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An open-label study of darbepoetin alfa administered once monthly for the maintenance of haemoglobin concentrations in patients with chronic kidney disease not receiving dialysis

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Abstract. Agarwal AK, Silver MR, Reed JE, Dhingra RK, Liu W, Varma N, Stehman-Breen C (Ohio State University, Columbus, OH; Case School of Medicine at MetroHealth Medical Center, Cleveland, OH; Nephrology Associates, Columbus, MS; Wright State University, Dayton, OH; and Amgen Inc., Thousand Oaks, CA; USA). An open-label study of darbepoetin alfa administered once monthly for the maintenance of haemoglobin concentrations in patients with chronic kidney disease not receiving dialysis. *J Intern Med* 2006; **260**: 577–585.

Objective. To demonstrate the efficacy and safety of once-monthly (QM) darbepoetin alfa administration in maintaining haemoglobin (Hb) 11.0–13.0 g dL^{-1} in subjects with chronic kidney disease (CKD) not receiving dialysis and previously treated with darbepoetin alfa every other week (Q2W).

Subjects. This open-label study enrolled subjects ≥18 years of age who had glomerular filtration rate ≥15 and ≤60 mL $min^{-1}/1.73\ m^2$, had Hb 11.0–13.0 g dL^{-1}, and were receiving Q2W darbepoetin alfa.

Design. Subjects were switched to QM darbepoetin alfa therapy for 28 weeks; the QM dose was titrated to maintain Hb levels. Primary end-point: proportion of subjects maintaining Hb ≥11.0 g dL^{-1} during the final 8 weeks of the study (evaluation phase). Secondary end-points: Hb concentration during evaluation, darbepoetin alfa dose during the study, adverse events, laboratory parameters, and blood pressure.

Results. The study enrolled 152 subjects (female 52%, white 64%). Mean Hb ≥11.0 g dL^{-1} during evaluation was achieved by 76% of the 150 subjects who received at least one dose of darbepoetin alfa [95% confidence interval (CI): 68%, 83%]. Mean (SD) Hb during evaluation was 11.71 (0.92) g dL^{-1}. Eighty-five per cent of 129 subjects who completed the study (95% CI: 78%, 91%) had Hb ≥11.0 g dL^{-1} during evaluation. The dose of darbepoetin alfa over the study period was median (95% CI) 124.4 μg (106.2, 140.0). Darbepoetin alpha administered QM was well tolerated in study subjects.

Conclusion. Darbepoetin alpha administered QM maintained Hb in study subjects with CKD not receiving dialysis.

Keywords: anaemia, chronic kidney disease, darbepoetin alfa, haemoglobin.

Introduction

Anaemia reduces the quality of life and physical capacity of patients with chronic kidney disease (CKD) [1–3]. Growing evidence indicates that anaemia is also a risk factor for cardiovascular complications in the CKD population [4–7]. Treatment of anaemia may reduce this risk and have a beneficial impact on the progression of CKD [8–11]. Anaemia of CKD can be effectively treated and haemoglobin (Hb) concentrations maintained by the

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use of an erythropoiesis-stimulating protein (ESP) such as recombinant human erythropoietin (rHuEPO; epoetin alfa) or darbepoetin alfa.

Darbepoetin alpha can be administered less frequently than rHuEPO because of its approximately threefold longer serum half-life and greater biological activity [12, 13]. Several clinical studies have demonstrated that darbepoetin alfa is efficacious in treating anaemia in patients with CKD not receiving dialysis when administered at an every-other-week (Q2W) dosing interval. This dosing regimen has proved efficacious both in study patients converting from previous once-weekly (QW) erythropoietic therapy with rHuEPO [14], and in those naïve to erythropoietic therapy [15–17].

Extending the darbepoetin alfa dosing interval may have advantages for both patients and their healthcare providers. Benefits for patients include increased convenience, as a result of fewer trips to the clinic for treatment, and greater comfort, owing to the reduced number of injections. These benefits may result in better treatment compliance. Advantages for healthcare providers include decreased health-resource utilization and a reduced logistical burden, leading to increased operational efficiency.

A single report has demonstrated that darbepoetin alfa effectively keeps study patients' Hb levels within a target range of 10.0–12.0 g dL^{-1} when the darbepoetin alfa administration interval is extended from Q2W to once monthly (QM) [18]. However, the lower limit of this Hb range (10 g dL^{-1}) is lower than that in current guidelines (11 g dL^{-1}) [19], and it is unknown whether targeting to a higher Hb concentration will result in reductions in the number of subjects achieving the Hb target and/or in increases in darbepoetin alfa dose requirements. Therefore, the primary aim of this study was to determine whether darbepoetin alfa administered QM could safely and effectively maintain Hb concentrations ≥11 g dL^{-1} in subjects with CKD who were not receiving dialysis and whose Hb had previously been stabilized in the range of 11.0–13.0 g dL^{-1} with Q2W darbepoetin alfa therapy.

Subjects and methods

Study design

This was a multicentre, open-label, single-arm study of patients with CKD not receiving dialysis who had been receiving subcutaneous (SC) Q2W darbepoetin alfa. Subjects' Hb levels were to be stable, in the range of 11.0–13.0 g dL^{-1}. Following a screening assessment, eligible individuals were enrolled within 14 days and were switched from Q2W darbepoetin alfa to QM darbepoetin alfa. Subjects received their first on-study dose of darbepoetin alfa within 4 days of enrollment, and darbepoetin alfa was administered QM (28 ± 7 days) for 28 weeks (at weeks 1, 5, 9, 13, 17, 21, 25 and 29). Efficacy was evaluated over the final 8-week period (weeks 25–33). The study design is summarized in Fig. 1.

Darbepoetin alpha (Aranesp®; Amgen Inc., Thousand Oaks, CA, USA) was provided in prefilled syringes (PFSs) containing 20, 30, 40, 50, 60, 80, 100, 150, 200, or 300 μg. The starting dose of darbepoetin alfa was equivalent to each subject's total dose in the month prior to enrollment. Doses were then titrated to maintain Hb concentrations within the target range of 11.0–13.0 g dL^{-1} (Hb was measured Q2W throughout the study). If the most recent Hb concentration prior to dose administration was >13.0 g dL^{-1} but ≤14.0 g dL^{-1}, the subsequent darbepoetin alfa dose was reduced to the next lower PFS. If the most recent Hb concentration prior to dose administration was >14.0 g dL^{-1}, darbepoetin alfa was withheld until Hb fell to ≤13.0 g dL^{-1}, when dosing was then resumed with the next lower PFS. If Hb increased by >1.0 g dL^{-1} in any 2-week period after receiving darbepoetin

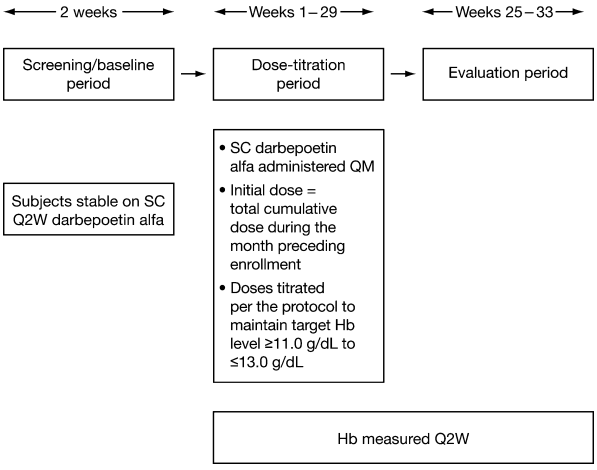

Fig. 1 Study design. SC, subcutaneous; Q2W, every other week; QM, once monthly; Hb, haemoglobin.

alfa, the subsequent planned administration was reduced to the next lower PFS. The dose was increased to the next higher PFS if the most recent Hb concentration prior to darbepoetin alfa administration was ≥11.0 g dL^{-1}. Darbepoetin alpha was dispensed and administered at study centres or in subjects' homes by trained medical personnel.

The primary end-point of the study was the proportion of subjects who maintained a Hb concentration of ≥11.0 g dL^{-1} during the evaluation phase. Secondary end-points included Hb values and darbepoetin alfa dose over the duration of the study, the frequency and relationship to treatment of adverse events, and changes in laboratory parameters and blood pressure.

Subjects

Subjects aged ≥18 years of age with a diagnosis of CKD, but not receiving or scheduled to receive dialysis for the duration of the study, were recruited from 36 centres across the US. All study participants gave written informed consent, and the study was approved by the Independent Ethics Committee/Institutional Review Board overseeing studies at each participating centre.

For inclusion, subjects were required to be clinically stable in the investigator's opinion, with an estimated glomerular filtration rate ≥15 and ≤60 mL $min^{-1}/1.73\ m^2$, using the Modification of Diet in Renal Disease equation [20, 21], and have a mean Hb concentration ≥11.0 and ≤13.0 g dL^{-1} (mean of two measurements taken at least 3 days apart during the screening period). Serum vitamin B_{12} and folate levels were required to be above the lower limit of the normal range, and transferrin saturation (TSAT) was to be ≥15.0%. Subjects had to be receiving stable, Q2W doses of SC darbepoetin alfa, stable defined as a ≤25% change in dose over the 6-week period prior to enrolment, with no missed doses during this period. Oral and intravenous iron therapies were permitted during the study.

Subjects were excluded from the study if they had received or were scheduled to receive a kidney transplant, were hypertensive (diastolic blood pressure >110 mmHg or systolic blood pressure >180 mmHg during screening), or had cardiovascular disease (acute myocardial infarction or hospitalization for chronic heart failure within the 12 weeks prior to enrolment). Subjects should not have an intact parathyroid hormone concentration of >1500 pg mL^{-1}, systemic infection, or protocol-defined haematologic disease (eg, sickle-cell anaemia, myelodysplastic syndromes, haematologic malignancy, myeloma, or haemolytic anaemia). Additional exclusion criteria were major surgery within the 12 weeks prior to enrolment (with the exception of vascular access surgery), and receipt of red blood cell (RBC) transfusions within the 8 weeks before enrolment. RBC transfusions were allowed following study initiation, but not within 90 days of, or during, the evaluation period. No treatment with another investigational agent or device was allowed either during the study or within 30 days prior to enrolment, and no treatment with darbepoetin alfa or any other ESP was allowed within 14 days prior to enrolment.

Study assessments

Study visits occurred Q2W until week 33. An end-of-study assessment was performed 4 weeks after administration of the last dose of darbepoetin alfa (week 33), or at the time of withdrawal if the subject discontinued the study prematurely. Hb concentrations were measured at week 1, and then at each study visit until end of study (week 33 or on withdrawal). Haematology (other than Hb concentration), serum chemistry, and TSAT were assessed at screening, week 15, and end of study; TSAT was also measured at weeks 7 and 23.

Adverse events observed by the investigator or reported by subjects were recorded at each study visit. The investigator assessed the severity of each adverse event and assigned a relationship to study treatment. Anti-erythropoietin seroreactivity assays were performed prior to administration of the first dose of darbepoetin alfa and at end of study to evaluate whether subjects developed neutralizing antibodies to darbepoetin alfa.

Statistical analysis

A target sample size of 150 was determined, based on a 95% confidence interval (CI) with a 16.5% length for the proportion of subjects receiving darbepoetin alfa QM and achieving a Hb concentration ≥11.0 g dL^{-1} during the evaluation period. A 70% estimated proportion was used in this

calculation, assuming a 20% dropout rate based on previous studies in this patient population.

Efficacy and safety analyses included data from all subjects who received at least one dose of darbepoetin alfa. Descriptive statistics were calculated for each end-point, including mean and standard deviation (SD) for continuous variables, and counts and percentages for categorical variables. Ninety-five per cent, two-sided CIs were calculated for mean values and proportions. The proportion of subjects achieving the primary end-point was calculated by dividing the number of subjects with a mean Hb concentration ≥11.0 g dL^{-1} during the evaluation period by the total number of subjects receiving at least one dose of the study drug or by the total number of subjects completing the study (completers analysis). Subjects who received an RBC transfusion within 90 days prior to the start of, or during, the evaluation period were considered not to have achieved the primary end-point. If subjects completed at least 8 weeks of the study, but discontinued the study prior to the evaluation period due to initiation of renal replacement therapy, the last available postbaseline Hb value was used to calculate the mean Hb during the evaluation period. Those subjects who did not complete the end of study and had no Hb data during the evaluation period, and/or who had withdrawn from the study for other reasons, were considered not to have achieved the primary end-point. As a nonparametric estimator of the median darbepoetin alfa dose, the Hodges–Lehmann distribution-free 95% CIs were calculated [22].

Results

Subject characteristics

In total, 152 subjects were enrolled at 36 study centres: the first subject was enrolled in March 2004 and the last subject completed the study in February 2005. Subject disposition is summarized in Table 1. Of the subjects enrolled, 150 received at least one dose of study drug and were included in the efficacy and safety analyses. The demographic and baseline characteristics of the study population are summarized in Table 2. The majority of subjects were female (52%) and White or Caucasian (64%). The mean (SD) age was 66.9 years (13.4) and 64% of subjects were ≥65 years of age. The most common cause of CKD was diabetes (51%), and the mean (SD) length of time since subjects' diagnosis of CKD was 38.4 months (31.6).

Table 1 Subject disposition

Disposition	Darbepoetin alpha, *n* (%)[a]
Subjects enrolled	152
Did not receive darbepoetin alfa	2 (1)
Received darbepoetin alfa	150 (99)
Received all planned doses	133 (88)
Discontinued darbepoetin alfa	17 (11)
Completed study	129 (85)
Discontinued study	23 (15)
Initiation of dialysis	11 (7)
Consent withdrawn	6 (4)
Adverse event	3 (2)
Death	3 (2)

[a]Percentages based on subjects enrolled.

Table 2 Demographic and baseline characteristics (all enrolled subjects)

Characteristics	Darbepoetin alpha ($N = 152$)
Sex, *n* (%)	
Female	79 (52)
Male	73 (48)
Race, *n* (%)	
White or Caucasian	97 (64)
Black or African-American	45 (30)
Hispanic or Latino	9 (6)
Other	1 (1)
Age group, *n* (%)	
<65 years	55 (36)
≥65 and <75 years	46 (30)
≥75 years	51 (34)
Age, years, mean (SD)	66.9 (13.4)
Weight,[a] kg, mean (SD)	88.9 (23.8)
Hb concentration,[b] g dL^{-1}, mean (SD)	11.9 (0.6)
TSAT,[c] %, mean (SD)	27.6 (10.9)
eGFR,[d] mL $min^{-1}/1.73\ m^2$, mean (SD)	28.0 (10.5)
Time since CKD diagnosis, months, mean (SD)	38.4 (31.6)
Cause of CKD, *n* (%)	
Diabetes	77 (51)
Hypertension	44 (29)
Glomerulonephritis	4 (3)
Polycystic kidney disease	2 (1)
Known other	23 (15)
Unknown	2 (1)

SD, standard deviation; Hb, haemoglobin; TSAT, transferrin saturation; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease. [a]$n = 151$. [b]$n = 150$. Baseline Hb defined as mean of all Hb measures taken during screening period (not including study day 1). [c]$n = 150$. Defined as last value prior to first dose of darbepoetin alfa on day 1. [d]Calculated as 186 × serum creatinine × (−1.154) × age × (−0.203) × (0.742 if female) × (1.212 if black or African American).

Hb concentrations

The primary end-point, a mean Hb concentration of ≥11.0 g dL^{-1} during the 8-week evaluation period, was achieved by 114 of 150 subjects who received at least one dose of QM darbepoetin alfa (76% [95% CI: 68%, 83%]; Table 3). Overall, of the 36 patients who were considered not to have achieved the primary end-point (24%), 14 discontinued participation before the evaluation phase (5, initiation of dialysis after the first 8 weeks of the study; 4, consent withdrawn; 3, death; and 2, adverse event). The 22 patients considered not to have achieved the primary end-point and who entered the evaluation phase all had Hb < 11 g dL^{-1} (with one also having had an RBC transfusion). Of the 129 subjects who completed the study, 110 achieved the target mean Hb concentration of ≥11.0 g dL^{-1} over the evaluation period (proportion: 85% [95% CI: 78%, 91%]). Hb concentrations remained stable over the course of the study (Fig. 2), and were maintained at a mean (SD) of 11.71 g dL^{-1} (0.92) over the evaluation period for all subjects with Hb values measured during the evaluation period ($n = 141$; Table 3).

Darbepoetin alpha dose

The median (95% CI) dose of darbepoetin alfa at baseline (the first QM dose) was 125.0 μg (115.0, 150.0) (weight adjusted 1.47 μg kg^{-1} [1.34, 1.61]). Median QM darbepoetin alfa doses remained steady during the study and are shown in Fig. 3. Over the entire study period, the median (95% CI) dose was 124.4 μg (106.2, 140.0).

Iron therapy

Overall, 106 subjects (71%) received oral iron therapy and 20 subjects (13%) received intravenous iron therapy. Mean (SD) TSAT was 27.6% (10.9%) at baseline and 29.5% (10.4%) at week 33. The mean TSAT level was at least 24% at each of the other assessments (weeks 7, 15 and 23).

Table 3 Summary of Hb results

Parameter	Result
Mean (SD) Hb over evaluation period (g dL^{-1})[a]	11.71 (0.92)
Change from baseline in mean (SD) Hb over evaluation period (g dL^{-1})[a]	−0.18 (1.0)
Subjects who received ≥1 dose of darbepoetin alfa who maintained Hb ≥11.0 g dL^{-1} over evaluation period[b]	
n	114
Proportion (95% CI)[c]	0.76 (0.68, 0.83)
Subjects completing the study who maintained Hb ≥11.0 g dL^{-1} over evaluation period[d]	
n	110
Proportion (95% CI)[d]	0.85 (0.78, 0.91)

SD, standard deviation; CI, confidence interval. [a]Subjects with Hb values during the evaluation period: $n = 141$. [b]$n = 150$. [c]Calculated using the exact method. [d]$n = 129$.

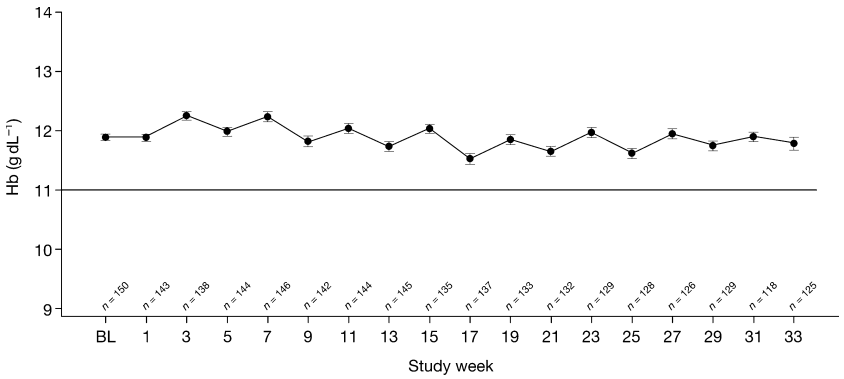

Fig. 2 Mean (standard error [SE]) Hb concentration over time. Vertical lines represent one SE above and below the mean. Horizontal line represents the Hb target (11.0 g dL^{-1}). *N* = subjects with Hb values available in each study week; BL = baseline Hb, defined as the mean of all Hb measures taken during the screening/baseline period (does not include study day 1).

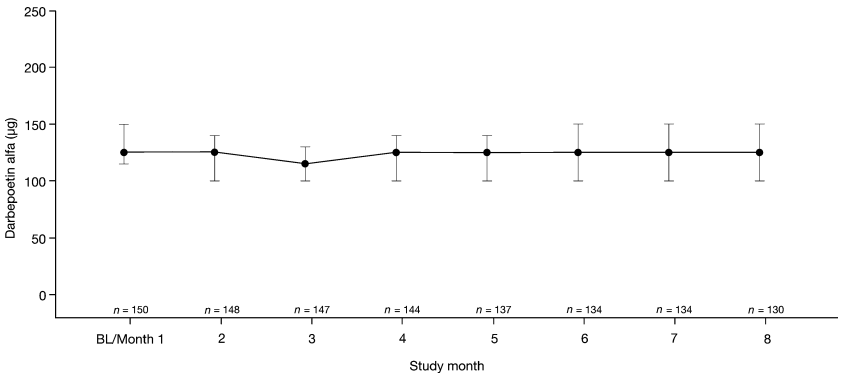

Fig. 3 Median (95% confidence intervals [CIs]) darbepoetin alfa dose over time. Vertical bars represent Hodges–Lehmann estimates of the 95% CIs. N = subjects who received a dose in each study month; BL/Month 1 = baseline and study month 1, defined as study weeks 1 and 2.

Safety assessments

Safety was assessed in all subjects who received a dose of darbepoetin alfa ($n = 150$). Adverse events occurred in 122 subjects (81%) during the study, and these were typical of the study population (Table 4). Most adverse events were mild to moderate in severity. Serious adverse events occurred in 43 subjects (29%), but none were considered by the investigator to be treatment related. Adverse events that were considered by the investigator to be treatment related occurred in nine subjects (6%), with three subjects experiencing hypertension. Three subjects (2%) were withdrawn from the study prematurely because of adverse events (one coronary artery disease, one asthenia, and one small-cell lung cancer), and three subjects (2%) died during the study or within 30 days of the last dose (one sepsis, one pancreatitis, and one acute renal failure). None of the events leading to discontinuation or death was considered to be treatment related. Five subjects (3%) required one or more RBC transfusions during the study.

Table 4 Summary of adverse events occurring in ≥5% of subjects

Adverse event	Darbepoetin alpha ($N = 150$), n (%)
Subjects experiencing adverse events	122 (81)
Back pain	11 (7)
Cough	11 (7)
Fatigue	11 (7)
Nasopharyngitis	11 (7)
Gout	10 (7)
Peripheral oedema	10 (7)
Congestive cardiac failure	9 (6)
Constipation	9 (6)
Urinary tract infection	9 (6)
Hypertension	8 (5)
Hypotension	8 (5)
Asthenia	7 (5)
Cellulitis	7 (5)
Diarrhoea	7 (5)
Hypoglycaemia	7 (5)
Oedema	7 (5)
Pyrexia	7 (5)

For the majority of subjects (88%), Hb concentrations remained ≤14.0 g dL^{-1} during the study. The proportion of Hb values >14.0 g dL^{-1} during the evaluation period was 1.3%. The proportion (95% CI) of Hb values >14 g dL^{-1} over the course of the study for all 150 subjects who received darbepoetin alfa was 1.5 (0.7, 2.3).

Four subjects tested positive for binding antibodies to darbepoetin alfa, but all bioassay tests for neutralizing antibodies to darbepoetin alfa were negative. Mean white blood cell counts, platelet counts, serum chemistries and vital signs did not change notably over the course of the study and did not suggest any adverse effects associated with darbepoetin alfa dosed QM.

Discussion

The aim of this study was to determine whether darbepoetin alfa administered QM could safely and effectively maintain Hb concentrations ≥11 g dL^{-1} in subjects with CKD who were not receiving dialysis and whose Hb had previously been successfully stabilized in the range of 11.0–13.0 g dL^{-1} with Q2W darbepoetin alfa therapy. Overall, 76% of subjects who received at least one dose of darbepoetin alfa and 85% of subjects who completed the study achieved the primary end-point. Mean Hb concentration did not change substantially from baseline through the evaluation period. The median dose of darbepoetin alfa over the 28 weeks of the

study was 124.4 μg (95% CI: 106.2, 140.0). Darbepoetin alpha was well tolerated in these study subjects and none of the serious adverse events reported were considered by investigators to be treatment related.

The lower limit of the target Hb concentration selected for this study (11.0–13.0 g dL^{-1}) is consistent with the lower limit of the Hb target range recommended in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI™) guidelines for the treatment of anaemia of CKD [19]. This is in contrast to the lower Hb target (10.0–12.0 g dL^{-1}) used in the earlier, 29-week study of QM darbepoetin alfa by Ling *et al.* [18]. The results of the two studies are consistent however, with 79% (95% CI: 71%, 87%) of the 97 subjects treated with darbepoetin alfa QM in the Ling *et al.* study achieving a Hb concentration within the 10.0–12.0 g dL^{-1} target range [of the subjects who completed the study, 85% (95% CI: 78%, 93%) achieved the target]. The positive results of our study newly show that darbepoetin alfa dosed at a QM interval can achieve Hb targets in the majority of study subjects, regardless of target Hb level.

In the study presented here, the dose of darbepoetin alfa was individually titrated to maintain Hb concentration within the target range. However, the median monthly dose remained stable over the course of the study. This suggests that there was no dose escalation following conversion from the Q2W regimen (via a doubling of the previous, stable Q2W dose) to the QM darbepoetin alfa dosing regimen. The median darbepoetin alfa dose required to maintain Hb levels above 11 g dL^{-1} was 125 μg, compared with a mean dose of 87 μg in the study by Ling *et al.* (median dose was not reported) [18]. The difference in darbepoetin alfa QM doses may be due to the lower Hb target in the earlier study, but could also have been influenced by the fact that the mean weight of subjects was also lower in the earlier study. The Ling *et al.* study also had a higher TSAT target (≥19.5% vs. ≥15%), but a regression analysis of the current results showed that TSAT level had no effect on the Hb response rate.

Darbepoetin alpha QM was well tolerated in these study subjects, confirming previous findings [18]. The safety profile is consistent with that expected for patients with CKD not receiving dialysis. No serious treatment-related adverse events were reported and no neutralizing antibodies to darbepoetin alfa were detected by bioassay. For the majority of subjects, Hb concentrations remained ≤14.0 g dL^{-1} during the study.

Less frequent administration of ESPs has potential benefits for both patients and healthcare providers. Extended-dosing intervals, with fewer injections and clinic visits, may be preferred by patients with CKD who do not have to visit patient care centres regularly for dialysis. A recent study assessing the treatment preferences of subjects with CKD who were switched from QW or Q2W epoetin alfa to QM darbepoetin alfa found that at week 21 of the study, the majority of subjects (88%) preferred the QM darbepoetin alfa regimen over more frequent therapy with epoetin alfa [23]. The benefits to healthcare providers of less frequent dosing regimens were demonstrated by a decrease in outpatient health resource utilization during the study: not unexpected given the reduction in the number of injections required for QM dosing over the other ESP dosing intervals, nurse visits decreased significantly during the 4 weeks prior to week 21 compared with baseline ($P < 0.001$) [23]. In the clinic, decreased nursing time would potentially allow for improved overall operational efficiency.

Previously reported data suggest that ESP therapy for anaemia in patients with CKD improves quality of life [24, 25], and may also have a beneficial impact on mortality [9], cardiovascular outcomes [8], and the progression of CKD [10, 11]. Reducing the dosing frequency has been shown in a number of chronic diseases to improve patients' adherence to treatment [26]. Therefore, more convenient treatment regimens with a dosing interval that fits patients' preferences may encourage better compliance with ESP therapy and may help to improve health outcomes.

Conclusions

The results presented here newly demonstrate that darbepoetin alfa administered QM maintained Hb in the target range of 11.0–13.0 g dL^{-1} in study subjects with CKD who were not receiving dialysis and who were previously stable on Q2W darbepoetin alfa therapy. The current study showed that QM darbepoetin alfa had a similar percentage of patients achieving the Hb target as in previous studies with lower target Hb levels. The adverse event profile of QM darbepoetin alfa was similar to that with Q2W

dosing. A QM darbepoetin alfa dosing regimen may help to optimise compliance with anaemia therapy in patients with CKD, as this extended-dosing interval offers the potential for more convenient erythropoietic therapy as well as potential benefits for both patients and healthcare providers.

Conflict of interest statement

A.K.A. has received consulting and lecture fees from Amgen Inc. and Abbott, and consulting fees from Shire. M.R.S. has received speaker honoraria and consulting fees from Amgen Inc. and consulting fees from Shire. J.E.R. has received speaker honoraria and consulting fees from Amgen Inc. R.K.D. has nothing to disclose. N.V. and C.S.B. are employees of Amgen Inc. W.L. was an employee of Amgen Inc. at the time the study and analysis was conducted.

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