Epoetin Alfa Once Every 2 Weeks Is Effective for Initiation of Treatment of Anemia of Chronic Kidney Disease

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There are limited data suggesting that initiation of epoetin alfa at extended dosing intervals of every 2, 3, or 4 wk may be efficacious for treating anemia in patients who have chronic kidney disease and are not on dialysis (CKD-NOD). This open-label, multicenter, single-arm study investigated the efficacy of administration of 20,000 IU of epoetin alfa once every 2 wk as initiation therapy in these patients. Adults with CKD-NOD were eligible when they had hemoglobin (Hb) <11 g/dl, GFR of 10 to 60 ml/min per 1.73 m^2, and stable serum creatinine for the past 6 mo. Patients received 20,000 IU of epoetin alfa subcutaneously every 2 wk for up to 27 wk, with dosage adjustments permitted after 4 wk of treatment. The primary efficacy end point was the proportion of patients with Hb response, defined as achievement of the target Hb range of 11 to 12 g/dl for at least two consecutive visits. Sixty-seven patients were enrolled; >88% (59 of 67) of patients achieved an Hb response. Mean Hb increased to the targeted range by week 6 and remained in the range through week 28. Hb increases of 1 and 2 g/dl were observed in 91 and 78% of patients, respectively. Epoetin Alfa was well tolerated; most adverse events were mild or moderate in nature and typical of the CKD patient population. In this study, results demonstrated that epoetin alfa can be initiated safely and effectively at an extended dosing interval of 20,000 IU every 2 wk in patients with CKD-NOD.

Anemia is a common complication of chronic kidney disease (CKD). McClellan *et al.* (1) conducted a large, cross-sectional, multicenter survey of anemia in patients who had CKD and were not on dialysis (CKD-NOD) and found that 48% of patients had hemoglobin (Hb) ≤12 g/dl and 9% had Hb ≤10 g/dl. Because anemia occurs frequently and has been associated with adverse clinical and functional outcomes in patients with kidney disease (2–10), anemia treatment strategies to maximize effectiveness and decrease the burden on patients and the health care system continue to be evaluated. For example, in both a retrospective chart review (11) and a randomized, multicenter trial (12) in anemic patients with CKD-NOD, administration of epoetin alfa once every 2 wk to once every 4 wk was effective in maintaining Hb ≥11 g/dl in patients whose therapy had been initiated on more frequent dosing intervals. These extended dosing intervals of epoetin alfa have been shown to be effective in maintaining Hb levels in patients who have CKD and already have received treatment with more frequent dosing intervals. However, there are limited published data on the efficacy of extended dosing intervals for initiation of epoetin alfa treatment for anemia of CKD. The objective of this study was to evaluate the efficacy of administration of 20,000 IU of epoetin alfa every 2 wk as initiation therapy in patients with anemia of CKD-NOD.

Materials and Methods

General Description

This was a single-arm, open-label, multicenter study conducted in 17 nephrology private practice and academic medical center sites in the United States between June 2004 and October 2005. The institutional review board at each participating site approved the study protocol, and all patients provided signed informed consent.

Study Population

The study population comprised adult (≥18 yr of age) patients with CKD-NOD, a GFR within the range of 10 to 60 ml/min per 1.73 m^2, a stable serum creatinine during the past 6 mo, and no expected need for dialysis during the study. Eligible patients had not received erythropoietic therapy within 6 wk before study entry and had Hb <11 g/dl and serum ferritin ≥50 ng/ml or transferrin saturation (TSAT) ≥20% at study entry. Patients were excluded when they had a current diagnosis of poorly controlled hypertension (systolic BP [SBP] >150 mmHg or diastolic BP [DBP] >100 mmHg) despite antihypertensive therapy, known hypersensitivity to human albumin or mammalian cell–derived products, iron overload (serum ferritin >1000 ng/ml or TSAT >70%), a current diagnosis of anemia as a result of causes other than CKD, a history of current significant cardiovascular disease, a history of thrombovascular events, previous nonresponse to erythropoietic therapy, new-onset seizures within 3 mo of study entry or uncontrolled seizures, a history of current liver disease, a life expectancy of ≤6 mo, or received a transplanted organ. Women were required to have a negative pregnancy test within 7 d of the first dose of epoetin alfa and to use adequate birth control measures (abstinence, intrauterine device, oral

contraceptives, barrier device with spermicide, or surgical sterilization) during treatment. Breastfeeding women also were excluded from study participation. The target enrollment was 60 patients.

Study Design

Patients received 20,000 IU of recombinant human erythropoietin (rHuEPO, epoetin alfa, PROCRIT; Ortho Biotech Products L.P.; Raritan, NJ) administered subcutaneously every 2 wk for up to 27 wk. Dosage holds and dosage adjustments (increases and decreases) were allowed during the study after week 4 as per rules established in the protocol. When Hb increased to >12 g/dl and/or if the cumulative Hb increase was >1 g/dl during any 1- or 2-wk period, all subsequent epoetin alfa dosing was withheld. Dosing was resumed when Hb decreased to between 11 and 12 g/dl or when the cumulative Hb rise over 2 wk was <1 g/dl, at a dosage of 2500 IU below the most recent dosage. When Hb decreased to <11 g/dl after a dosage hold for an Hb >12 g/dl, treatment was resumed at the most recent dosage. Patients could have more than one dosage hold throughout the study. Dosage increases of 5000 IU at 4-wk intervals were permitted after 4 wk of treatment (week 5 visit) if all of the following criteria were met: Receipt of the same epoetin alfa dosage for at least two consecutive study visits, Hb increase was ≤0.5 g/dl during the previous 4 wk, and Hb was below the target range of 11 to 12 g/dl. The maximum allowed dosage was 40,000 IU every 2 wk.

All patients received a minimum of 200 mg/d oral elemental iron unless and until serum ferritin was >800 ng/ml and/or TSAT was ≥50%. When baseline serum ferritin was 50 to 100 ng/ml or TSAT was <20%, patients received a minimum oral dosage of 400 mg/d elemental iron until serum ferritin was >100 ng/ml and TSAT was ≥20%, at which point patients were maintained on 200 mg/d elemental iron. If TSAT remained <20% despite oral iron supplementation, patients were administered parenteral iron at the discretion of the investigator.

Assessments

Patients were seen weekly, and Hb and hematocrit testing were alternated weekly with testing for a complete blood count that included reticulocyte count throughout the study. Transfusions, concomitant medications, and the incidence and the severity of adverse events were recorded weekly. Blood chemistry, serum iron, serum ferritin, and total iron-binding capacity were evaluated at screening (blood chemistry also was evaluated at week 1 [baseline]), week 4, and then every 4 wk thereafter. GFR was calculated at screening and at weeks 14 and 28 (or early withdrawal) using the simplified Modification of Diet in Renal Disease equation that incorporated race, age, gender, and serum creatinine levels (13).

Quality of life (QOL) was measured at baseline and weeks 7, 14, 21, and 28. Two self-report instruments were used to evaluate QOL: The Linear Analog Scale Assessment (LASA) and the Short Form-36 (SF-36) health survey. The LASA evaluates three domains of QOL (energy level, ability to do daily activities, and overall QOL) on a 100-mm visual analog scale. The SF-36 is a self-assessment scale that consists of 36 questions that evaluate eight areas or domains of function: Physical functioning, role physical, body pain, general health, vitality, social functioning, role emotional, and mental health. For minimization of bias, QOL assessments were obtained before any study-related procedure was performed, and patients were not aware of their Hb before QOL testing.

Study End Points

The primary efficacy end point was the proportion of patients with Hb response, defined as achievement of the target Hb range of 11 to 12 g/dl for at least 2 consecutive weeks. Additional analyses included time to Hb response, proportion of patients with a 1- and 2-g/dl increase in Hb from baseline, time to achieve a 1- and 2-g/dl rise in Hb from baseline, change in Hb over time, transfusion requirements, the proportion of patients with Hb response by week 14 (midstudy), the proportion of patients who maintained an Hb response for weeks 15 to 28, change in QOL, and the correlation of change in QOL scores with change in Hb values.

A patient was considered a treatment failure when all of the following criteria were met: Receipt of the maximum epoetin alfa dosage of 40,000 IU every 2 wk for 6 consecutive weeks, Hb decreased >1 g/dl from baseline, and no clinical explanation for lack of Hb response.

Statistical Analyses

A sample size of 60 patients was based on achieving a 10% precision for a 95% confidence interval (CI) of an estimated 80% response rate. The modified intention-to-treat population was defined as all enrolled patients who received at least 1 dose of epoetin alfa. All efficacy and safety analyses were based on the modified intention-to-treat population. All analyses were performed using observed values only, without imputation for missing data.

Baseline demographic and clinical characteristics are presented using summary statistics. The proportion of Hb responders was summarized using percentages and 95% CI, and a logistic regression analysis was conducted to evaluate the impact of demographic and clinical variables on Hb response status (responder *versus* nonresponder). The Kaplan-Meier method was used to estimate time to Hb response and time to achieve a 1- and 2-g/dl increase in Hb. Mean changes in Hb from baseline over time were summarized by mean and SD, with 95% CI calculated for mean changes at weekly time points. Mean epoetin alfa dosages were summarized using descriptive statistics. Change in QOL from baseline to each assessment was summarized using descriptive statistics. The incidence and the severity of all adverse events were summarized.

Results
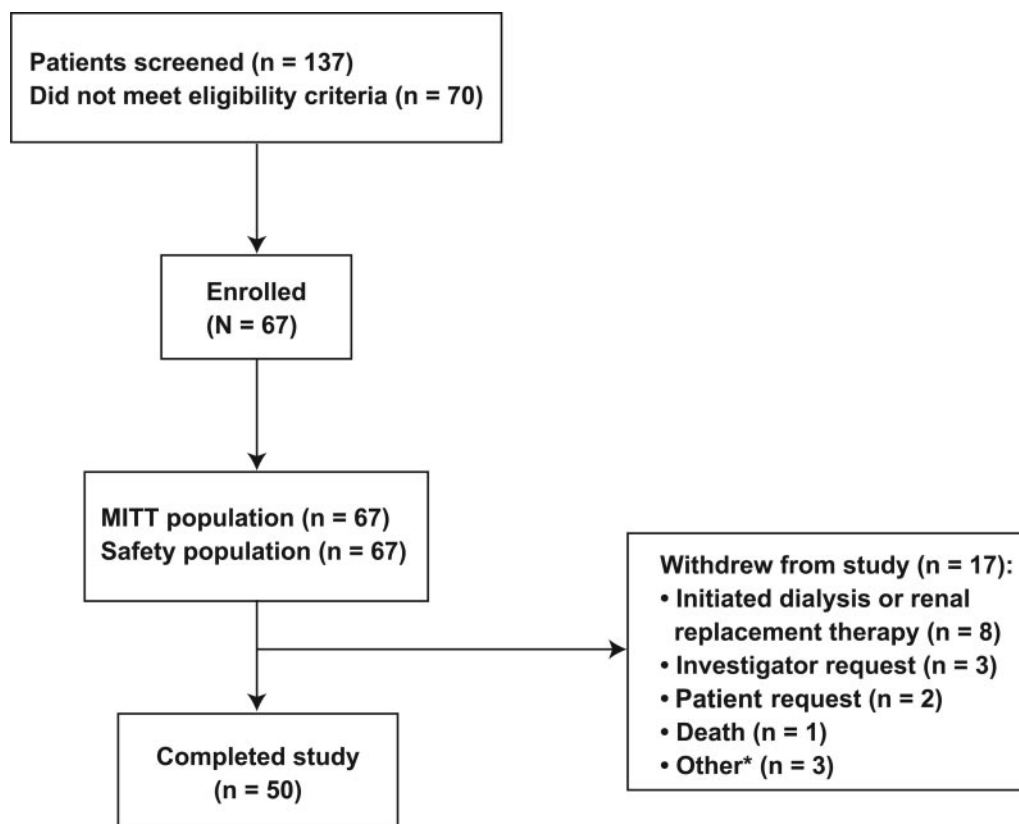
Patient Demographics

Of the 67 enrolled patients, all received at least one dose of epoetin alfa and were included in the efficacy and safety analyses. Fifty patients completed all visits through week 28; 17 patients withdrew from the study. Reasons for early withdrawals are presented in Figure 1. There were no withdrawals as a result of treatment failure. Patient demographics are listed in Table 1.

Laboratory Values

Mean baseline Hb and hematocrit levels were 9.8 ± 0.9 g/dl and 29.2 ± 2.5%, respectively. Mean calculated GFR at baseline was 21.0 ± 7.2 ml/min per 1.73 m^2. Mean changes in laboratory values from baseline to final measurement are presented in Table 2.

Hb Response

Hb response (defined as achievement of the target Hb range of 11 to 12 g/dl for at least 2 consecutive weeks) was achieved in 59 (88.1%; 95% CI 77.8 to 94.7) of 67 patients by week 28. Twenty-two (32.8%) patients had a Hb response by week 5, and 44 (65.7%) patients had a Hb response by week 9. Of the eight patients who did not reach the Hb target of 11 to 12 g/dl by week 28, five had withdrawn early, two had a rapid rise in Hb

*Other = 1 patient due to kidney transplant, 1 due to relocation, and 1 due to move out of state >3 months.

Figure 1. Patient disposition. MITT, modified intention to treat.

Table 1. Demographics[a]

Variable	Value ($N = 67$)
Age (yr; mean $\pm$ SD)	69.3 $\pm$ 14.2
Gender (n [%])	
men	36 (53.7)
women	31 (46.3)
Race (n [%])	
white	43 (64.2)
black	19 (28.4)
Hispanic	3 (4.5)
Asian	1 (1.5)
other	1 (1.5)
BMI (kg/m^2; mean $\pm$ SD)	28.4 $\pm$ 5.8
Primary cause of CKD (n [%])	
diabetes	25 (37.3)
hypertension	20 (29.9)
glomerular diseases	8 (11.9)
obstruction	2 (3.0)
congenital	1 (1.5)
other	11 (16.4)

[a]BMI, body mass index; CKD, chronic kidney disease.

and numerous dosage holds, and one had a baseline Hb value of 7.9 g/dl and a final value of 9.6 g/dl. There were no treatment failures.

Mean time to Hb response was 7.1 $\pm$ 6.3 wk; median time to Hb response was 5.1 wk. As shown in Figure 2, after mean Hb increased to the targeted range, it then remained in the target range through week 28.

Mean time to the first 1- and 2-g/dl rise in Hb was 4.2 $\pm$ 3.1 and 7.7 $\pm$ 4.8 wk, respectively. Figure 3 presents the proportion of patients with a 1- and 2-g/dl increase in Hb from baseline by weeks 5, 9, and 28.

Epoetin Alfa Dosing

Table 3 presents the mean doses every 2 wk during the study. The mean epoetin alfa dosage every 2 wk before week 8 was 17,947 $\pm$ 3759 IU. After week 8, the mean dosage every 2 wk was 13,420 $\pm$ 7657 IU. The dosing algorithm for this study mandated dosage holds and dosage titration after week 4 in response to Hb level and rate of Hb rise. These dosage holds and dosage adjustments were designed to maintain the patient's Hb within the target range of 11 to 12 g/dl. Fifty-two (77.6%) patients had at least one dosage held during the study. Forty-nine (73.1%) patients had at least one dosage held for a

Table 2. Mean changes in laboratory values from baseline to final measurement ($N = 67$)[a]

Laboratory Value	Baseline (Mean ± SD)	Change from Baseline (Mean ± SD)	P
Hemoglobin (g/dl)	9.8 ± 0.9	1.9 ± 1.0	<0.01
Hematocrit (%)	29.2 ± 2.5	6.8 ± 3.1	<0.01
Transferrin saturation (%)	26.4 ± 9.8	0.5 ± 13.2	NS
Serum ferritin (ng/ml)	282.5 ± 224.8	−67.0 ± 181.3	<0.01
GFR (ml/min per 1.73 m^2)	21.0 ± 7.2	−0.7 ± 5.4	NS
Serum creatinine (mg/dl)	3.2 ± 1.2	0.3 ± 0.9	<0.01
Serum albumin (g/dl)	3.7 ± 0.4	−0.01 ± 0.3	NS
Reticulocyte count (%)	1.9 ± 0.8	0.3 ± 1.1	NS
Systolic BP (mmHg)	134.3 ± 19.9	1.3 ± 21.2	NS
Diastolic BP (mmHg)	67.9 ± 11.4	1.7 ± 11.0	NS

[a]NS, not significant.

Hb >12 g/dl; 28 (41.8%) patients had at least one dosage held for a Hb increase of >1 g/dl during any 1- or 2-wk period.

QOL

All three domains of the LASA showed significant and clinically meaningful improvements from baseline ($P < 0.05$) during the study. Mean increases from baseline to week 28/end of study in LASA scores were as follow: Overall QOL 15.0 ± 24.0 mm, Energy 20.6 ± 21.8 mm, and Activity 17.0 ± 21.9 mm. Four of the eight domains of the SF-36 showed significant and clinically meaningful improvements from baseline ($P < 0.05$) to week 28/end of study: Physical functioning 7.8 ± 20.9, role physical 13.6 ± 48.3, vitality 14.1 ± 23.9, and social functioning 10.6 ± 31.3. There were no significant improvements in body pain, general health, role emotional, and mental health. For both the LASA and the SF-36, maximum rate of improvement from baseline occurred by week 7 and was sustained for the duration of the study.

Adverse Events

The most common adverse events (those that occurred in ≥10% of patients) were cough (nine patients; 13.4%), hyperten-

sion (nine patients; 13.4%), nausea (eight patients; 11.9%), constipation (seven patients; 10.4%), and peripheral edema (seven patients; 10.4%). Overall, 54 (80.6%) patients experienced at least one adverse event. Twelve (17.9%) patients had an adverse event that was severe, 25 (37.3%) patients had an adverse event that was moderate, and 17 (25.4%) patients had an adverse event that was mild. One reported event (adverse reaction to epoetin alfa injection [fever, chills, mild shortness of breath]) was deemed by investigators to be related very likely to epoetin alfa treatment. All adverse events were typical of the CKD population.

A total of 15 (22.4%) patients experienced a total of 29 serious adverse events during the study. The most common were renal and urinary disorders (seven patients; 10.4%) and cardiac disorders (six patients; 9.0%). The renal and urinary disorders included progressive chronic renal failure (five patients; 7.5%); acute renal failure (three patients; 4.5%); and azotemia, toxic nephropathy, and renal impairment (each one patient; 1.5%). In eight patients, renal function deteriorated such that renal replacement therapy was required. The mean baseline GFR of these eight patients was 13.3 ml/min per 1.73 m^2 compared
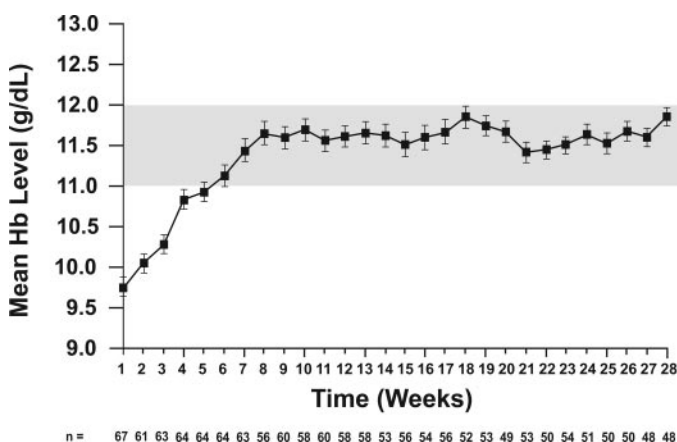
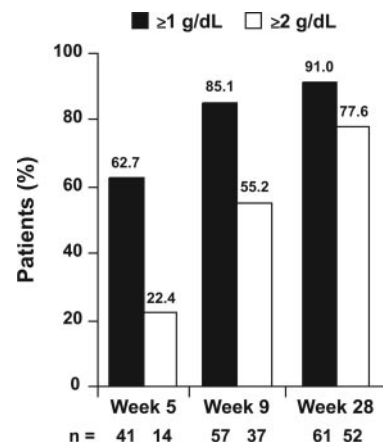*Figure 2.* Mean hemoglobin (Hb) values (±SE) over time ($N = 67$).

Figure 3. Proportion of patients with a 1- and 2-g/dl increase in Hb from baseline by week 5, week 9, and week 28 ($N = 67$).

Table 3. Mean dosages every 2 wk during the study

Time	N	Dosage (IU)[a]				
		Mean	SD	Median	Minimum	Maximum
Weeks 1 to 4	67	19,402.99	2135.98	20,000.00	10,000.00	20,000.00
Weeks 5 to 8	65	16,775.64	6619.41	20,000.00	0	25,000.00
Weeks 9 to 12	62	13,416.67	9265.55	12,500.00	0	30,000.00
Weeks 13 to 16	59	13,456.21	8697.65	12,500.00	0	35,000.00
Weeks 17 to 20	57	13,444.44	9751.02	10,833.33	0	37,500.00
Weeks 21 to 24	55	14,901.52	8879.83	15,000.00	0	40,000.00
Weeks 25 to 28	51	14,161.76	9946.59	12,500.00	0	40,000.00
Overall	67	15,602.91	5673.02	15,178.57	6428.57	32,500.00

[a]Statistics for each interval were calculated from the average of each patient's average dosage for the interval.

with a mean baseline GFR of 22.1 ml/min per 1.73 m^2 for the remaining 59 patients. One of these patients who required renal replacement therapy also required transfusion at week 22. The cardiac disorders included congestive cardiac failure (three patients; 4.5%), angina pectoris (two patients; 3.0%), and tachycardia (one patient; 1.5%). Other serious adverse events included hypertension (two patients; 3.0%) and gastrointestinal hemorrhage, urinary tract infection, pneumonia, head contusion, pathologic fracture, diabetic ketoacidosis, syncope, subclavian vein thrombosis associated with a central line, and sudden death (each one patient; 1.5%). All of the serious adverse events were typical of this patient population, and only one (severe hypertension) was deemed as possibly related to study drug. No event that led to permanent withdrawal was considered to be related to study drug.

Both SBP and DBP changes from baseline over time were analyzed. No significant changes in SBP or DBP were observed during the course of the study. The mean baseline SBP was 134.3 ± 19.9 mmHg; the mean change from baseline was 1.3 ± 21.2 mmHg at week 28/end of study. The mean baseline DBP was 67.9 ± 11.4 mmHg; the mean change from baseline was 1.7 ± 11.0 mmHg at week 28/end of study.

Discussion

This single-arm, open-label, multicenter study demonstrated that initiation of therapy with epoetin alfa at a dosing interval of 20,000 IU every 2 wk was effective for patients with anemia of CKD-NOD. Fifty-nine (88.1%) of 67 patients achieved the primary end point of a target Hb range of 11 to 12 g/dl. More than 90% of patients achieved a 1-g/dl increase and 78% of patients achieved a 2-g/dl increase in Hb from baseline by week 28. In addition, targeted Hb levels were achieved early, with 62.7% of patients achieving a 1-g/dl increase in Hb from baseline after 4 wk of therapy (week 5). After 8 wk of therapy (week 9), 55.2% of patients had achieved a 2-g/dl increase (Figure 3). These findings are similar to the rate of Hb rise that was seen with more frequent epoetin alfa dosing intervals (14; data on file, Ortho Biotech Clinical Affairs, L.L.C.). Approximately 78% of patients had at least one dosage held during the study. Early in the study, most dosages were held as a result of a rapid rate of Hb rise. Later in the study, dosage holds usually

occurred for Hb >12 g/dl. The dosing algorithm may account for the variability in mean dosage during the course of the study (Table 3).

Many measures of QOL showed clinically meaningful and sustained improvements from baseline values. Although the findings are consistent with clinical observations, a double-blind, placebo-controlled trial is warranted to validate these results.

There was a 67.0 ± 181.3-ng/ml decline in mean serum ferritin from baseline. The decline most likely was due to increased erythropoiesis, but mean ferritin at study end remained >200 ng/ml.

Treatment with 20,000 IU of epoetin alfa every 2 wk was well tolerated, with most adverse events being mild or moderate in severity and typical of those that are observed in this patient population.

Extended dosing intervals of every 2 wk to once every 4 wk have been shown to be effective in maintaining Hb levels ≥11 g/dl after initial correction of Hb to 11 to 12 g/dl with more frequent dosing (11,12,15). There also are publications describing the efficacy of weekly epoetin alfa dosing when initiating treatment of anemia in patients with CKD (16–18). The results of our study demonstrated that initiation of epoetin alfa therapy at extended dosing intervals of every 2 wk also was effective in achieving and maintaining Hb levels within a target range of 11 to 12 g/dl.

The results of our study are comparable to those reported by Provenzano *et al.* (16), who evaluated once-weekly initiation dosing in patients with anemia of CKD. Approximately 90% of patients in the once-weekly study achieved a 1-g/dl increase in Hb from baseline, and 71% achieved a 2-g/dl increase (16). Moreover, our results complement the findings of another large, randomized, prospective study in which dosing every 2 wk was effective in maintaining target Hb levels ≥11 g/dl in 89.5% of patients who had CKD and had previously been receiving epoetin alfa for 2 mo or more (12). As with our study, these studies also demonstrated that increasing Hb levels with epoetin alfa therapy in patients with anemia of CKD is associated with improved QOL (12,16).

This was an exploratory study to examine the feasibility of an every-2-wk dosing regimen for initiation of epoetin alfa therapy

and, as such, had several limitations: The sample size was relatively small; the design was single arm; the study tested only initiation, not maintenance; and the study population was restricted to patients with anemia as a result of CKD. However, sample size was calculated to detect a Hb response; therefore, it was adequate for this study. The single-arm design was chosen because Hb is recognized as an acceptable end point, and this was an exploratory study. The single-arm, nonblinded design limits the ability to compare results against other treatment regimens. The inclusion and exclusion criteria restricted the study population to patients with anemia as a result of CKD; therefore, the results may not be generalizable to patients with anemia as a result of other causes.

Studies that have compared the pharmacokinetic profiles of erythropoietin molecules have suggested that a longer half-life allows for less frequent dosing (19,20). In our study, 88.1% of enrolled patients achieved a Hb response, despite the relatively short half-life of epoetin alfa. This suggests that *in vivo* efficacy of extended epoetin alfa dosing intervals may be a result of several factors, such as binding affinity of epoetin alfa to the erythropoietin receptors and iron repletion, and not solely a function of half-life.

Extending the frequency of epoetin alfa administration may offer advantages for patients and health care practitioners in terms of convenience, flexibility, and improved compliance. Less frequent administration also may reduce the costs that are associated with anemia treatment. A recent meta-analysis that evaluated the impact of a change in dosing frequency on patient outcomes and health care costs found that reduced dosing frequencies were associated with improved compliance, QOL, and satisfaction with care and decreased cost (given that the extended dosing interval and the conventional dosing interval had similar profiles of efficacy and safety) (21). Although our study was not designed to assess the effect of less frequent epoetin alfa dosing on patient compliance and health care resource utilization, it would be of interest to evaluate these associations in future studies.

Conclusion

The results of our study demonstrated that initiation dosing of 20,000 IU of epoetin alfa every 2 wk was effective and safe for treating patients with anemia of CKD-NOD. Target Hb levels of 11 to 12 g/dl were achieved after 6 wk of treatment and maintained throughout the study, and many measures of QOL showed significant improvement from baseline values. Epoetin alfa was well tolerated, with most adverse events being mild or moderate in severity and typical of this patient population. These findings, taken together with the results of previous studies of extended dosing, support the dose scheduling flexibility of epoetin alfa use for initiation treatment in anemic patients with CKD-NOD. These results should be corroborated further by controlled studies.

Acknowledgments

Disclosures

R.B. is a member of the speakers bureau for Ortho Biotech and for Amgen but has no financial conflict to report. R.S. also is on the speakers bureau for Ortho Biotech. K.K. and M.W. are employees of Ortho Biotech Clinical Affairs, L.L.C.

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