



Original

©2009 Dustri-Verlag Dr. K. Feistle
ISSN 0301-0430

Intercurrent events and comorbid conditions influence hemoglobin level variability in dialysis patients

A.L.M. DeFrancisco¹, I.C. Macdougall², F. Carrera³, J. Braun⁴, P. Bárány⁵, I. Bridges⁶, T. Wheeler⁷, D. Tran⁷ and A. Dietrich⁸

¹Hospital Universitario Valdecilla, Servicio de Nefrología, Santander, Spain,

²Department of Renal Medicine, King's College Hospital, London, UK,

³Eurodial, Dialysis Unit, Leiria, Portugal, ⁴KfH Kuratorium für Dialyse und

Nierentransplantation eV, Nürnberg, Germany, ⁵Division of Renal Medicine,

Department of Clinical Science, Intervention, and Technology, Karolinska Institute,

Karolinska University Hospital, Stockholm, Sweden, ⁶Amgen International Biostatistics,

Cambridge, UK, ⁷Amgen International Biostatistics, Uxbridge, UK, and

⁸Amgen International Medical Affairs, Zug, Switzerland

Key words

dialysis – hemoglobin variability – intercurrent events – patient characteristics – erythropoiesis-stimulating agents

Abstract. **Background:** To help identify factors contributing to intra-patient Hb variability, pooled records were analyzed from 5,592 patients undergoing hemodialysis (HD) in European, multicenter, open-label, single-arm Phase 3b trials. **Patients and methods:** Patients previously treated with recombinant human erythropoietin (rHuEPO) were switched to darbepoietin- α administered once a week (QW) or once every 2 weeks (Q2W), maintaining the same dosing schedule and route of ESA administration (intravenous or subcutaneous) up to and through the evaluation period. Patients were treated with darbepoietin- α to maintain Hb levels between 10 and 13 g/dl. Inpatient variability was calculated using the SD model, taking all of an individual patient's Hb values during the evaluation period (Weeks 21 – 24 after conversion) and calculating the SD of these Hb values. Adverse events (AE) of infection or inflammation were recorded. **Results:** Smaller variability was seen for patients 65 years of age or older compared with younger patients ($p = 0.0044$) and greater variability for patients less than 40 years of age compared with older patients ($p < 0.01$). Little difference in variability was seen in relation to sex overall or to the presence or absence of diabetes. Intra-patient Hb variability was greater in the presence of intercurrent conditions, including infection or inflammation ($p = 0.0032$), blood transfusion ($p < 0.0001$), hospitalization ($p < 0.0001$), or hospitalization for cardiovascular (CV) causes ($p = 0.0012$), than in their absence. Iron status differences had little detectable effect on intra-patient Hb variability. A larger number of changes made to the ESA dose during the evaluation period was also associated with greater Hb variability compared

with fewer dose changes, but this association could not be proved as being causative. Although p values were calculated for some comparisons, statistical significance might not indicate clinical significance because of the large sample size. Multivariable analysis to assess the association between AE status and intra-patient Hb variability, adjusting for age, sex, diabetes status, number of dose changes and iron status showed that AE status was significantly associated with Hb variability. **Conclusion:** Additional studies would be needed to further investigate causes and effects of Hb variability and intercurrent events.

Introduction

Following the assessment of outcomes data relating patients' serum hemoglobin (Hb) concentrations to their exercise performance, quality of life, and even rates of cardiovascular disease and survival, Hb target ranges have been recommended in various anemia management guidelines. These include the guidelines produced by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative [National Kidney Foundation 2007] and the European Best Practices Guidelines Working Group [Locatelli et al. 2004a]. The study populations in clinical trials of erythropoiesis-stimulating agents (ESAs) in patients with chronic renal failure (CRF) generally achieved and maintained mean Hb concentration within the target range [Mann 2007].

Received;
August 7, 2008;
accepted in revised form
September 29, 2008

Correspondence to
Dr. A.L.M. DeFrancisco
Presidente de la
Sociedad Espanola de
Nefrología, Servicio de
Nefrología, Hospital
Universitario Valdecilla,
Santander, Spain
martinal@unican.es

However, Hb concentrations in individual patients treated in trials or routine clinical practice showed substantial fluctuations [Berns et al. 2003, Ebben et al. 2006, Eschbach et al. 1987, Lacson et al. 2003].

Hb levels and their variability are generally calculated to facilitate the comparison of patient populations in clinical trials (i.e., between-patient or interpatient Hb variability) rather than to assess the degree of variability for individual patients (ie, within-patient or intra-patient Hb variability). Interpatient Hb variability is usually reported as the estimated standard deviation (SD) for an overall study population. However, the interpatient variability data may sometimes be misinterpreted as indicating stable Hb levels in individual patients, and the population mean does not give an indication of how individuals' Hb levels vary over time.

Individual patients' Hb levels are unlikely to follow the variation pattern of the population mean, and a large variety of individual Hb variability patterns has been recognized [Ebben et al. 2006]. In clinical practice, Hb levels often are not maintained within the target range in patients with CRF receiving ESAs to manage their anemia [Lacson et al. 2003, Pisoni et al. 2004]. In fact, studies have shown that Hb concentrations are in flux in a high percentage of patients during any period investigated [Ebben et al. 2006] and 3-month rolling average Hb concentrations were below 10 mg/dl in 12% of patients in the large observational study by Lacson et al. [2003].

Failure of an individual patient's Hb to remain within the target range may be especially deleterious for patients undergoing hemodialysis (HD) and may be associated with increased morbidity and mortality [Brunelli et al. 2008, Foley et al. 1996, Locatelli et al. 2004b, Ofsthun et al. 2003, Yang et al. 2007]. The inpatient Hb variability observed in patients with CRF might be linked with a large number of factors such as "normal" biological variation, with patient-related factors that change in the course of time such as aging, with comorbid conditions such as inflammatory states, with intercurrent complications, such as infections, which may affect red blood cell production, or with blood loss. Variability in Hb concentrations might also be promoted by changes in Hb testing procedures or by changes in treatment practice patterns

such as dialysis regimen, fluid shifts, adequacy of dialysis, iron supplementation, and changes in ESA dosing.

Studies, now being conducted, to analyze the cause-and-effect relationships of various conditions with Hb variability are prerequisite to try to minimize Hb variability caused by modifiable factors. To help identify factors associated with intra-patient Hb variability, data collected from 5,592 patients during previous clinical trials investigating the efficacy and safety of darbepoietin- α for managing anemia in patients with CRF undergoing HD were analyzed post-hoc. The analyses were exploratory and the results are described below.

Patients and methods

Data source

To establish the methodology to be applied to the pooled data set, analyses were initially performed on data from 522 dialysis patients from a multicenter, open-label, randomized, ESA conversion trial as a pilot trial for the Phase 3b studies. Results of these analyses were presented at the American Society of Nephrology meeting in 2007 and described preliminary information on relationships between Hb concentrations and some patient characteristics [Burnier et al. 2007, Canaud et al. 2007].

A post-hoc analysis of Hb concentrations and their relationship with various potentially influential factors was performed for the present study on the pooled records of 5,592 patients undergoing HD from a series of European, multicenter, open-label, single arm Phase 3b trials on the efficacy and safety of darbepoietin- α for management of anemia. These analyses also included additional patient characteristics, beyond those analyzed in the pilot study, for which data had been collected on the case report forms.

In the Phase 3b trials, patients previously treated with recombinant human erythropoietin (rHuEPO) twice a week (BIW) or 3 times a week (TIW) were switched to darbepoietin- α once a week (QW), while patients previously treated with rHuEPO QW were switched to darbepoietin- α once every 2 weeks (Q2W). The same dosing schedule and route of ESA administration (intravenous or subcutaneous)

were maintained throughout the study. Patients were treated with darbepoietin- α to maintain Hb levels between 10 and 13 g/dl. If a patient's Hb fell below the target range in two consecutive weekly assessments, the dose of study drug was increased to the next higher fixed dose. If a patient's Hb fell above the target range on two consecutive weekly assessments, the dose of study drug was decreased to the next lower fixed dose. Hb assessments were conducted weekly during the evaluation period of the study (Weeks 21 – 24).

Data on patient characteristics and intercurrent events hypothesized to affect Hb variability were obtained from the case report form, including hospitalization, infection, or inflammation. Patients having an adverse event (AE) of infection or inflammation were identified by a medical review of the AE preferred terms from the study. Events that started in the 4 weeks prior to the evaluation period were included.

Hospitalizations were included if they started in the 4 weeks prior to the evaluation period. Hospitalizations, due to cardiovascular AEs and vascular access AEs occurring at any time during the study, were also recorded. Information on blood transfusions was included if the transfusions occurred in the two weeks prior to the evaluation period.

Iron status values were evaluated for patients who had iron measurements at two or more visits. Iron status was assessed by measuring the transferrin saturation (TSAT), serum ferritin, or both, at Weeks 8, 16 and 24. The patient was classified as having adequate iron levels if the TSAT was $\geq 20\%$ or the serum ferritin was $\geq 100 \mu\text{g/l}$ (depending on which parameter was recorded) or if both were true when both were recorded.

Although the original dataset included patients undergoing both hemodialysis and peritoneal dialysis, the number of patients undergoing peritoneal dialysis was very small, therefore, the present analysis was performed on the data derived from patients undergoing HD only.

Statistical analysis

Two different methods for assessing intra-patient Hb variability were evaluated in the pilot study: the linear regression method and

the standard deviation (SD) method [Burnier et al. 2007]. In the linear regression model, the mean squared error was calculated around linear regression lines fitted to the Hb levels for the individual patient over the relevant time period. With the SD model, all of an individual patient's Hb values during the evaluation period (at least four values required) were used and the SD of these Hb values was calculated. This SD for each patient is used as a measure of Hb variability for the patient. Results of the pilot study indicated that although the use of the linear regression method might have some utility in describing short-term trends in Hb variability in individual patients, the SD methodology appeared to give a clearer overall picture of Hb variability in a single patient. Therefore the SD method was applied in the present analysis. It was also thought that the SD method would be more understandable to investigators and a more appropriate measure of the variability within a fixed time period.

Extensive checks on all data collected had been performed for the original Phase 3b studies, and no further data screening or acceptance procedures were performed for the post-hoc analyses. No imputation of missing data was performed, all summaries were based on observed data only. Data were included only for patients whose Hb values were at least 4 available and during the evaluation period. Comparisons between patient factors were performed using the Wilcoxon signed-rank test.

The analyses performed on this dataset are exploratory. It should be noted that although p values have been calculated for various comparisons and are useful for indicating potential data trends and differences between groups, the clinical relevance of the factors being compared is of primary importance. The large sample size used might result in statistically significant differences being found that might not be clinically relevant. A multivariate analysis was performed to assess the association between AE status and intra-patient Hb variability, adjusting for age, sex, diabetes status, number of dose changes, and iron status.

Results

The present analysis is based on the safety analysis population, which includes all sub-

Table 1. Patient Baseline Characteristics (N=5557).

Characteristic	
Age – years (mean (SD))	61.6 (15.0)
Sex (n, %)	
Male	3228 (58)
Female	2329 (42)
Time since initiation of dialysis – months	
Mean (SD)	55.2 (57.0)
Median	36.0
Primary cause of renal failure (n, %)	
Diabetes mellitus	828 (15)
Hypertension	760 (14)
Glomerulonephritis	1,364 (25)
Other non-urologic	932 (17)
Unknown	843 (15)
Polycystic kidney disease	434 (8%)
Other urologic	396 (7%)
Comorbid conditions (n, %)	
Diabetes	1,201 (22)
Hypertension	4,769 (86)
Peripheral vascular disease	1,118 (20)
Vascular access thrombosis	1,214 (22)
Myocardial infarction	496 (9%)
Cerebral vascular accident	416 (7%)
Transient ischemic attack	306 (6%)

Safety population for HD subgroup.

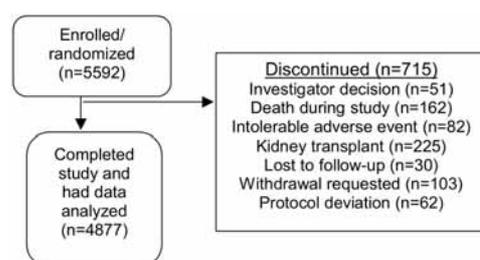


Figure 1. Patient disposition (pooled Phase 3b studies, patients undergoing HD, safety population).

jects who received at least 1 dose of study medication in any of the Phase 3b studies. Patient disposition and discontinuation information for the pooled Phase 3b trials is presented in Figure 1. Baseline characteristics of the patients are presented in Table 1.

Figure 2 shows the intra-patient Hb variability in relation to selected baseline characteristics (age, sex, sex by age group, and diabetes status). Variability for each patient is calculated as the within-patient SD of the

evaluation period Hb values. The data are summarized for the population using the standard set of descriptive statistics: mean, standard deviation, median, interquartile range, and the range.

Figure 3 illustrates the inpatient Hb variability in relation to the presence or absence of certain intercurrent events. The inpatient Hb variability was greater in the presence of any of these intercurrent conditions than in their absence: infection or inflammation ($p = 0.0032$), blood transfusion ($p < 0.0001$), hospitalization ($p < 0.0001$), or hospitalization for cardiovascular (CV) causes ($p = 0.0012$). The small number of patients with infections precluded making comparisons between acute and chronic infections in terms of inpatient Hb variability.

Inpatient Hb variability is shown in Figure 4 in relation to the number of darbepoietin- α dose changes made during the 4 weeks prior to the evaluation period and throughout the evaluation period. Patients with no dose changes during the evaluation period had lower mean variability than those in either the 1–2 change or > 2 changes group, $p < 0.0001$. However, no conclusions can be drawn from these data regarding cause-and-effect relationships between ESA dose changes and Hb variability.

Iron status differences had little detectable effect on intra-patient Hb variability among patients for whom at least two iron status measurements were available. In patients with all measurements adequate ($n = 3,277$), 1 measurement inadequate ($n = 527$), and > 1 measurements inadequate ($n = 257$), the within-patient Hb variability was (mean \pm SD) 0.417 ± 0.25 , 0.42 ± 0.28 , and 0.42 ± 0.25 , respectively. Regardless of whether values for serum ferritin, transferrin saturation, or both (depending on which measurements were performed in the study patients) were all adequate, 1 measurement was inadequate, or > 1 measurement was inadequate, there was no appreciable difference in within-patient Hb variability. It should be noted that too few iron measurements were available to draw meaningful conclusions.

Some other factors were considered, but it was impossible to produce meaningful comparisons because of the small numbers of patients in some of the comparison groups. These factors include death from CV causes, hospi-

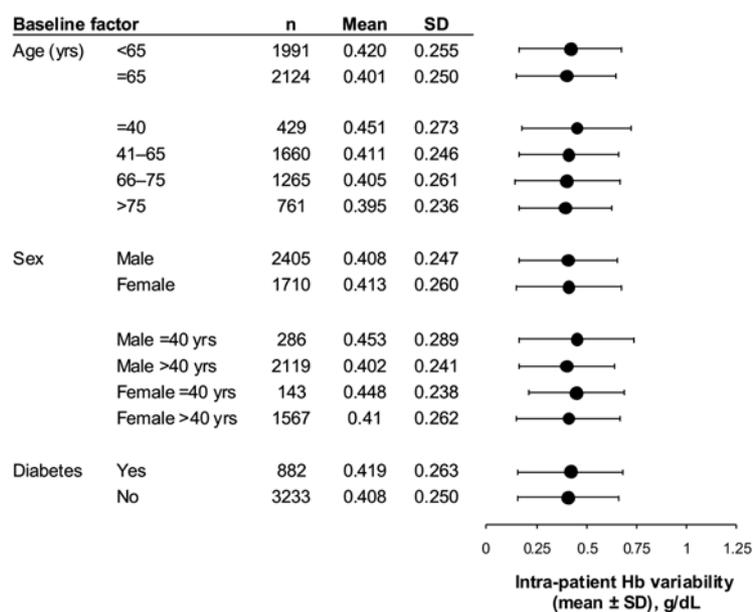
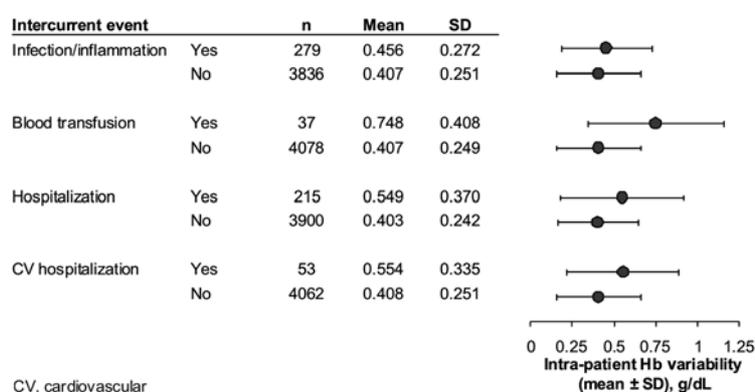


Figure 2. Hb variability (mean \pm SD) at evaluation vs patient baseline characteristics*. *Only patients who had 4 Hb values during the evaluation period, are included in the summaries.



CV, cardiovascular

Figure 3. Hb variability (mean \pm SD) at evaluation vs intercurrent events*. *Only patients who had 4 Hb values during the evaluation period are included in the summaries.

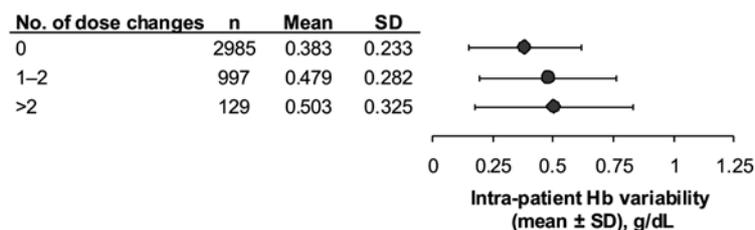


Figure 4. Hb variability (mean \pm SD) at evaluation vs anemia management practices (ESA dose frequency, number of changes in ESA dose)*. *Only patients who had 4 Hb values during the evaluation period are included in the summaries.

talizations due to CV AEs, and hospitalizations due to vascular access AEs during the 4 weeks prior to the evaluation period. These factors all showed indications that Hb variability was increased in patients experiencing the events, but there were too few in each of these groups to make meaningful comparisons. This observation is also true for acute vs. chronic infection AEs, in that there were very few chronic infection AEs. The results of the multivariate analysis to assess the association between AE status and intra-patient Hb variability, adjusting for age, sex, diabetes status, number of dose changes, and iron status found that AE status was significantly associated with Hb variability after this adjustment. Similar analyses were performed for hospitalization status, blood transfusion status, and cardiovascular- (CV) related hospitalization status, and the same results were observed.

Figure 5 shows the differences in the Hb means (with 95% CI and P values). For the total group (both sexes), greater variability was seen for patients 65 years of age or younger compared with older patients ($p = 0.0044$), and greater variability was seen for patients 40 years of age or younger compared with older patients ($p < 0.01$). The latter comparison is applicable for both males ($p = 0.0016$) and females ($p = 0.0194$) in the study population. Little difference in the variability was seen in relation to sex overall or to the presence or absence of diabetes.

Discussion

These findings from a re-analysis of clinical trial data support the hypothesis that patient-related factors such as intercurrent events and comorbid conditions influence the degree of Hb variability in patients undergoing HD. Hb concentrations are probably governed by a combination of anemia management practices and numerous patient-related factors that affect erythropoietic response along with the timing of these factors and their interactions.

More changes made in the ESA dose during the evaluation period were associated with greater Hb variability compared with fewer dose changes, it should be noted that this association could not be proved as being causative. This result is in accordance with

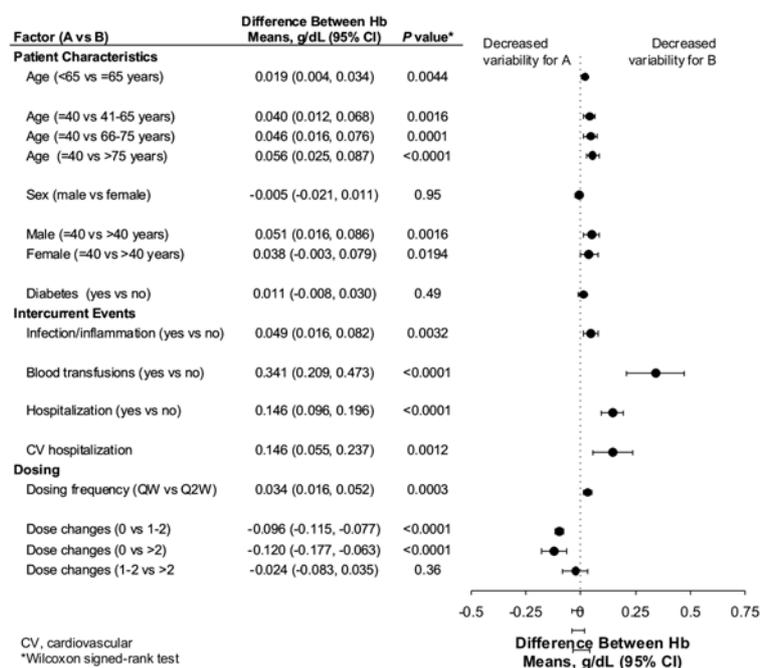


Figure 5. Differences between Hb levels (mean, 95% CI) by presence of specified patient characteristics*. *Only patients who had 4 Hb values during the evaluation period are included in the summaries.

other publications, for example, Singh and colleagues discuss the case of a patient with a vascular access thrombosis whose hemoglobin concentration increased by 60% over her baseline level (approximately 6 g/dl over a 6-week period) to 16.8 g/dl following a large increase in epoietin- α dose from 12,000 to 300,000 U/wk over a 12-week period [Singh et al. 2008].

The present exploratory, retrospective analyses give indications of differences in hemoglobin variability between individual patients with different characteristics, but the conclusions drawn should be regarded with caution. Firstly, when interpreting these results, it should be kept in mind that this was a clinical study with an evaluation period of only 4 weeks duration rather than a long-term observational study. It is difficult to draw conclusions regarding cause and effect, for example, whether a dose change was made in reaction to an intercurrent event, which initially influenced the Hb level, or whether the dose adjustment, itself, induced variability. Additional limitations in this study include the post-hoc nature of the analyses, with identification of intercurrent events from case report forms, and the small numbers of patients who

had some of the conditions. To get a better understanding of the cause-effect relationship, it would be necessary to conduct a prospective study.

An interesting but unexplained finding in this analysis was the fact that younger patients had greater Hb variability compared with older patients, but this finding should be interpreted with caution due to the small number of patients in the ≤ 40 -year-old group.

It is noted in the European Best Practices Guidelines that the most common causes of incomplete response to ESAs are iron deficiency, either absolute or functional, and inflammation [Locatelli et al. 2004a]. The patients included in the studies comprising this analysis were adequately treated with iron overall, but unfortunately our data on the relationship of iron levels to Hb variability are limited because only 3 measurements of actual iron levels were taken, and the results were categorized only as “adequate” or “inadequate.” Therefore, no conclusions can be drawn from the fact that these results did not show a relationship between iron changes and Hb variability.

Other conditions previously reported to be associated with ESA hyporesponsiveness, including hyperparathyroidism, malnutrition, inadequate dialysis, and drug effects, were not assessed in relation to Hb variability in the present study.

In addition to the complex interactions of intercurrent events and anemia management practices, the interactions of multiple intercurrent conditions and events further complicate the picture. A 3-month observational study of 78 patients undergoing HD for CRF included the recording of intercurrent events at each dialysis session (total of 2,808 sessions). A total of 1,516 peridialysis events such as fistula bleeding, puncture problems, hypotension, clotting in the lines or dialyzer, or delayed coagulation resulting in blood loss were observed, along with 279 interdialysis events such as cardiovascular, digestive, infectious, hemorrhagic, and vascular access complications. This amounted to a mean of 7.7 events per month with the potential to interfere with erythropoiesis. The population mean Hb and darbepoietin- α doses remained stable during the study period, but approximately 55% of patients required 1 or more dose changes [Rottembourg et al. 2007].

It would have been of interest to compare patient outcomes with Hb variability in this retrospective study, but the data are not representative because the study period was too short. However, this aspect has been looked at in several other studies [Brunelli et al. 2008, Foley et al. 1996, Gilbertson et al. 2008, Ishani et al. 2007, Yang et al. 2007]. It was reported in the studies of Yang and Brunelli that there was a strong association between Hb variability and increased mortality [Brunelli et al. 2008, Yang et al. 2007] Gilbertson could not find a strong association between these 2 factors, but confirmed that the longer the time spent at Hb levels below 11, the greater was the risk of mortality. This observation was confirmed by the results of two other studies [Foley et al. 1996, Ishani et al. 2007] On the other hand, several investigators have reported that mortality is increased when Hb levels exceed 13 g/dl [Drüeke et al. 2006, Fishbane and Besarab 2007, Phrommintikul et al. 2007, Singh et al. 2006] although this finding was not confirmed by the data of Gilbertson et al. [2008] and Brunelli et al. [2008].

The consequences of Hb variability are still an open question: Is it harmful per se or it is just a reflection of other pathological processes? The present analysis does not provide much assistance in answering this question for the reasons mentioned above. However, without pinpointing the exact limiting Hb level, our study results suggest that the aim of the treating physician should be to control Hb levels in his or her patients as carefully as possible.

In conclusion, increased Hb variability appears to be associated with patient-related factors such as age (although the finding of higher Hb variability in lower age groups was unexpected), infectious or inflammatory events, blood transfusion, hospitalization, and hospitalization for CV causes. Factors related to anemia management, such as numbers of dose changes, are also associated with greater Hb variability. In the future, it would be of interest to investigate the correlation of Hb variability and possible influential factors and in particular, to examine patient outcomes in relation to Hb variability by means of naturalistic, observational studies, or longer term, prospective, randomized studies.

Acknowledgment

We thank Dr. Claire Foster (Amgen Europe GmbH) for editorial assistance with the manuscript.

Funding: The study was funded by Amgen Europe GmbH, Zug, Switzerland. The study sponsor was involved in the design of the study, analysis of the data, and preparation of the manuscript. The authors collected data, performed the analyses, and contributed to the writing and review of the manuscript.

Conflict of interest statement

The authors received study grants from Amgen Europe GmbH to perform the study. There were no conflicts of interest of any of the authors.

References

- Barany P. Inflammation, serum C-reactive protein, and erythropoietin resistance. *Nephrol Dial Transplant*. 2001; 16: 224-227.
- Berns JS, Elzein H, Lynn RI, Fishbane S, Meisels IS, Deoreo PB. Hemoglobin variability in epoietin-treated hemodialysis patients. *Kidney Int*. 2003; 64: 1514-1521.
- Brunelli SM, Joffe MM, Israni RK, Yang W, Fishbane S, Berns JS, Feldman HI. History-adjusted marginal structural analysis of the association between hemoglobin variability and mortality among chronic hemodialysis patients. *Clin J Am Soc Nephrol*. 2008; published online March 12, 2008.
- Burnier M, Canaud B, De Francisco ALM, Braun J, Robbins S, Bridges I, Graebe A. Hemoglobin (Hb) variability: how should it be calculated and presented? A comparison of inter- versus intra-patient (Pt) variability (Abstract SU-PO820). Abstract and poster presented at the Annual Meeting of the American Society of Nephrology, October 31 to November 5. San Francisco: CA, USA; 2007.
- Canaud B, De Francisco ALM, Braun J, Burnier M, Bridges I, Robbins S, Graebe A. Intercurrent events and comorbidities related to intra-patient hemoglobin variability (Abstract SA-PO782). Abstract and poster presented at the Annual Meeting of the American Society of Nephrology, October 31 to November 5. San Francisco: CA, USA; 2007.
- Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med*. 2006; 355: 2071-2084.
- Ebben JP, Gilbertson DT, Foley RN, Collins AJ. Hemoglobin level variability: associations with comorbidity, intercurrent events, and hospitalizations. *Clin J Am Soc Nephrol*. 2006; 1: 1205-1210.
- Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal dis-

- ease with recombinant human erythropoietin. Results of a combined Phase I and II clinical trial. *N Engl J Med.* 1987; *316*: 73-78.
- Fishbane S, Besarab A.* Mechanism of increased mortality risk with erythropoietin treatment to higher hemoglobin targets. *Clin J Am Soc Nephrol.* 2007; *2*: 1274-1282.
- Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE.* The impact of anemia on cardiomyopathy, morbidity, and mortality in end-stage renal disease. *Am J Kidney Dis.* 1996; *28*: 53-61.
- Gilbertson DT, Ebben JP, Foley RN, Weinhandl ED, Bradbury BD, Collins AJ.* Hemoglobin level variability: associations with mortality. *Clin J Am Soc Nephrol.* 2008; *3*: 133-138.
- Ifudu O, Uribarri J, Rajwani I, Vlacich V, Reydel K, Delosreyes G, Friedman EA.* Low hematocrit may connote a malnutrition/inflammation syndrome in hemodialysis patients. *Dial Transplant.* 2002; *31*: 845-878.
- Ishani A, Solid CA, Weinhandl ED, Gilbertson DT, Foley RN, Collins AJ.* Association between number of months below K/DOQI hemoglobin target and risk of hospitalization and death. *Nephrol Dial Transplant.* 2007. (published online December 8, 2007).
- Lacson E Jr, Ofsthun N, Lazarus JM.* Effect of variability in anemia management on hemoglobin outcomes in ESRD. *Am J Kidney Dis.* 2003; *41*: 111-124.
- Locatelli F, Aljama P, Barany P, Canaud B, Carrera F, Eckardt KU et al.* Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure. *Nephrol Dial Transplant.* 2004a; *19* (Suppl. 2): ii1-ii47.
- Locatelli F, Pisoni RL, Combe C, Bommer J, Andreucci VE, Piera L et al.* Anaemia in hemodialysis patients of five European countries: association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant.* 2004b; *19*: 121-132.
- Mann J, Kessler M, Villa G, Martinez Castela A, Feldt Rasmussen B, Cruz J, Hörl WH, Mattin C, Praml C, Wilkie M.* Darbepoetin alfa once every 2 weeks for treatment of anemia in dialysis patients: a combined analysis of eight multicenter trials. *Clin Nephrol.* 2007; *67*: 140-148.
- National Kidney Foundation.* KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. *Am J Kidney Dis.* 2007; *50*: 471-530.
- Nurko S, Spirko R, Law A, Dennis VW.* Dosing intervals and hemoglobin control in patients with chronic kidney disease and anemia treated with epoetin- α or darbepoetin- α : a retrospective cohort study. *Clin Ther.* 2007; *29*: 2010-2021.
- Ofsthun N, Labrecque J, Lacson E, Keen M, Lazarus JM.* The effects of higher hemoglobin levels on mortality and hospitalization in hemodialysis patients. *Kidney Int.* 2003; *63*: 1908-1914.
- Phrommintikul A, Haas SJ, Elsik M, Krum H.* Mortality and target hemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a metaanalysis. *Lancet.* 2007; *369*: 381-388.
- Pisoni RL, Bragg-Gresham JL, Young EW, Akizawa T, Asano Y, Locatelli F et al.* Anemia management and outcomes from 12 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis.* 2004; *44*: 94-111.
- Rottembourg J, Kpade F, Tebibel F, Dansaert A, Chenuc G.* Stable hemoglobin (Hb) in hemodialysis (HD) patients: Forest for the trees – a 12-week pilot observational study. Abstract and poster presented at the Annual Meeting of the American Society of Nephrology, October 31 to November 5, San Francisco: CA, USA; 2007.
- Singh AK, Milford E, Fishbane S, Keithi-Reddy SR.* Managing anemia in dialysis patients: Hemoglobin cycling and overshoot. *Kidney Int.* 2008 (published online March 12, 2008).
- Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D.* Correction of anemia with epoetin- α in chronic kidney disease. *N Engl J Med.* 2006; *355*: 2085-2098.
- Yang W, Israni RK, Brunelli SM, Joffe MM, Fishbane S, Feldman HI.* Hemoglobin variability and mortality in ESRD. *J Am Soc Nephrol.* 2007; *18*: 3164-3170.