Hemoglobin Variability With Extended Dosing of Epoetin Alfa in Patients With Chronic Kidney Disease and Not on Dialysis

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OBJECTIVES: Hemoglobin (Hgb) variability when treating anemia in pre-dialysis chronic kidney disease (CKD) patients with erythropoietin stimulating agents (ESAs) may be an important safety consideration, as significant Hgb fluctuations over time appear to be associated with worse outcomes, especially cardiovascular-related outcomes. We analyzed Hgb variability in subjects receiving epoetin alfa (EPO) with extended dosing regimens.

METHODS: We conducted a post-hoc analysis to evaluate Hgb variability in 2 trials of EPO in CKD anemia; both examined Hgb response during dosing intervals up to 4 weeks. Study 1 examined 4 EPO maintenance regimens of every 1 to 4 weeks for 16 weeks. Study 2 examined EPO initiation and maintenance dosing of every 2 weeks for 28 weeks.

RESULTS: During the maintenance periods evaluated, Hgb variability (mean within-subject standard deviations) was 0.75 (0.32), 0.66 (0.29), 0.65 (0.30), and 0.74 (0.36) g/dL, with 10KQW, 20KQ2W, 30KQ3W, and 40KQ4W regimens in study 1 (10,000 IU [10K] once weekly [QW], 20,000 IU [20K] every 2 weeks [Q2W], 30,000 IU [30K] every 3 weeks [Q3W], or 40,000 IU [40K] every 4 weeks [Q4W]), and was 0.59 (0.27) g/dL with 20KQ2W in study 2. Serious thrombovascular events were seen in 4 patients in study 1 and in 3 patients in study 2.

CONCLUSIONS: Our analysis of CKD patients treated with extended dosing of EPO revealed no relationships between Hgb variability and administered dose or dose interval, comparable with published results of other ESAs.

In individuals with normal renal function, production of erythropoietin by the kidney stimulates erythrocyte maturation, insuring adequate levels of circulating hemoglobin.[1] This is critical in maintaining proper oxygen delivery to body tissues, and is particularly important for normal function of the cardiovascular system. In patients with kidney disease, the inability of the diseased kidneys to produce adequate amounts of erythropoietin frequently leads to anemia as a secondary complication.[1]

Anemia is observed not only in dialysis patients with end-stage renal disease (ESRD), but also in patients with chronic kidney disease (CKD) who are not on dialysis.[2] Erythropoiesis stimulating agents (ESAs) such as epoetin alfa (EPO) are used to manage anemia and decrease the need for red blood cell transfusions in both ESRD and CKD patients. Extended dosing regimens in which EPO is administered once every 1 to 4 weeks in CKD patients with anemia have been shown to be as effective as more frequent EPO dosing regimens in managing anemia.[3]

However, administration of EPO in extended dosing intervals has led some clinicians to express concern that these regimens may lead to greater hemoglobin (Hgb) variability. The labeling of ESAs, which require the practitioner to individualize dosing to achieve and maintain Hgb levels within the range of 10 to 12 g/dL,[4,5] has led to further concerns that attempting to manage Hgb within a relatively narrow range may lead to variability in Hgb levels. In dialysis patients, Hgb variability has been associated with poorer outcomes.[6]

To investigate these concerns in extended dosing regimens of EPO, we analyzed the Hgb data from 2 previously published EPO clinical trials in CKD patients to provide new insights into the relationship among extended dosing regimens and Hgb variability within individual subjects.

Methods

In the 2 studies included in our post-hoc analyses, patients had anemia of CKD and were not on dialysis.[3,7,8] Hemoglobin variability was analyzed in patients from 2 separate previously published studies denoted as studies 1 and 2.

Study 1 was a 16-week, open-label, multicenter, study with patients randomized to 1 of 4 EPO treatment arms as maintenance therapy: 10,000 IU (10K) once weekly (QW), 20,000 IU (20K) every 2 weeks (Q2W), 30,000 IU (30K) every 3 weeks (Q3W), or 40,000 IU (40K) every 4 weeks (Q4W).[8] Patients included in study 1 must have been receiving EPO for 2 or more months prior to study initiation. Dose reductions but not escalations were permitted in study 1. ➲

DOI: 10.1002/dat.20365

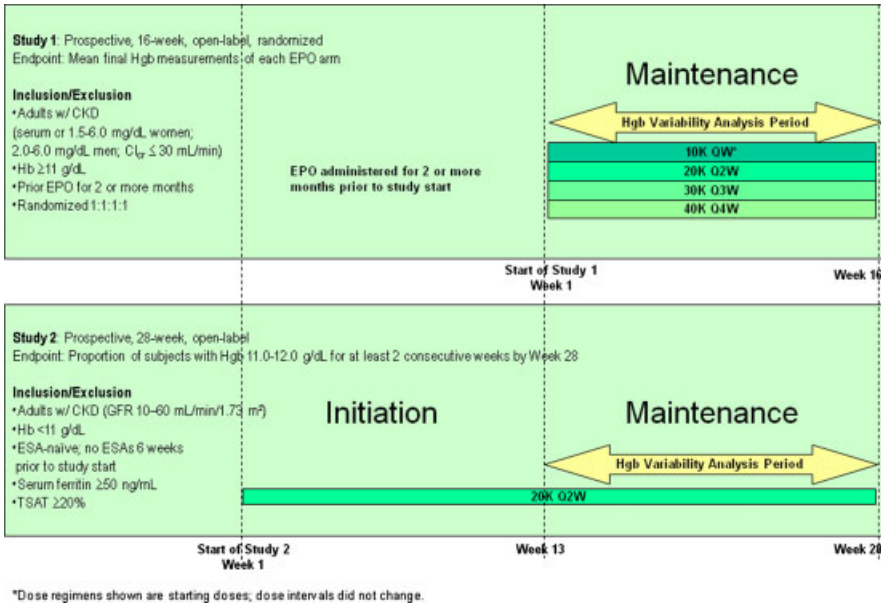

FIGURE 1. *Periods used for Hgb variability analyses from 2 clinical studies.*

TABLE I. Baseline characteristics and laboratory parameters.

	Study 1* n = 410	Study 2** n = 56
Mean age, years (SD)	68.7 (13.2)	69.8 (13.9)
Male, %	50.8	53.6
Race, %		
White	66.4	60.7
African American	25.6	32.1
Hispanic	5.6	3.6
Asian	1.5	1.8
Other	1.0	1.8
Primary cause of CKD, %		
Diabetes	44.9	33.9
Hypertension	29.8	32.1
Glomerular disease	6.3	12.5
Other	19.0	21.5
Hgb, g/dL (SD)	12.0 (0.7)	11.6 (1.0)
GFR, mL/min/1.73 m² (SD)	20.7 (7.3)	22.1 (7.0)

**Study 1: The study population was comprised of adult CKD patients with stable Hgb levels (≥11.0 g/dL) who had been receiving EPO for 2 or more months.*
***Study 2: Hemoglobin at week 12 is presented for baseline as this was an initiation study, and Hgb values between week 13 and week 28 were used in the analysis to estimate Hgb variability.*

Study 2 was an open-label, multicenter, single-arm, 28-week initiation study in which participants received 20K EPO 20K. Treatment was continued up to 27 weeks.[3] Dosage holds and dosage adjustments (increases and decreases) were allowed during the study after week 4 as per rules established in the protocol. For study 2, week 12 Hgb values were used as baseline Hgb values, and the maintenance phase Hgb values (weeks 13–28) were used to evaluate Hgb variability. Hemoglobin variability was defined as the within-subject standard deviation (SD) of Hgb values.

Patients included in the Hgb variability analysis were selected from the modified intent-to-treat (mITT) population of the 2 studies, and were those who had at least 4 Hgb values recorded during the analysis period and who were dosed with EPO every week or less frequently. Dose regimens included 10KQW, 20KQ2W, 30KQ3W, and 40KQ4W in study 1 and 20KQ2W in study 2. The period used to evaluate Hgb variability included weeks 1 to 16 of study 1 and weeks 13 to 28 of study 2, as subjects were considered to be in the maintenance phase of treatment during these periods (*Figure 1*).

Results

Of the 445 mITT patients in study 1 and of the 67 mITT patients in study 2, 466 (410 and 56 respectively) met the selection criteria and were included in our analysis of Hgb variability. There were no clinically important differences in the demographic and baseline clinical characteristics among the subjects in the 2 studies with the exception of baseline Hgb as study 2 evaluated an EPO-naïve population (*Table I*).

Hemoglobin Variability With Extended EPO Dosing

The observed variability of Hgb in studies 1 and 2 is shown in *Figure 2*. In study 1, Hgb levels demonstrated mean within-subject SDs of 0.75 (0.32), 0.66 (0.29), 0.65 (0.30), and 0.74 (0.36) g/dL, with the 10KQW, 20KQ2W, 30KQ3W, and 40KQ4W regimens respectively. In study 2, the mean within-subject SD for Hgb was 0.59 (0.27) g/dL with 20KQ2W dosing.

Safety

In both studies analyzed, the incidence of adverse events was similar across all dosing groups. In general, reported adverse events were typical of the CKD population. ➲

Hgb Variability with Epoetin

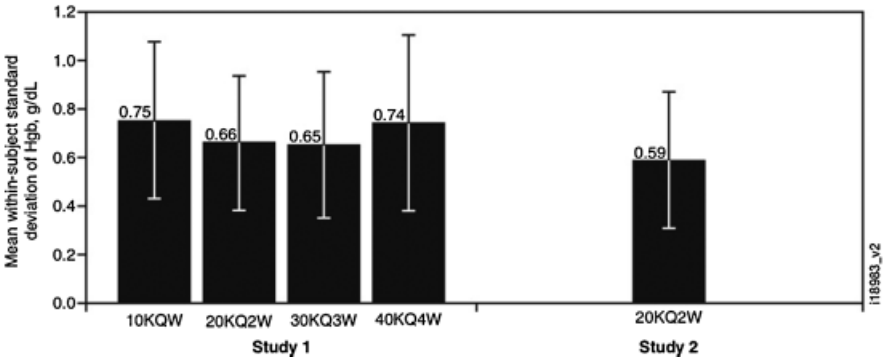

FIGURE 2. *Hemoglobin variability in studies 1 and 2 (n = 105, 107, 101, and 97 for 10KQW, 20KQ2W, 30KQ3W, and 40KQ4W in study 1 and n = 56 in study 2, respectively).*

TABLE II. Patients reporting serious thrombovascular events in both trials.

Serious Adverse Event	Study 1* (n = 410)	Study 2 (n = 56)
Angina pectoris	…	2
Cardiac arrest	1	…
Chest pain	1	…
Coronary artery occlusion	1	…
Deep vein thrombosis	1	1
Peripheral vascular disorder	…	…

**By dosing regimen in study 1, serious thrombovascular events; 10KQW 1 subject w/chest pain; 20KQ2W 1 subject coronary artery occlusion; 30KQ3W 1 subject w/deep vein thrombosis and 1 subject w/cardiac arrest; 40KQ4W none.*

Serious thrombovascular events reported from both studies are listed in *Table II*. Among the 410 patients evaluated in study 1, 3 (0.7%) subjects died during the course of the study. These deaths were considered to be unrelated to study treatment. In addition, 4 (1.0%) patients in study 1 experienced a serious thrombovascular adverse event. Among the 56 patients evaluated from study 2, no deaths occurred, while 3 (5.4%) experienced a serious thrombovascular adverse event. Of these 3, 1 patient experienced deep vein thrombosis at week 6 during initiation treatment, and 2 patients experienced angina pectoris at weeks 18 and 26, respectively, during the maintenance phase.

Discussion

Erythropoiesis-stimulating agent labeling calls for Hgb to be maintained within a range of 10 to 12 g/dL, as opposed to an upper limit.[4,5] However, maintaining Hgb levels within a narrow range in CKD patients as required by ESA labeling has led to concerns that this will result in greater variability of Hgb concentrations over time.[6,9] In a retrospective analysis of ESRD patients on hemodialysis, over 90% of patients were found to experience major variability in Hgb levels, usually resulting in regular excursions both above and below the desired Hgb range.[9] Fishbane and Berns concluded that frequent dosage adjustment in ESAs to avoid Hgb excursions over target range led to increased Hgb variability. They found that frequent dose adjustments might have been a factor responsible for subsequent variability and excursions in approximately 80% of cases.[9] Individual patient responsiveness to ESAs is another likely factor contributing to these variations.[9]

Poor outcomes, especially those associated with cardiovascular events have also been associated with variability in Hgb values over time in patients treated with ESAs. In a study of ESRD patients that evaluated the frequency of adverse events as related to Hgb variability, it was observed that patients with consistently stable Hgb values had a lower percentage of adverse events.[6] Conversely, those with larger variability in Hgb levels had higher rates of hospitalizations. Although most studies of Hgb variability have focused on ESRD patients who undergo hemodialysis, a recent analysis in which CKD patients were studied during their first year of ESA treatment suggested that the time spent within the desired Hgb range was correlated with better renal survival.[10]

While protocols are now in use in which patients are treated with extended ESA dosing regimens, little is known about potential variability in Hgb levels in patients receiving higher ESA doses at longer intervals. Thus, understanding variability of Hgb levels in ESA-treated CKD patients is important for optimizing management of the ESA-treated patient.

Yee et al have reported that in large studies in the general population such as the National Health and Nutrition Examination Survey (NHANES) and the Scripps-Kaiser Database, Hgb levels ranged from 13 to 15 g/dL with an SD of 0.8 to 1.2 g/dL.[11] Thus, Hgb variability seen in our analyses of 2 trials of EPO in CKD patients was similar to or lower than the variability seen in the general population (SD: 0.59–0.75 g/dL).

The findings of our analyses also are similar to the findings of an analysis of data from a randomized controlled trial of ESRD patients on hemodialysis comparing darbepoetin alfa and EPO, in which Nissenson et al found no significant difference in Hgb variability between treatment groups.[12] Results of our analyses were also similar to an analysis performed on data from a trial of another ESA, methoxypolyethylene glycol epoetin beta, in subjects with ESRD on dialysis.[13]

One limitation of our study is that these analyses were carried out in subjects enrolled in clinical trials where Hgb levels were tightly controlled by protocols. Additionally, the subjects enrolled in these trials were selected based on strict inclusion and exclusion criteria, which may not reflect characteristics of the ➲

general CKD population. In the clinical setting, Hgb variability for CKD patients receiving ESA treatment may be different from those found in the clinical trial setting. Additionally, dose adjustments (up or down) in the clinical setting may be very different from protocol-dictated dose adjustments used in the clinical trials analyzed here. Lastly, the reported results here are from post-hoc exploratory analyses of data from clinical trials, which were not designed or powered to fully assess the magnitude and impact of Hgb variability. Nonetheless, results from these analyses may give clinicians some insight into how their treatment practices with ESAs may affect Hgb variability.

Conclusions

Hemoglobin variability analyses from 2 studies of extended dosing regimens of EPO in subjects with CKD suggest that Hgb variability is similar despite different dosing regimens. Results show that Hgb variability reported as the mean within-subject SD of Hgb was also comparable across all extended EPO dosing regimens studied. Moreover, the Hgb variability observed in this analysis is similar to that reported with other ESAs.[11,12] Further research is needed to determine the clinical relevance of Hgb variability in CKD patients.

Disclosure

This study received support from Centocor Ortho Biotech Services. D&T

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