AUC), terminal half-life ($t_{1/2}$), and total apparent clearance (CL/F). AUC was estimated from time 0 to the last measurable time point (AUC_t) and over 1wk ($AUC_{1\,wk}$), 2 wk ($AUC_{2\,wk}$), and 4 wk ($AUC_{4\ wk}$) for all treatments. $AUC_{1\,wk}$, $AUC_{2\,wk}$, and $AUC_{4\,wk}$ were estimated on the basis of observed data and calculated on the basis of the equations presented in Table 1. CL/F was calculated as the total weekly dosage divided by $AUC_{1\,wk}$ in the three-times-weekly group and the once-weekly group, $AUC_{2\,wk}$ in the every-2-wk group, and $AUC_{4\,wk}$ in the every-4-wk group.

Pharmacodynamics

Hematologic response was assessed using pharmacodynamic (PD) markers including percentage of reticulocytes, Hb, and total RBC count. Complete blood count was performed on days 1, 3, 5, 8, 10, 12, 15, 22, 29, and 36 in each group. In the every-4-wk group, additional samples for complete blood count were obtained on days 43, 50, 57, and 64.

PD response was measured using noncompartmental methods for each PD marker after individual values were corrected for the baseline value (WinNonlin Enterprise, version 5.1; Pharsight Corp.). The primary PD parameters presented include the area under the response-time curve over a 1-wk ($AUR_{1\,wk}$), 2-wk ($AUR_{2\,wk}$), and 4-wk period ($AUR_{4\,wk}$).

Safety

Adverse event data were collected throughout the study. Serious adverse event data were collected through 30 d after the last dose for the three-times-weekly, once-weekly, and every-2-wk groups and through day 64 for the every-4-wk group. For each treatment group, treatment-emergent adverse events and changes from baseline in laboratory test results, physical examinations, and vital signs were summarized. Thrombotic vascular events were evaluated separately.

Statistical Analyses

No formal statistical comparisons were planned. Descriptive summary statistics and mean (SD) concentration-time profiles were used to evaluate the PK and PD profiles of the four regimens.

The safety population included patients who were randomly assigned and received one dose or more of study drug. A pharmacokinetically assessable patient was defined as one who received the first scheduled administration of study drug, had at least 75% of the PK samples collected up to and including day 29, and did not receive RBC transfusions before day 8. Patients in the three-times-weekly group were required to receive all scheduled study doses in the first week. To be pharmacodynamically assessable, patients must have at least met the criteria to be pharmacokinetically assessable.

Results

Study Population

Thirty-nine patients were randomly assigned to treatment: 10 in the three-times-weekly group, nine in the once-weekly group, 10 in the every-2-wk group, and 10 in the every-4-wk group. Of the 38 patients included in the safety population, 36 (95%) completed the study.

Baseline demographic and clinical characteristics are summarized in Table 2. Statistical comparisons were not performed for demographics and baseline characteristics; however, the groups generally seemed similar. Mean (SD) age of patients in the safety population was 68.2 yr (12.47). Most patients were male (53%) and white (58%). GFR ranged from 12.0 to 54.9 ml/min per 1.73 m^2, with a mean (SD) of 31.2 ml/min per 1.73 m^2 (12.7). Hb ranged from 8.4 to 11.6 g/dl, with a mean (SD) of 10.1 g/dl (0.72). Serum ferritin levels were highly variable, ranging from 10.9 to 1003.2 μg/L, with a mean (SD) of 210 μg/L (260). Transferrin saturation levels also varied greatly, with a range of 13 to 69% and a mean (SD) of 32.2% (15.7%). Baseline erythropoietin levels ranged from below the quantification limit (<7.8 mU/ml in three patients) to a maximum of 55.6 mU/ml, with a mean (SD) of 16.0 mU/ml (10.4).

Table 1. Determination of AUC values by study group[a]

Parameter	50 IU/kg Three Times Weekly for 4 wk	10,000 IU Weekly for 4 wk	20,000 IU Every 2 wk for 4 wk	40,000 IU Every 4 wk for 8 wk
$AUC_{1\,wk}$	$(2 \times AUC_{48\,h}) + AUC_{72\,h}$	Observed data	Observed data	Observed data
$AUC_{2\,wk}$	$2 \times AUC_{1\,wk}$	$2 \times AUC_{1\,wk}$	Observed data	Observed data
$AUC_{4\,wk}$	$2 \times AUC_{2\,wk}$	$2 \times AUC_{2\,wk}$	$2 \times AUC_{2\,wk}$	Observed data

[a]AUC, area under the curve.

Table 2. Demographic and baseline characteristics (safety population)[a]

Characteristic	50 IU/kg Three Times Weekly for 4 wk (n = 10)	10,000 IU Weekly for 4 wk (n = 9)	20,000 IU Every 2 wk for 4 wk (n = 9)	40,000 IU Every 4 wk for 8 wk (n = 10)	All (n = 38)
Age (yr)					
mean (SD)	66.0 (14.2)	73.1 (11.5)	65.0 (13.3)	68.8 (11.1)	68.2 (12.5)
range	36.0 to 83.0	52.0 to 90.0	42.0 to 81.0	53.0 to 84.0	36.0 to 90.0
Gender (n [%])					
male	7 (70)	6 (67)	4 (44)	3 (30)	20 (53)
female	3 (30)	3 (33)	5 (56)	7 (70)	18 (47)
Race (n [%])					
white	5 (50)	6 (67)	4 (44)	7 (70)	22 (58)
Asian	3 (30)	2 (22)	2 (22)	2 (20)	9 (24)
Hispanic	3 (30)	2 (22)	1 (11)	1 (10)	7 (18)
black	2 (20)	0 (0)	3 (33)	1 (10)	6 (16)
other	0 (0)	1 (11)	0 (0)	0 (0)	1 (3)
GFR (ml/min)					
n	10	9	9	10	38
mean (SD)	32.1 (14.5)	33.5 (13.8)	25.4 (10.0)	33.50 (12.2)	31.2 (12.7)
range	12.0 to 53.8	20.0 to 54.6	14.3 to 43.1	16.4 to 54.9	12.0 to 54.9
Endogenous erythropoietin (mU/ml)					
n	10	7	9	10	38
mean (SD)	14.4 (10.9)	21.9 (15.6)	14.9 (8.64)	14.8 (7.82)	16.0 (10.4)
range	BQL to 31.30	9.14 to 55.6	BQL to 24.50	8.02 to 34.7	BQL to 55.6
Hematocrit (%)					
n	9	9	9	10	37
mean (SD)	32 (3)	33 (1)	31 (2)	34 (2)	32 (2)
range	25 to 36	31 to 35	28 to 34	32 to 37	25 to 37
Hemoglobin (g/dl)					
n	9	9	9	10	37
mean (SD)	9.9 (0.85)	10.3 (0.34)	9.6 (0.63)	10.5 (0.71)	10.1 (7.23)
range	8.4 to 11.1	9.8 to 10.6	8.7 to 10.8	9.6 to 11.6	8.4 to 11.6
Serum ferritin (μg/L)					
n	10	9	9	10	38
mean (SD)	220 (300)	195 (256)	245 (290)	183 (230)	210 (260)
range	43.4 to 1003	28.2 to 859	26.8 to 941	10.9 to 763	10.9 to 1003
Transferrin saturation (%)					
n	10	9	9	10	38
mean (SD)	26.6 (9.0)	42.0 (18.6)	27.6 (10.8)	33.3 (19.2)	32.2 (15.7)
range	14.0 to 40.0	17.0 to 64.0	18.0 to 54.0	13.0 to 69.0	13.0 to 69.0

[a]BQL, below quantifiable limit (7.80 mU/ml).

Other Treatments

All patients (100%) received at least one concomitant therapy during the study. Use of specific therapeutic classes of medications was similar across treatment groups. The most commonly used therapeutic classes of medications were those for the alimentary tract and metabolism in 97% of patients and those for the cardiovascular system also in 97% of patients. Concomitant medications for the nervous system were used by 47% of patients. No patient received a RBC transfusion. Iron supplements were administered to 68% of patients. The most commonly used iron supplements were polysaccharide-iron complex (50% of patients) and ferrous sulfate (18%).

PK Results

Thirty-six patients were assessable for pharmacokinetics. Mean (SD) serum erythropoietin concentration-time profiles for the four treatment groups up to day 29 are displayed in Figure 1. Endogenous erythropoietin concentrations for PK blood samples collected at predose ranged from below the quantification limit (<7.8 mU/ml) to 56.8 mU/ml. After the third scheduled dose of epoetin alfa on day 5 in the three-times-weekly group and after the first dose of epoetin alfa in the once-weekly, every-2-wk, and every-4-wk groups on day 1, erythropoietin concentrations declined multiexponentially to baseline values by approximately day 8.

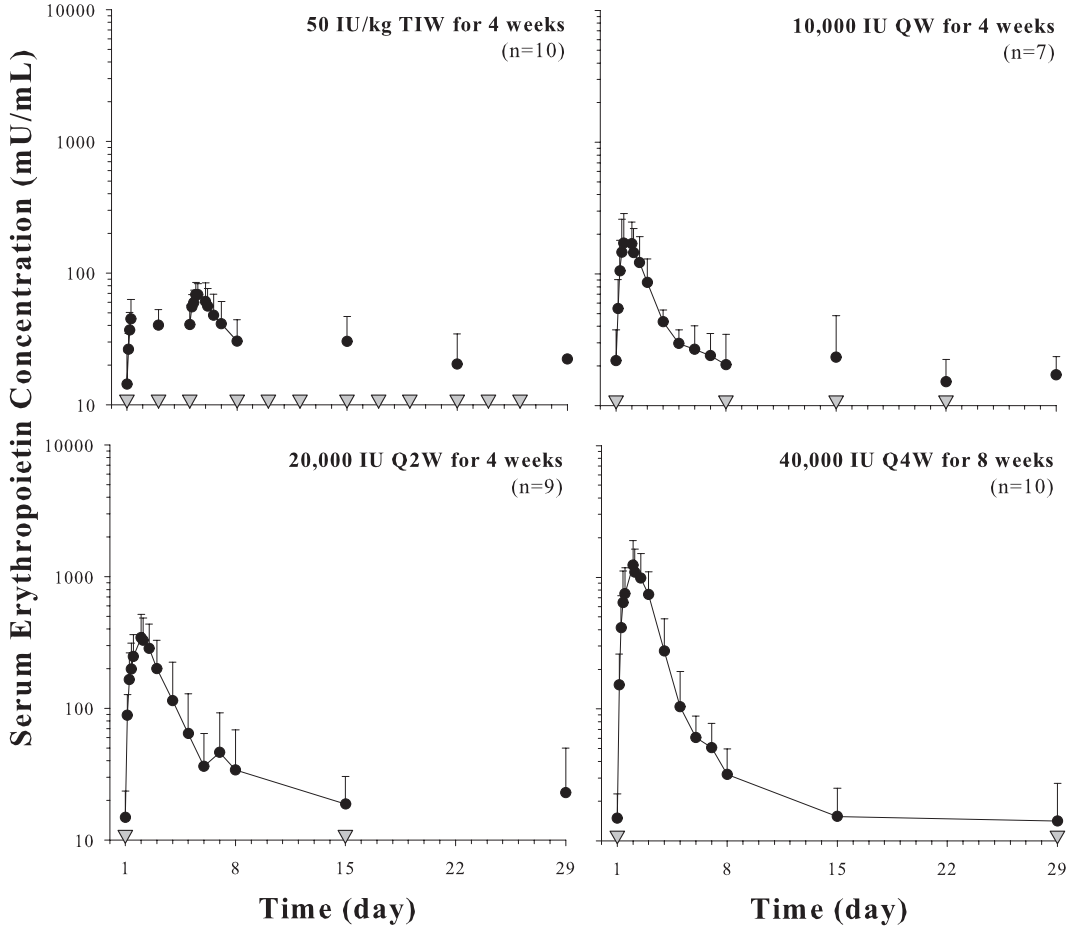

Figure 1. Mean (SD) serum concentration-time profiles of erythropoietin (pharmacokinetically assessable population). Gray symbols represent study drug administration. QW, every week; Q2W, every 2 wk; Q4W, every 4 wk; TIW, three times weekly.

Mean (SD) PK parameters for each treatment group are presented in Table 3. After subcutaneous administration, C_{max} was reached at median times ranging from 12 to 24 h across all treatment groups. Mean C_{max} and AUC values increased in a dosage-related manner. Mean $t_{1/2}$ values were similar across the once-weekly, every-2-wk, and every-4-wk groups. The $t_{1/2}$ value was difficult to estimate in the three-times-weekly group, which may have been the result of an inability to assess accu-

Table 3. Mean (SD) pharmacokinetic parameters of epoetin alfa (pharmacokinetically assessable population)[a]

Pharmacokinetic Parameter	50 IU/kg Three Times Weekly for 4 wk (n = 10)	10,000 IU Weekly for 4 wk (n = 7)	20,000 IU Every 2 wk for 4 wk (n = 9)	40,000 IU Every 4 wk for 8 wk (n = 10)
C_{max} (mU/ml; mean [SD])	75.9 (18.1)	193 (104)	368 (166)	1246 (647)
t_{max} (h; median [range])	12.0 (9.0 to 27.0)	24.0 (12.0 to 24.0)	24.0 (12.0 to 72.0)	24.0 (24.0 to 27.0)
AUC_{last} (mU × h/ml; mean [SD])	3565 (1157)[b]	10,419 (4377)[c]	25,275 (14,418)[d]	68,908 (27,238)[e]
$t_{1/2}$ (h; mean [SD])	43.2 (7.65)[f]	28.7 (9.94)	30.6 (22.5)	27.2 (17.6)[f]
CL/F (ml/h; mean [SD])	1386 (425)	1103 (425)	961 (450)[g]	600 (193)[g]

[a]CL/F, total apparent clearance; C_{max}, maximum observed concentration; $t_{1/2}$, half-life; t_{max}, time of maximal concentration.
[b]Data to approximately 72 h.
[c]Data to approximately 168 h.
[d]Data to approximately 336 h.
[e]Data to approximately 672 h.
[f]n = 9.
[g]n = 7.

Table 4. Mean (SD) AUC estimates of epoetin alfa over 1, 2, and 4 wk (pharmacokinetically assessable population)

Pharmacokinetic Parameter	50 IU/kg Three Times Weekly for 4 wk (n = 10)	10,000 IU Weekly for 4 wk (n = 7)	20,000 IU Every 2 wk for 4 wk (n = 9)	40,000 IU Every 4 wk for 8 wk (n = 10)
$AUC_{1\,wk}$ (mU × h/ml)	8977 (2754)	10,419 (4377)	21,285 (11,172)	60,914 (27,954)
$AUC_{2\,wk}$ (mU × h/ml)	17,955 (5508)	20,837 (8753)	26,906 (16,064)[a]	64,860 (27,369)
$AUC_{4\,wk}$ (mU × h/ml)	35,909 (11,017)	41,674 (17,507)	53,813 (32,128)[a]	72,867 (23,423)[a]

[a] n = 7.

rately the terminal elimination phase because of the frequent, lower dose regimen of the three-times-weekly group. Mean CL/F values decreased with extension of the dosing interval from 1103 to 600 ml/h in the once-weekly to every-4-wk dose groups.

Mean (SD) AUC estimates for each treatment group from time 0 to 168 h (1 wk), 336 h (2 wk), and 672 h (4 wk) after dose are presented in Table 4. Compared with the three-times-weekly group, the relative exposure over 4 wk of the once-weekly, every-2-wk, and every-4-wk groups was 116, 150, and 203%, respectively.

PD Results

Of the 36 patients who were assessable for pharmacokinetics, 35 were assessable for pharmacodynamics, because one patient's baseline PD laboratory values were not available. There was substantial variability in most PD parameters that were associated with all PD markers, as evidenced by SD values that were >50% of the mean values. Mean (SD) changes in concentration *versus* time up to day 36 for percentage of reticulocytes, Hb, and total RBC count are displayed in Figures 2, 3, and 4, respectively. Mean (SD) overall PD response over 1, 2, and 4 wk

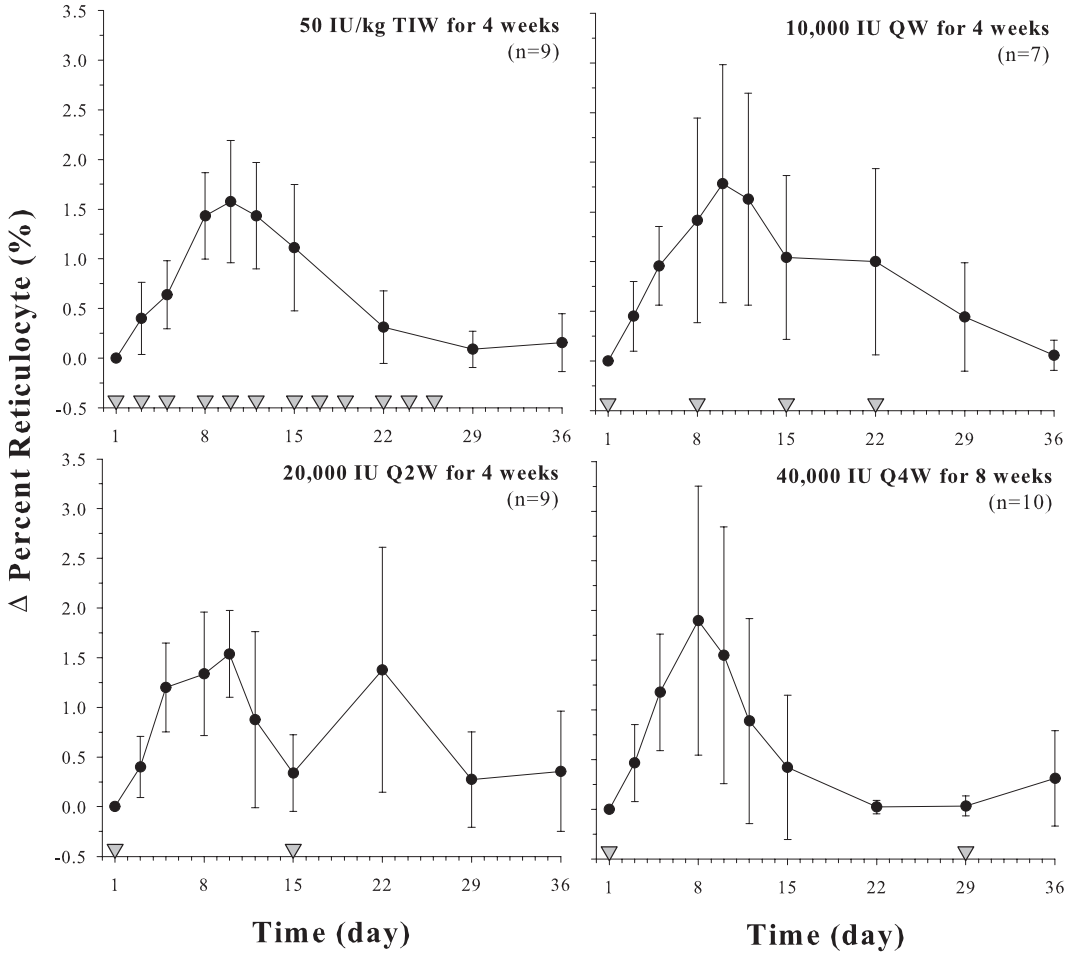

Figure 2. Mean (SD) change from baseline in percent reticulocyte *versus* time (pharmacodynamically assessable population). Gray symbols represent study drug administration. QW, every week; Q2W, every 2 wk; Q4W, every 4 wk; TIW, three times weekly.

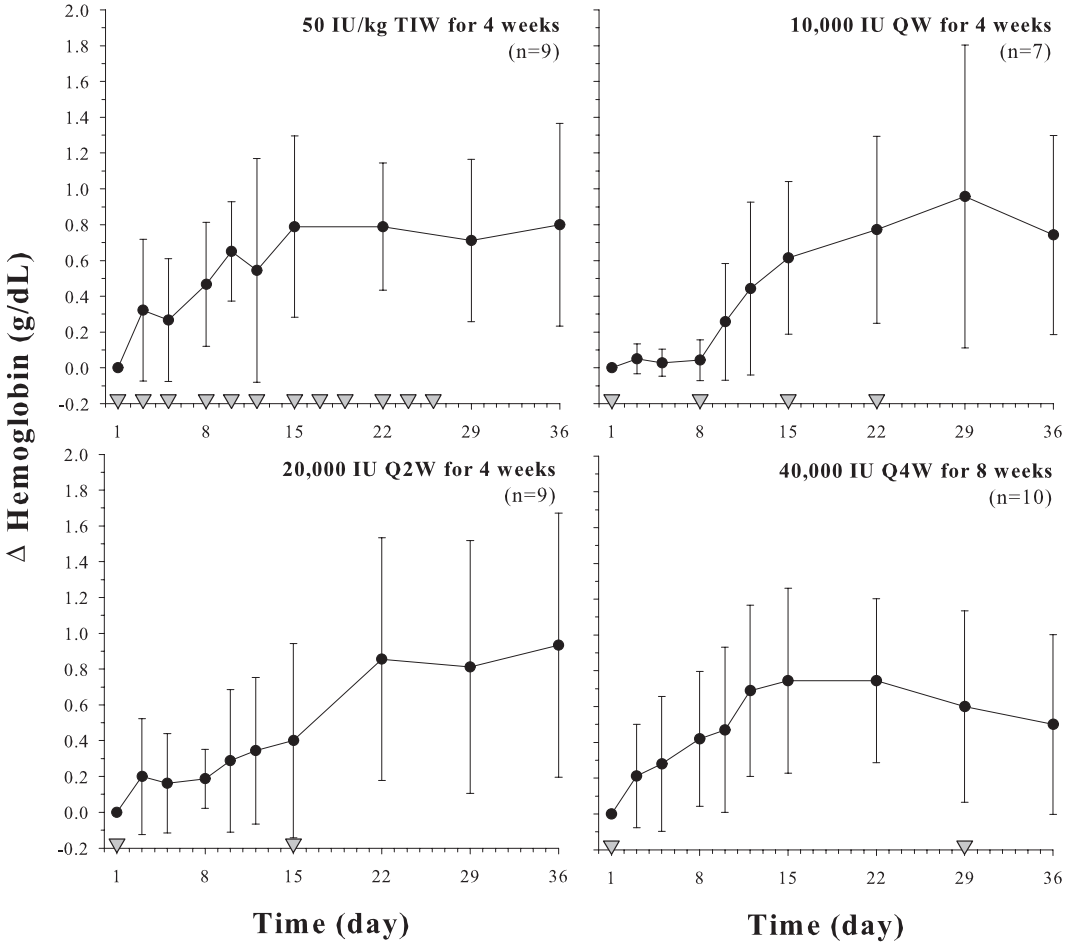

Figure 3. Mean (SD) change in hemoglobin *versus* time (pharmacodynamically assessable population). Gray symbols represent study drug administration. QW, every week; Q2W, every 2 wk; Q4W, every 4 wk; TIW, three times weekly.

for percentage of reticulocytes, Hb, and total RBC count are presented in Table 5.

Mean percentage of reticulocyte responses over 1, 2, and 4 wk (AUC) were similar for the once-weekly group compared with the three-times-weekly group. Mean percentage of reticulocyte responses showed a dosage-related trend for the first week and a similar overall response across regimens over the first 2 wk. The reticulocyte response for the every-4-wk group was initially ($AUC_{1\ wk}$) greater than for the other dosing regimens, similar over the first 2 wk ($AUC_{2\ wk}$) and lower over the 4-wk evaluation period ($AUC_{4\ wk}$).

Mean overall response, based on Hb and total RBC count over 1 wk ($AUR_{1\ wk}$), 2 wk ($AUR_{2\ wk}$), and 4 wk ($AUR_{4\ wk}$), was generally similar across dosing regimens except in the once-weekly group, in which the mean observed overall response was lower over the first week, possibly as a result of a high degree of interpatient variation.

Safety Results

Adverse events experienced by more than one patient are summarized in Table 6. Of the 38 patients in the safety population, 21 (55%) experienced at least one adverse event. No differences were observed in the incidence of adverse events among groups. The most common adverse events were peripheral edema in five (13%) patients and gout, back pain, rheumatoid arthritis, headache, and hypertension each in two (5%) patients. Investigators did not consider any adverse event to be related to study treatment.

No deaths were reported. Three patients experienced a total of five serious adverse events, as follows: one patient in the every-4-wk group had a myocardial infarction and gout; study treatment was stopped. Another patient in the every-4-wk group had cellulitis and peripheral edema, and one patient in the three-times-weekly group had hyperkalemia. Neither patient required discontinuation of study treatment. None of the serious adverse events was considered related to study treatment. Aside from the myocardial infarction, there were no other thrombotic vascular adverse events. No apparent trends in clinical laboratory values, vital signs, or weight occurred. One patient in the every-2-wk group had normal lactate dehydrogenase levels before study treatment and a markedly elevated level on day 17 that was returning toward normal on day 36.

According to the study protocol, patients were to discontinue study treatment permanently if at any time the Hb was ≥13 g/dl or increased by >1 g/dl in a 2-wk period. Two (5%) patients, both in the

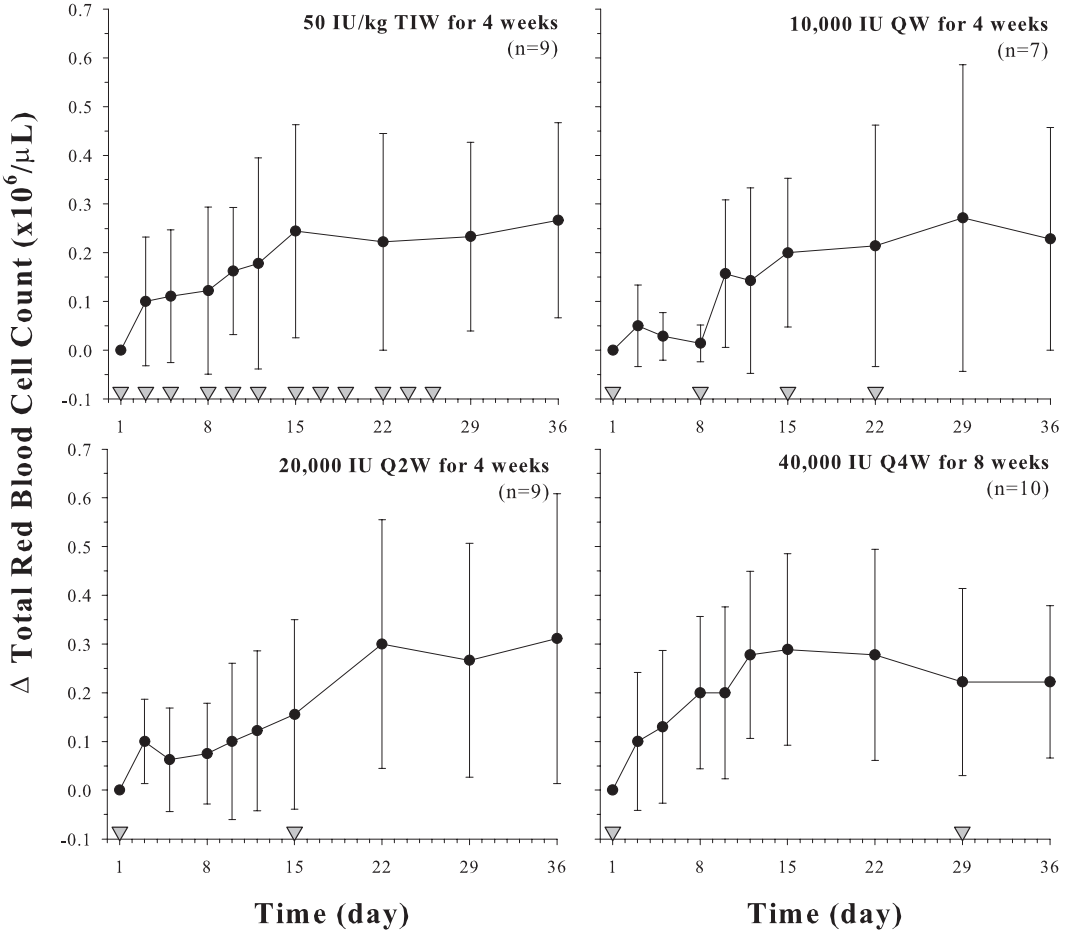

Figure 4. Mean (SD) change from baseline in total red blood cell count *versus* time (pharmacodynamically assessable population). Gray symbols represent study drug administration. QW, every week; Q2W, every 2 wk; Q4W, every 4 wk; TIW, three times weekly.

every-4-wk group, discontinued study treatment because of a single Hb ≥13 g/dl. Eighteen of 38 (47%) patients discontinued study treatment because Hb increased by >1 g/dl in a 2-wk period, including 10 of 10 (100%) patients in the three-times-weekly group, three (33%) of nine patients in the once-weekly group, three (33%) of nine patients in the every-2-wk group, and two (20%) of 10 patients in the every-4-wk group. One patient in the three-times-weekly group did receive additional study treatment after initial discontinuation.

Patients in the three-times-weekly group received a wide range of cumulative doses (from 9000 to 42,930 IU), which reflected not only the weight-based dosing regimen in this group, but also that at different time points every patient eventually required discontinuation of dosing. Only two (20%) patients in the three-times-weekly group received a cumulative dosage of epoetin alfa ≥40,000 IU. The full scheduled dosage of 40,000 IU over 4 wk was given to five (56%) patients when administered once weekly and to six (67%) patients when administered every 2 wk. Patients in the every-4-wk group were evenly divided between those who received a cumulative dosage of 80,000 and 40,000 IU.

Discussion

This study examined the pharmacokinetics, pharmacodynamics, and safety of epoetin alfa between the Food and Drug Administration–approved dosing regimen of 50 IU/kg three times weekly and extended dosing regimens of 10,000 IU once weekly, 20,000 IU every 2 wk, and 40,000 IU every 4 wk. Serum erythropoietin concentrations peaked 12 to 24 h after the first dose of each regimen and increased in a dosage-related manner with increasing dosage. Similar findings were reported in previous studies of healthy volunteers (11,12). After the final epoetin alfa dose of the first week, erythropoietin concentrations declined multiexponentially to baseline values by approximately day 8. Mean $t_{1/2}$ values were similar (27.2 to 30.6 h) across the once-weekly, every-2-wk, and every-4-wk groups but were difficult to estimate in the three-times-weekly group. During the 4-wk study period, approximately the same total dosage was administered to patients in each treatment group; however, the PK results showed that systemic exposure increased with extended dosing. Compared with the three-times-weekly dosing regimen, estimated systemic exposure during the 4-wk study period was 16, 50, and 103% higher for the once-weekly, every-2-wk, and every-4-wk regimens, respectively. This indicates a decrease in systemic clearance, an increase in systemic bioavailability, or both with increasing dosage or less frequent dosing.

The overall reticulocyte response over 1, 2, and 4 wk of treatment was similar for the three-times-weekly and once-weekly regimens. This was not unexpected, given the similarity of the weekly dose and

Table 5. Mean (SD) overall pharmacodynamic response (pharmacodynamically assessable population)[a]

Pharmacodynamic Parameter	50 IU/kg Three Times Weekly for 4 wk ($n = 9$)	10,000 IU Weekly for 4 wk ($n = 7$)	20,000 IU Every 2 wk for 4 wk ($n = 8$)	40,000 IU Every 4 wk for 8 wk ($n = 10$)
Reticulocytes (% × h)				
$AUR_{1\ wk}$	110 (34.9)	130 (66.0)	144 (49.6)[b]	161 (85.6)
$AUR_{2\ wk}$	349 (89.4)	387 (228)	375 (45.8)[c]	402 (249)[d]
$AUR_{4\ wk}$	597 (208)[e]	645 (151)[e]	959 (243)[e]	458 (336)[b]
Hemoglobin (g × h/dl)				
$AUR_{1\ wk}$	48.3 (40.7)	5.31 (10.5)	32.7 (37.3)[b]	42.2 (44.3)
$AUR_{2\ wk}$	149 (108)	70.7 (62.9)	90.1 (95.4)	141 (108)[f]
$AUR_{4\ wk}$	406 (217)	328 (227)	365 (251)	391 (218)[f]
Total red blood cell count ($\times 10^6 \times$ h/μl)				
$AUR_{1\ wk}$	15.9 (15.3)	4.29 (7.71)	11.8 (13.0)[b]	19.8 (19.5)
$AUR_{2\ wk}$	45.2 (43.5)	32.8 (24.3)[g]	33.7 (31.0)	62 (44.6)[f]
$AUR_{4\ wk}$	123 (109)	119 (92.4)[g]	130 (92.7)	157 (86.1)[f]

[a]AUR, area under the response-time curve.
[b]$n = 7$.
[c]$n = 5$.
[d]$n = 8$.
[e]$n = 4$.
[f]$n = 9$.
[g]$n = 6$.

Table 6. Adverse events experienced by more than one patient (safety population)

Adverse event (n [%])	50 IU/kg Three Times Weekly for 4 wk ($n = 10$)	10,000 IU Weekly for 4 wk ($n = 9$)	20,000 IU Every 2 wk for 4 wk ($n = 9$)	40,000 IU Every 4 wk for 8 wk ($n = 10$)	All ($n = 38$)
Peripheral edema	1 (10)	2 (22)	1 (11)	1 (10)	5 (13)
Gout	0 (0)	0 (0)	0 (0)	2 (20)	2 (5)
Back pain	0 (0)	1 (11)	1 (11)	0 (0)	2 (5)
Rheumatoid arthritis	0 (0)	1 (11)	0 (0)	1 (10)	2 (5)
Headache	0 (0)	0 (0)	0 (0)	2 (20)	2 (5)
Hypertension	1 (10)	0 (0)	0 (0)	1 (10)	2 (5)

relatively modest extension of the dosing interval. A further extension of the dosing interval to every 2 wk resulted in a similar reticulocyte response over the first 2 wk. The overall percentage of reticulocyte response was higher over 4 wk, although the data were limited and highly variable. When the dosing interval was further extended to every 4 wk, reticulocyte response was greater over the first week, similar over the first 2 wk, and somewhat lower over the 4-wk evaluation period. The Hb and RBC responses over 1, 2, and 4 wk of treatment were similar across groups; however, it should be noted that the sample sizes in each treatment group were small and the variability in response was high, making it difficult to draw firm conclusions as to the impact of these dosing regimens on PD response. There was no apparent difference in the incidence of adverse events between treatment groups, and there were no deaths; however, the small sample size of this study limits the generalizations that can be made about the safety of extended dosing regimens of epoetin alfa in anemic patients with CKD.

It is interesting to note that the results of this study for patients with CKD are very similar to those seen for normal healthy volunteers, particularly with respect to drug clearance and reticulocyte response. A recent meta-analysis of population pharmacokinetics of recombinant human erythropoietin in healthy individuals by Olsson-Gisleskog *et al.* (13) noted an increased bioavailability of subcutaneous epoetin alfa with increased dosage administered. Similarly, a study by Cheung *et al.* (14) that administered both single and multiple subcutaneous doses of epoetin alfa to healthy volunteers noted, as did this study, that clearance was dosage dependent and that reticulocyte response increased in parallel with an increased AUC for erythropoietin. The erythropoietin concentrations from the three-times-weekly arm in this study are very similar to results seen in a PK/PD study of patients who were treated with maintenance hemodialysis, which also used three-times-weekly dosing; however, this study did not include patients who were treated with hemodialysis; therefore, we cannot extrapolate the results from the extended dosing arms of this study to the hemodialysis patient population.

Two patients in the every-4-wk group discontinued study treat-

ment for a single Hb value ≥13 g/dl, and 47% of patients overall discontinued treatment early because of a Hb rise >1 g/dl. These cases draw attention to the importance of following dosing algorithms to avoid exceeding the Hb target. Further studies of extended dosing regimens with appropriate dosing modification algorithms are warranted.

Conclusions

This prospective, randomized clinical study of patients who had anemia of CKD and were not on dialysis demonstrated that there were modest differences in the pharmacokinetics of epoetin alfa when given at extended dosing intervals of 10,000 IU once weekly, 20,000 IU every 2 wk, and 40,000 IU every 4 wk relative to the 50-IU/kg three times weekly regimen; however, the PD effects and safety of the extended interval regimens were comparable to the approved dosing regimen of 50 IU/kg three times weekly. Extended dosing regimens of epoetin alfa may represent useful alternatives that can improve patient convenience and compliance without significant differences in PD effect. These results provide further support for the clinical studies in which extended dosing intervals of epoetin alfa increased hematocrit and Hb effectively (3–10).

Acknowledgments

Financial support for this study was provided by Ortho Biotech Clinical Affairs.

Results from this study were presented in part as a poster at the annual meeting of the American Society of Nephrology; October 31 through November 5, 2007; San Francisco, CA; and published in abstract form (*J Am Soc Nephrol* 18: 758A, 2007).

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We thank Elise Mazzola, BS, and Jonathan Latham, PharmD, for work in the preparation of this manuscript.

Disclosures

T.M. and M.W. were employees of Ortho Biotech Clinical Affairs; N.M.V. and J.M. were employees of Johnson & Johnson Pharmaceutical Research & Development; and J.S.B. was employed by Johnson & Johnson Pharmaceutical Research & Development during the conduct of this study and during the preparation of this manuscript. Epoetin alfa is marketed by Ortho Biotech Products, LP, a Johnson & Johnson Company.

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See related editorial, "Erythropoietin Stimulating Agents and Epoetin Alfa Revisited: What's Really Relevant?" on pages 935–937.