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Reduced Responsiveness to Epoetin at Re-exposure after Prolonged Epoetin-free Period in Anemic Hemodialysis Patients with End-stage Renal Disease

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Aim To determine if temporary discontinuation of epoetin therapy in anemic patients with end stage renal disease (ESRD) influences their responsiveness to epoetin.

Methods We performed a *post hoc* analysis of the data from two consecutive single-center randomized trials (T1 and T2) comparing the efficacy of two epoetin products (E1 and E2) in anemic patients with ESRD. The analysis included a subset of 44 patients who participated in both trials and were not receiving epoetin in the period (median, 12 months; range 5-15) between the trials due to epoetin shortage. Two co-primary outcomes were average weekly hemoglobin difference from the baseline and average weekly epoetin dose.

Results With adjustment for potential differences between E1 and E2, average weekly hemoglobin difference of 1.21 g/dL from the baseline was lower in T2 than that of 1.71 g/dL in T1: difference -0.49 (95% confidence interval [CI], −0.68 to −0.29; $P<0.001$). Average weekly epoetin dose of 107 IU/kg in T2 was higher than 96 IU/kg in T1 (ratio, 1.13; 95% CI, 1.04-1.24; $P=0.009$). With additional adjustment for within-subject changes in baseline covariates from T1 to T2 (baseline hemoglobin, body mass index, serum albumin, ferritin and transferrin saturation, intact parathormone, C-reactive protein, dialysis dose, and use of angiotensin converting enzyme inhibitors), hemoglobin response remained lower (adjusted difference, -0.44 g/dL; 95% CI, -0.73 to -0.16; $P=0.004$) and weekly epoetin dose remained higher in T2 than inT1 (adjusted ratio, 1.17; 95% CI, 1.03-1.34; $P=0.016$).

Conclusions In patients with ESRD, responsiveness to epoetin was lower in T2 after a period of epoetin therapy discontinuation than in T1 epoetin trial. Since this could not be explained by within-subject changes in factors known to affect response to epoetin, a prolonged withdrawal of epoetin in patients with ESRD might independently contribute to a reduced responsiveness to epoetin at a later re-exposure.

Clinical Trial Registration ClinicalTrials.gov Identifier for T1 trial: NCT00322413

Treatment of anemia with recombinant human erythropoietin (epoetin) is a standard care for patients suffering from chronic renal failure. In these patients, correction of anemia confers the benefits of reduced cardiovascular morbidity and mortality and improved quality of life (1). Typically, the response to epoetin varies considerably, both between and within subjects. This is manifested as a variability in time needed to attain anemia correction in previously anemic patients and as a variability in the epoetin dose requirements for attainment and maintenance of certain hemoglobin levels (2). There are several well-defined factors known to reduce responsiveness to epoetin: iron deficiency, especially absolute iron deficiency usually defined as transferrin saturation <20% combined with serum ferritin levels <100 ng/mL; on-going infection or inflammation, diagnosed in patients with C-reactive protein levels of >30 mg/mL (especially patients with >50 mg/mL need higher epoetin doses); neglected secondary hyperparathyroidism (although there is no consensus about the "critical" levels of the intact parathormone); inadequately low dialysis dose, as patients with Kt/V ≤1.2 or urea reduction ratio ≤65% can be expected to respond poorly; and overall poor nourishment or nutrition, as patients with serum albumin <30 g/L may be expected to respond poorly (2-8). Furthermore, higher epoetin dose requirements are associated with the intravenous, as opposed to subcutaneous, route of epoetin delivery, female sex, use of high-dose of inhibitors of angiotensin-converting enzyme (ACE), aluminum overload, carnitine deficiency, and a higher level of oxidative stress. In situations where patients suffer from other causes of anemia beside renal failure, eg, hemolysis, hemoglobinopathies, cancer, anemia-inducible therapies, and nutrient deficiencies (folate, vitamin B_{12}, and vitamin C), responsiveness to epoetin is also reduced (2-8).

The question of improvement of response to epoetin in patients with chronic renal failure has attracted much attention, mainly with the goal of improving the benefits for the patient and the cost-effectiveness of epoetin therapy. Although epoetin has been in clinical use for this indication for almost two decades, the continuous treatment with epoetin is still rather expensive (5-9). It is for the economical reasons that shortages of epoetin are not uncommon in financially less privileged countries like Croatia, and many patients with renal disease in need of epoetin receive it only intermittently. Such an inadequate renal anemia management negatively affects morbidity, mortality, and quality of life in these patients. Considering the contribution of a prolonged anemia to the overall "uremic toxicity" (10), and considering that both anemia and "uremic toxicity" may affect the response to epoetin (8), we assumed that the practice of epoetin withdrawal might have an additional drawback in that it might result in a reduced responsiveness to epoetin once the treatment has been re-established. Since a trial designed specifically to investigate the effects of "off-epoetin" periods on epoetin responsiveness would not be ethically justified, we performed a *post hoc* analysis of data on a group of patients with end-stage renal disease (ESRD) on hemodialysis maintenance therapy who participated in two consecutive clinical trials of epoetin efficacy and who were deprived of epoetin during the time between the trials due to financial reasons.

Patients and methods

The analysis included patients with ESRD who participated in both consecutive single-center prospective randomized 12-week clinical trials (T1 and T2) that compared efficacy of two recombinant human erythropoietin preparations (E1 and E2) (11). The T1 and T2 trials compared the efficacy of two epoetin products, E1 and E2, based on a between-subject comparison with adjustment for the effects of known confounders of responsiveness to epoetin ("baseline covariates") (11). The average time of 12 months

(range, 5-15) between the trials was an "off-epoetin" period during which the patients again became severely anemic.

Both trials were approved by the local Ethics Committee of Holy Ghost General Hospital, Zagreb, and the patients were enrolled after they had given a written informed consent. The identical protocol was used in both trials (11). The dialysis conditions and equipment (membranes, dialyzers, and tubing) were not changed and the dialysis water quality was kept in line with the standards and recommendations (12,13) throughout both trials and the period in-between.

Trial protocols

For both trials, the patients were eligible if maintained on regular hemodialysis (3 times a week, approximately 4 hours per session), were ≥18 years of age, and were severely anemic (hemoglobin <9.5 g/dL). Patients were excluded if they had poorly controlled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg), absolute iron deficiency defined as transferrin saturation (TSAT) <20% and serum ferritin <100 ng/mL, vitamin B12 or folic acid deficiency, hyperparathyroidism with suspect osteitis fibrosa, other causes of anemia (eg, continuous blood loss, hemolysis, or hemoglobinopathies), pregnancy or lactation, on-going chronic or acute inflammatory disease or infection within 30 days before enrollment, malignant disease, and serum albumin levels <30 g/L. Patients were not to receive blood transfusions, recombinant erythropoietin, cytotoxic agents, radiation therapy or immune-suppressants within 30 days before the enrollment.

Epoetin preparations compared in the two trials were epoetin omega (Epomax, Lek d.d., Slovenija and Elanex Pharma, WA, USA) and epoetin alfa (Eprex®, Janssen-Cilag, Switzerland). The preparation were supplied as 1 mL prefilled syringes containing 2000, 4000, or 8000 IU of epoetin. Epoetin was administered subcutaneously in the upper arm, twice weekly, after the first and the last dialysis session, according to the post-dialysis ("dry") body weight determined in patients wearing indoor clothing without shoes. The dose to be administered (IU) was calculated from the scheduled dose (IU/kg) and rounded to the nearest hundred. The starting dose of 2 × 50 IU/kg was not changed for the initial 4 weeks. Thereafter, it was gradually adjusted to achieve 0.25-0.30 g/dL of weekly hemoglobin (Hb) increase rate and to reach and maintain the target Hb level of 10-12 g/dL and at least 1.5 g/dL above the baseline value. Baseline was determined as an average of 2 values determined over a 2-week pretrial screening period. Folic acid and vitamin B12 were supplemented routinely to all patients (1.0-5.0 mg/d orally and 200-500 IU once a month intravenously, respectively). Iron saccharate was supplied intravenously to keep TSAT >20% and serum ferritin >100 ng/mL (1 × 50 mg/week to 3 × 100 mg/week, depending on the iron status). A continuous follow-up was ascertained through regular weekly visits.

Two co-primary efficacy endpoints were determined. One endpoint was average weekly difference in hemoglobin from the baseline value determined as time-adjusted area under the curve (AUC) of weekly differences (14). Baseline hemoglobin value was subtracted from each weekly hemoglobin value of the treatment period; AUC of differences was calculated and "adjusted" for the number of weeks spent in the trial to yield a weekly average (g/dL). The other endpoint was average weekly epoetin dose determined for each patient as the sum of weekly doses (IU/kg) per number of weeks in the trial (14).

Patients

A total of 56 patients who completed 12 weeks of treatment (regular epoetin and nutrients delivery and regular dialysis and follow-up) in T1 were included in T2. In T2, one of these patients died of cerebrovascular insult early in week 1. Of the remaining 55 patients, 11 experienced con-

founding events either in T1 or in T2: 5 patients received transfusions (a unit of packed red cells) either before the first epoetin dose in the trial or during week 1 due to low entry hemoglobin level; 6 patients received transfusions in weeks 2-5 due to blood loss caused by rectal bleeding (1 patient), metrorrhagia (1 patient), dialyzer clots with hemolysis (1 patient), upper gastrointestinal bleeding (2 patients) or accidental blood loss (1 patient). This left 44 patients who completed both trials with regular treatment and follow-up and did not experience co-morbidity, including infection or inflammation, or other treatments (eg, cytotoxic or immunosuppressive therapy) that could have interfered with responsiveness to epoetin. These patients were included in the analysis.

Statistical analysis

Average weekly Hb difference from the baseline and average weekly epoetin dose were taken as co-primary outcomes. In addition, summary statistics was reported for all variables determined in T1 and T2 in all 44 patients.

Analysis of the co-primary outcomes was performed in two steps. The first step was to estimate the unadjusted difference between T2 and T1. Since each patient received two different epoetin products, one in T1 (E1 or E2) and the other one in T2 (E2 or E1), repeated measures analysis of variance (ANOVA) was applied, with two within-subject factors, each with two levels: trial (T1 or T2) and epoetin product (E1 or E2). The second step was to estimate the adjusted difference between T2 and T1, ie, the within-subject differences in response to epoetin (T2-T1) while further accounting for potential effects of within-subject changes in the known confounding factors of response to epoetin ("baseline covariates"). The confounding factors included hemoglobin (severity of anemia); serum ferritin and TSAT (available iron); serum CRP (inflammation); dialysis dose as urea reduction ratio (URR); serum albumin (overall nutritional status and inflammation); body mass index (might affect availability of subcutaneous epoetin); serum levels of intact parathormone (iPTH) (level of hyperparathyroidism); and proportion of patients using ACE inhibitors (2-8). For this purpose, each of the co-primary outcomes was analyzed by multiple regression on repeated measures data (15). In this procedure, data on the outcome and independent variables were entered as two values per patient, one from T1 and the other from T2. The procedure partitioned the variability of the outcome variable to differences between and within patients. The difference within patients was further partitioned among the within-subject covariates (analysis of covariance). Regression of the outcome variable on the "trial" factor disclosed whether higher or lower values were associated with either of the trials (times of measurement) (16). Value of the regression coefficient was the mean difference between the two trials.

Data on average weekly epoetin dose were ln-transformed for both analyses to meet the normality assumption. We used NCSS 2005 (NCSS, Kaysville, UT, USA) statistical software for all data analyses. $P<0.05$ was considered statistically significant.

Results

Baseline patient characteristics

Anemia in our patients was less pronounced at the start of T2 (Table 1). The values of serum ferritin, TSAT, albumin, CRP, iPTH, and URR were satisfactory at baseline of both trials (Table 1). The same 3 patients had CRP >30 mg/L at the start of T1 and T2. For one additional patient who had serum CRP >30 mg/L at the start of T2, the actual value was 33 mg/L, as compared to 29 mg/L at the start of T1. The same 8 patients had TSAT <20% at the beginning of T1 and T2. None of the patients was treated with l-carnitine or vitamin C during T1 and T2 or in-

Table 1. Characteristics and baseline values of measured parameters in 44 patients included in two epoetin trials*

Parameter	Baseline values trial 1	Baseline values trial 2	Reference values†
Age (y)	54 ± 12	56 ± 12	NA
HD vintage (mo)	36 (12–88)	48 (25–101)	NA
BMI (kg/m²)	25.7 ± 3.9	24.8 ± 4.1	18.5-25
Albumin (g/L)	39.3 ± 4.8	38.1 ± 5.2	35-52
URR (%)	71 (66-74)	70 (66-73)	NA
Hb (g/dL)	7.6 ± 0.6	7.8 ± 0.8	11.9-15.7
MCV (fL)	92.5 ± 3.4	93.0 ± 4.2	83.0-97.2
CRP (mg/L)	14.0 (10.3-22.0)	15.5 (11.3-23.0)	0-10.0
CRP>30 mg/L (No. of patients)	3	4	NA
TSAT (%)	29.2 (21.9-40.8)	29.5 (21.9-46.1)	22.6-41.6
TSAT<20% (No. of patients)	8	8	NA
Ferritin (ng/mL)	285 (131-768)	577 (300-1003)	10-120
iPTH (pmol/L)	16.6 (7.4-43.2)	18.5 (6.3-38.3)	0.1-6.0
Systolic BP (mm Hg)	148 ± 21	154 ± 22	100-120
Diastolic BP (mm Hg)	84 ± 8	87 ± 9	60-80
Use of ACEi (No. of patients)	7	8	NA

*Abbreviations: HD – hemodialysis; BMI – body mass index; URR – urea reduction ratio; Hb – hemoglobin; MCV – mean corpuscular volume; CRP – C-reactive protein; TSAT – transferrin saturation; iPTH – intact parathormone; BP – blood pressure; ACEi – angiotensin converting enzyme inhibitors; NA – not applicable. Data are presented as either mean ± standard deviation or median with interquartile range.
†Holy Ghost General Hospital Laboratory.

Table 2. Development of serum ferritin and transferrin saturation (TSAT) over time in 44 patients included in two epoetin trials

Time variable	Value (median, interquartile range) trial 1	Value (median, interquartile range) trial 2
Baseline:		
ferritin (ng/mL)	285 (131-768)	577 (300-1033)
TSAT (%)	29.2 (21.9-40.8)	29.5 (21.9-46.1)
After 4 weeks:		
ferritin (ng/mL)	241 (100-541)	317 (197-873)
TSAT (%)	22.0 (17.7-27.7)	20.8 (17.3-26.1)
After 8 weeks:		
ferritin (ng/mL)	352 (210-727)	417 (240-890)
TSAT (%)	21.9 (19.1-31.5)	22.3 (19.5-27.6)
After 12 weeks:		
ferritin (ng/mL)	343 (188-659)	350 (192-702)
TSAT (%)	25.1 (21.4-31.5)	23.2 (17.9-28.2)

Table 3. Differences between trial 2 (T2) and trial 1 (T1) in average weekly hemoglobin difference vs baseline and average weekly epoetin dose, with adjustment for the differences between two epoetin products*

Predictors	Average weekly hemoglobin difference vs baseline (g/dL) F	*P*	Ln (average weekly epoetin dose) (IU/kg) * F	*P*
Subject	2.82	<0.001	1.43	0.122
Treatment	58.29	<0.001	19.28	<0.001
Trial	23.31	<0.001	7.52	0.009
T2-T1 difference (95% CI)	-0.49 (-0.68 to -0.29)		1.13 (1.04-1.24)	

*Difference between means for the ln-transformed data (average weekly epoetin dose) is expressed as an exponent, ie, geometric means ratio.

between period, while the same 22 patients were treated with calcitriol (with calcitriol-free periods).

Iron availability

In both trials, serum ferritin and TSAT dropped after the initial 4 weeks of treatment and then again increased toward the end of the trials (iron supplementation). They were continuously kept at satisfactory levels (Table 2).

Responsiveness to epoetins

In both trials, patients experienced a considerable Hb increase with typical inter-individual variability (Figure 1). However, the increase in Hb seemed more pronounced and the delivered epoetin doses were somewhat lower in T1 than in T2 (Figure 1). Accounting for potential differences between the two epoetin products, Hb response defined as average weekly Hb difference from the baseline was significantly lower in T2 than in T1(mean difference T2-T1= -0.49 g/dL, $P<0.001$), whereas the mean weekly epoetin dose was around 13% higher in T2 than in T1 ($P=0.009$) (Table 3).

In the second-step analysis, the differences between T2 and T1 were estimated, accounting not only for the differences between epoetin products, but with further adjustment for within-subject differences in the use of ACEi, baseline Hb, CRP, iPTH, URR, serum albumin levels, serum ferritin and TSAT, and BMI (Table 4). Hb response remained significantly lower in T2 in comparison with T1 (Table 4). The regression coefficient (B) for factor "trial" indicated a mean difference T2-T1 of -0.44 g/dL (95% CI, -0.73 to -0.16). Also, the average weekly epoetin dose remained significantly higher in T2 in comparison with T1 (Table 4). The coefficient (B=0.162) for factor "trial" obtained by regression of the ln-transformed data indicated a geometric means ratio T2/T1 of 1.17 (95% CI, 1.03-1.34), ie, around 17% higher average weekly epoetin dose in T2 in comparison with T1.

Table 4. Summary of the within-subject analysis of covariance and regression coefficients (B) for the two co-primary outcomes in trial 1 (T1) and trial 2 (T2)*

	Average weekly hemoglobin difference vs baseline			Average weekly epoetin dose†		
Independent variables	F-ratio	B	*P*	F-ratio	B	*P*
ACEi	0.177	-0.098	0.677	0.066	0.027	0.799
Albumin	4.409	0.047	0.044	3.621	-0.019	0.065
Baseline hemoglobin	2.375	-0.260	0.133	0.246	-0.038	0.623
BMI	1.210	-0.094	0.279	1.627	0.049	0.211
CRP	2.371	0.005	0.133	0.246	-0.0007	0.623
Ferritin	0.338	0.0001	0.565	2.646	-0.0001	0.113
TSAT	0.420	-0.004	0.521	0.879	0.002	0.355
iPTH	5.727	0.02	0.023	6.024	-0.009	0.020
URR	2.805	-0.056	0.103	1.196	0.017	0.282
Treatment (E1)	37.160	-0.692	<0.001	10.044	0.162	0.003
Trial (T2)	9.602	-0.442	0.004	6.404	0.162	0.016
Difference between subjects	2.699		0.002	1.333		0.197

*Abbreviations: ACEi – angiotensin converting enzyme inhibitors, BMI – body mass index, CRP – C-reactive protein, TSAT – transferrin saturation, iPTH – intact parathormone, URR – urea reduction ratio.
†Natural logarithm.

Discussion

Treatment of renal anemia with epoetin is long-lasting and rather expensive. Much effort has been put into optimization of the use of epoetin with the intention of improving both benefits for the patients and cost-effectiveness of the treatment (5-9), which is of special interest in financially less privileged countries where shortages of epoetin due to financial reasons are not uncommon. To assess if the withdrawal of epoetin treatment, which leads to a relapse of anemia in patients with ESRD, would affect responsiveness to epoetin at a later re-exposure independently of other contributing factors, we used the data on patients with ESRD who participated in two consecutive epoetin clinical trials (T1 and T2) (11) and were not treated with epoetin during the in-between period due to a shortage of epoetin. Therefore, we had a situation of epoetin withdrawal (time between the trials) after a period of treatment (T1), followed by a re-exposure (T2). The fact that the two trials were conducted according to identical protocols allowed for (*a*) regular follow-up on different parameters, including the known confounders of response to epoetin; (*b*) uniform dose-adjustment algorithm with identical targeted hemoglobin development and iron and nutrients supplementation strategies; and (*c*) exclusion of confounding events

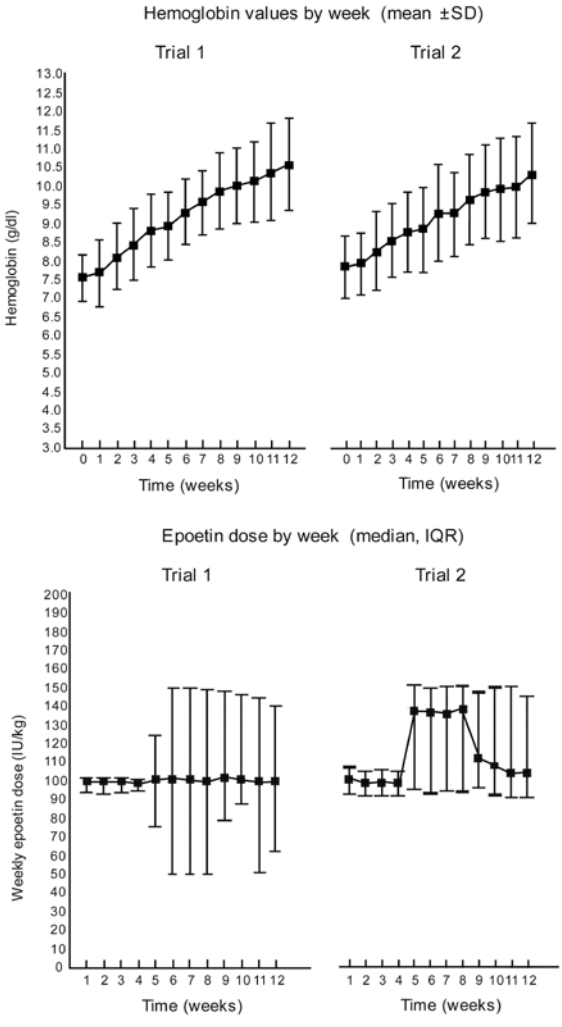

Figure 1. Development of hemoglobin (Hb) and weekly epoetin doses over time in 44 patients in trial 1 (T1) and trial 2 (T2).

both before and during the epoetin treatment periods, including concomitant treatments that might have been anemia-inducible (like cytotoxic or immunosuppressive agents) or "anemia-improving", like l-carnitine (17). Furthermore, both trials were conducted in the same center within a relatively short time-period. Approximately 2 years and 8 months had elapsed between the "first patient in" (T1) and "last patient out" (T2). During that time period, the dialysis water quality was maintained in line with the standards and recommendations minimizing the risk of possible interference of chemical or biological impurities, and the dialysis conditions and equipment did not change. Although the two trials were relatively short in duration, 12 weeks has been recognized as a period sufficient for estimation of a response to epoetin (18), and the outcomes used for this analysis have been confirmed as valid and informative for the purpose (14).

We found a reduced responsiveness to epoetin (higher doses of epoetin and lower Hb response) at re-exposure (T2) in comparison with the period before the withdrawal (T1) in our group of patients. This phenomenon could not be fully accounted for by the apparent difference between the two epoetin products that were used or by within-subject variations in known confounders of response to epoetin. In particular, the iron parameters indicated a satisfactory and comparable iron availability, mobilization, and utilization throughout the treatment periods. Cumulatively, these observations suggest that the "off-epoetin" period itself was a contributing factor. Our analysis did not distinguish between the effect of "epoetin withdrawal" and a 12 months longer "history of hemodialysis" (HD vintage) in our patients at the start of the re-exposure treatment period. However, there has been no evidence that increased HD vintage, as an isolated factor, might be a source of within-subject variability in response to epoetin, ie, that responsiveness to epoetin would decrease over time in patients on chronic epoetin treatment who receive an adequate overall care for renal failure simply because of the elapse of time (3,4,19). Therefore, our results indirectly suggest that discontinuation of epoetin treatment independently contributed to reduced responsiveness to epoetin at re-exposure. The current analysis provides no clues about the potential mechanisms involved. However, it seems plausible to assume that a combination of several factors that might have worsened during the "off-epoetin" period, none of which should have necessarily caused changes in commonly monitored parameters, could have affected responsiveness to epoetin in this group of patients. It is well known that anemia contributes to the overall "uremic toxicity" (10). Furthermore, both anemia and "uremic toxins" are known to contribute to oxidative stress through tissue hypoxia, alterations in catecholamine metabolism, or suppression of the endogenous "scavenging" potential (8), and that oxidative stress reduces responsiveness to epoetin by promoting lipid peroxidation in the cell membranes, leading to increased red cell fragility and reduced life-span, and through propagation of inflammation (8).

T1 and T2 analysis revealed a difference in responsiveness to epoetin as well as a difference in response to two epoetin products. It also suggested that better responsiveness to epoetin, ie, lower doses and greater Hb response, was associated with higher serum albumin concentration and higher serum iPTH values. The fact that other factors, such as iron availability, inflammation, or dialysis dose were not identified as "statistically significant" does not imply their irrelevance for responsiveness to epoetin. Rather it implies that within-subject variations in these parameters between the two treatment periods were modest and did not affect the analyzed outcomes to a relevant extent. Although all the patients had serum albumin levels >30 g/L at the beginning of either trial, better responsiveness to epoetin was associated with higher serum albumin. Low serum albumin, ie, the acute-phase response delineated

by low albumin and transferrin and high CRP and ferritin levels, was suggested as the most important predictor of poorer response to epoetin (20). We did not find that CRP, or rather the intra-individual changes in CRP and ferritin, was associated with changes in responsiveness to epoetin (likely due to only modest within-subject changes in these parameters). It is, therefore, uncertain whether the part of the within-subject variability in responsiveness to epoetin that was explained by changes in serum albumin was due to changes in the inflammatory or nutritional status, or both.

In contrast to published evidence, we found an association of higher serum iPTH values and greater Hb response combined with lower epoetin doses. Several studies suggested that a reduction of serum iPTH values is associated with an improvement in anemia (increase in Hb) or reduced epoetin requirements (21). There are several potential mechanisms by which severe hyperparathyroidism can worsen anemia in patients with ESRD – a direct toxic effect of PTH on erythroid progenitors and induction of marrow fibrosis (8). However, the role of hyperparathyroidism in renal anemia and hyporesponsiveness to epoetin is relatively minor as compared with the relevance of other factors, primarily iron deficiency and inflammation (8). Also, there seems to be no consensus on the "critical" or "cut-off" level of circulating iPTH that would be predictive of reduced response to epoetin (21), or direct correlation between iPTH levels and responsiveness to epoetin as illustrated by epoetin dose-demands (22). Furthermore, our analysis was largely influenced by the fact that there were 3 patients who had much higher iPTH values at the beginning of the epoetin treatment period characterized by better responsiveness than at the beginning of the epoetin-treatment period characterized by poorer responsiveness to epoetin. When these 3 patients were excluded from the analysis, the findings were the same as reported for the "full data set", except for the fact that there was no statistically significant association between the serum iPTH values and the measures of responsiveness to epoetin. Therefore, present observations of the relationship between responsiveness to epoetin and serum iPTH values should be taken with caution.

In conclusion, we performed a *post hoc* analysis of data on a cohort of patients with ESRD who participated in two consecutive clinical trials with epoetin that were separated by a prolonged epoetin-free period. Responsiveness to epoetin was reduced in the second trial as compared with the first one. This within-subject reduction in responsiveness to epoetin could not be explained by the within-subject changes in "classical" confounders of response to epoetin. The data suggest that the fact that the patients were deprived of epoetin (and anemic) between the trials independently contributed to reduction of responsiveness to epoetin at re-exposure. This implies that the practice of epoetin withdrawal commonly seen in financially less privileged countries due to shortages is not only directly medically harmful for the concerned patients, with respect to cardiovascular morbidity and mortality and quality of life, but is also counterproductive in the sense that re-installment of treatment requires utilization of larger amounts of epoetin for a certain effect and is, therefore, less cost-effective.

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