Original Article

Prevalence and predictors of epoetin hyporesponsiveness in chronic kidney disease patients

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Abstract

Background. The required erythropoiesis-stimulating agent (ESA) dose varies when correcting anaemia in chronic kidney disease (CKD) patients. This analysis was performed to identify the prevalence of and factors associated with ESA hyporesponsiveness.

Methods. This analysis was a *post hoc* evaluation of epoetin alfa dosage requirements in a subgroup of patients from the Effect of early Correction of Anemia on the Progression of CKD study. The patients in this subgroup were randomly assigned to the high haemoglobin target group (14–15 g/dl for men and 13–14 g/dl for women) and completed a 4-month haemoglobin stabilization phase with complete epoetin dosage data. The relationship of demographics, disease characteristics and laboratory measures with epoetin dosage were evaluated using Pearson's correlation, association measures and analysis of covariance (ANCOVA) models.

Results. Of the 93 patients evaluated in this subgroup analysis, 14 (15%) were hyporesponsive to epoetin (maximum dosage >100 IU/kg/week during stabilization). An ANCOVA analysis showed that 52% of the observed variability in epoetin dosage at completion of the stabilization phase could be accounted for by diabetes as the primary cause of kidney disease, angiotensin-converting enzyme (ACE) inhibitor/ angiotensin receptor blocker (ARB) use, proteinuria, transferrin saturation, age, pre-treatment haemoglobin, geographical region, serum iron and body mass index (BMI). Unidentified patient characteristics accounted for an additional 16% of the dosage variance.

Conclusions. Older age, higher BMI, anaemia, ACE inhibitor/ARB use and diabetes as the primary cause of kidney disease are associated with increased epoetin requirements when normalizing haemoglobin in anaemic CKD patients.

Keywords: anaemia; chronic kidney disease; dosage; epoetin; erythropoietin; hyporesponsive

Introduction

Anaemia is an independent risk factor for cardiac disease and mortality in chronic kidney disease (CKD) patients [1–5]. Haemoglobin concentration also correlates with quality of life (QOL) [6]. Both European and American treatment standards recommend correcting anaemia to a haemoglobin level >11 g/dl [European Best Practice Guidelines (EBPG) 2004, National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Guidelines 2001] [4,7]. Large clinical studies of dialysis patients have not shown cardiac disease regression or reduced mortality when haematocrit is normalized [8–10]. QOL measures, however, have shown benefits in physical, emotional and social domains with haemoglobin normalization in dialysis patients and CKD patients not on dialysis [9–13]. Several small studies have shown a delay in renal function decline when anaemia is treated with erythropoiesis-stimulating agent (ESA) compared with no ESA for anaemia, but studies to evaluate the effect of haemoglobin normalization on progression of CKD are lacking [14]. Data from the Correction of Haemoglobin and Outcomes in Renal Insufficiency study suggest an increased risk in targeting a haemoglobin level of 13.5 g/dl as compared with 11.3 g/dl in CKD patients (personal communication, Dr Ajay K. Singh, Brigham and Women's Hospital/Harvard Medical School, MA, USA).

Recently, the Effect of early Correction of Anemia on the Progression of CKD (ECAP) study evaluated decline in renal function in patients with CKD randomized to receive subcutaneous epoetin alfa (EPREX®) to achieve either a high (13–15 g/dl)

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or low (11–12 g/dl) target haemoglobin level [15]. The ESA dosage required to achieve anaemia correction varies among CKD patients. Several factors are associated with hyporesponsiveness to ESA, including iron deficiency, chronic blood loss, inflammation/infection, vitamin deficiencies, inadequate dialysis, hyperparathyroidism and malignancy [4]. In addition, some of the variability among dosage requirements to achieve anaemia correction is related to biological heterogeneity [16]. Few studies have been conducted in CKD patients not on dialysis to investigate resistance to ESAs. The current analysis is a post hoc observational analysis of a subgroup of patients from the ECAP study treated to a high haemoglobin target that was conducted to identify factors associated with hyporesponsiveness to epoetin alfa. This secondary exploratory analysis was conducted on the basis of the hypothesis that there are identifiable factors for hyporesponsiveness to ESAs.

Patients and methods

Patients and study design

The design of the ECAP study along with the inclusion and exclusion criteria has been described in detail elsewhere [15]. A total of 390 patients were recruited in Australia, Canada and Europe. Adults aged between 18 and 75 years with CKD and an estimated glomerular filtration rate (GFR) of 25–60 ml/min were included if they had at least 6 months of follow-up, anaemia without active blood loss or iron deficiency, an estimated rate of GFR decline <0.6 ml/min/month calculated using the Cockcroft–Gault formula [17] and a blood pressure ≤160/100 mmHg. Patients were randomly assigned to either the high (13–15 g/dl) or low (11–12 g/dl) haemoglobin target group and treated with epoetin alfa (EPREX®), if needed, to correct anaemia and reach the target haemoglobin level. The study design consisted of a 4-month stabilization phase to increase haemoglobin levels to the target range, correct iron and vitamin deficiencies and optimize factors known to affect progression of CKD, followed by a 36-month (planned) maintenance phase. Epoetin was administered subcutaneously once per week. The initial epoetin dose was 25–100 IU/kg. Dose adjustments were permitted in steps of 4 weeks as needed to achieve the target haemoglobin level, with a recommended increase in weekly dose of 25 IU/kg.

At study enrolment, height, weight, blood pressure and laboratory measures, including haematology, iron status, serum folate and vitamin levels, and complete serum and urine chemistry, were recorded. Epoetin dosage was recorded monthly. A variety of measurements were obtained at the completion of stabilization, including epoetin dosage, height, weight and laboratory measures, including serum albumin, pre-albumin, cholesterol, haematology, iron, transferrin saturation (TSAT), folate, vitamin B12, serum and urine chemistries, and iohexol clearance.

Data analysis

The distribution of the maximum weekly epoetin dosage requirement during the stabilization phase is graphically
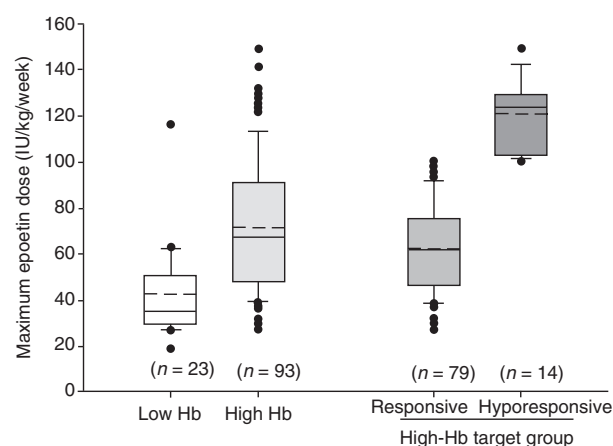
Fig. 1. Box-whisker plot showing the maximum epoetin dose required during the stabilization phase. Epoetin dose (IU/kg/week) is shown for patients in the low-haemoglobin (Hb) and high-Hb groups who had dosing information during the stabilization phase and required an epoetin dose at the start of the maintenance phase, and for the responsive and hyporesponsive patients in the high-Hb group. Of the 93 patients in the high-Hb group, 14 received a maximum epoetin dose >100 IU/kg/week during the stabilization phase. Of the 23 patients in the low-Hb group, only one received an epoetin dose >100 IU/kg/week during the stabilization phase. The upper and lower boundaries of the box represent the 75th and 25th percentiles, respectively. Whiskers above and below the box indicate the 90th and 10th percentiles, respectively. The solid line within the box marks the median and the dashed line marks the mean. Outlying data points represent extreme values.

summarized by treatment group in a box-whisker plot (Figure 1). The dosage plot revealed that most patients had a maximum epoetin dose below 100 IU/kg/week. This threshold, which corresponded to the 85th percentile in the high haemoglobin target group, was approximately twice the median epoetin dose required for the entire population. The level of 100 IU/kg/week was arbitrarily selected as the cut-off dose to classify patients into two strata corresponding to a binary marker of epoetin hyporesponsiveness.

Patients always treated with ≤100 IU/kg/week were defined as 'responsive' patients and those requiring >100 IU/kg/week at any time point during stabilization were classified as 'hyporesponsive' patients. This hyporesponsiveness factor was considered potentially important to predict the epoetin dosage requirement at the start of maintenance.

Within the low-haemoglobin target group, 23 patients had dosing information during the stabilization phase and required epoetin treatment at the start of the maintenance phase. Only one patient in the low-haemoglobin target group received an epoetin dose >100 IU/kg/week during the stabilization phase (Figure 1); therefore, only the patients in the high-haemoglobin target group were considered for this subgroup analysis.

Pearson's linear correlation and odds ratio analyses were initially performed to identify the key prognostic factors that were significantly associated with the epoetin dosage at the start of the maintenance phase, as well as with the epoetin hyporesponsiveness factor. Several demographic and disease characteristics at baseline and at the completion of the stabilization phase were evaluated, including age, geographical region, primary cause of kidney disease,

haemoglobin level at study entry, body mass index (BMI), systolic and diastolic blood pressure, use of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), iron, TSAT, C-reactive protein (CRP), cholesterol, serum albumin, proteinuria, GFR as measured using iohexol clearance and serum creatinine.

In addition, the most relevant demographic, laboratory and disease-related factors that were independently associated with epoetin dosage were compared between the responsive and hyporesponsive patients in the two epoetin responsiveness strata.

Analysis of covariance (ANCOVA) models were used to further examine the association between key patient characteristics selected by the correlation analysis and the epoetin dosage. In the ANCOVA models, the epoetin dose at the beginning of the maintenance phase was used as the dependent variable. In this *post hoc* analysis, the goal was to determine which factors contributed most to the explanation of the variance of the dependent variable. The main and interaction effects of categorical variables on the epoetin dosage required at the beginning of the maintenance phase were examined after controlling for the effects of selected other continuous variables which covary with the dependent variable. Demographics, blood pressure readings and laboratory measures of anaemia, renal function and cholesterol were evaluated as possible predictive factors for the epoetin dose. The factor of epoetin hyporesponsiveness during stabilization was then introduced into the model. This factor was considered as the proxy of unknown patient characteristics not accounted for by the other demographics, and laboratory and disease-related measures.

The R^2-value was compared between ANCOVA models because it provides a measure of goodness-of-fit on the basis of the partition of the total sum of squares into the portion of variation of the epoetin dosage accounted for by the factors and covariates included in the model *vs* the portion of variance that was not explained and therefore attributed to the error component.

Results

Patients

A total of 108 patients treated to the high-haemoglobin target completed the stabilization phase, with complete epoetin dosage data available at the start of the maintenance phase for 93 (86%). Using the cut-off criteria of 100 IU/kg/week during the stabilization phase for hyporesponsiveness to epoetin, 79 (85%) patients were epoetin responsive and 14 (15%) were epoetin hyporesponsive. Demographics and key disease characteristics varied between responsive and hyporesponsive patients (Table 1). A higher percentage of hyporesponsive patients were male (71 *vs* 58%) and reported diabetes as the primary cause of kidney disease (50 *vs* 21%). Only responsive patients (28%) reported glomerulonephritis as the primary cause of kidney disease.

The use of ACE inhibitors and/or ARBs during the study was associated with epoetin hyporesponsiveness. Epoetin hyporesponsiveness was more frequent in patients who used ACE inhibitors and/or ARBs during the study (9/37; 24%) compared with patients who did not use these agents (5/56; 9%).

Geographical region

To determine what factors might vary between the geographical regions, age, BMI and diabetes as the primary cause of kidney disease were compared among the three regions. Age and BMI, but not diabetes as the primary cause of kidney disease, were significantly different between regions. The mean age of patients from Europe (52 ± 15 years) was significantly lower than that of patients from Australia (61 ± 12 years; $P = 0.02$) and Canada (64 ± 8 years; $P < 0.001$). The mean BMI was also lower in patients from Europe (26.5 ± 4.6 kg/m^2) than in patients from Australia (29.4 ± 6.5 kg/m^2; $P = 0.04$) and Canada (29.1 ± 4.8 kg/m^2; $P = 0.04$). Of the 93 patients evaluated, the proportion of epoetin hyporesponsive patients was higher in Canada (6/24; 25%) than in Europe (7/51; 14%) or Australia (1/18; 6%). This result can be partly explained by the significantly higher mean BMI for patients enrolled in Canada and Australia than for those in Europe, and the significant positive correlation between BMI and epoetin dosage requirements.

Correlation between patient characteristics and epoetin dosage

Age, BMI and measures of anaemia were significantly correlated with epoetin dosage at the start of the maintenance phase (Figure 2). Weekly epoetin requirements were higher in patients with older age and a greater BMI. As expected, haemoglobin, iron and TSAT were inversely related to epoetin dosage. In addition, older age was associated with a higher BMI ($r = +0.25$; $P = 0.01$), and higher serum iron was associated with higher TSAT ($r = +0.88$; $P < 0.001$). Measures of renal dysfunction, cholesterol and blood pressure readings did not significantly correlate with epoetin dosage.

ANCOVA models were generated to identify those factors that explained most of the variance in epoetin dosage required at the start of the maintenance phase. In addition to the continuous variables, diabetes as the primary cause of kidney disease, ACE inhibitor/ARB use prior to the study, interaction between ACE inhibitor/ARB use and history of diabetes, and geographical region were also included in the ANCOVA evaluation. This analysis revealed that 52% of the observed variability in epoetin dosage could be accounted for by diabetes as the primary cause of kidney disease, the interaction between ACE inhibitor/ARB use and diabetes, TSAT, proteinuria level, age, pre-treatment haemoglobin level, ACE inhibitor/ARB use, geographical region, serum iron and BMI (Table 2). To determine whether additional unknown variables may also contribute to epoetin dosage requirements, the same ANCOVA model

Table 1. Patient demographics and disease characteristics

	ECAP cohort			Selected cohort				
	All patients (n = 390)	Low Hb (n = 195)	High Hb (n = 195)	All patients (n = 93)	Hyporesponsive (n = 14)	Responsive (n = 79)	P-value	OR (95% CI)
Mean ± SD age, years	n = 388 58.2 ± 13.58	n = 193 57.6 (13.28)	n = 195 58.5 (13.57)	56.8 ± 14.05	60.4 ± 9.53	56.2 ± 14.7	0.3	N/A
Gender, n (%)								
Male	231 (59)	113 (58)	118 (61)	56 (60)	10 (71)	46 (58)	0.4	1.79 (0.52–6.22)
Female	159 (41)	82 (42)	77 (39)	37 (40)	4 (29)	33 (42)		
Mean ± SD haemoglobin at study entry, g/dl	n = 385 11.6 ± 0.97	n = 193 11.6 ± 0.92	n = 192 11.5 ± 1.02	11.8 ± 0.84	11.3 ± 0.65	11.9 ± 0.85	0.02	N/A
Mean ± SD haemoglobin,[a] g/dl	n = 241 12.9 ± 1.40	n = 133 11.9 ± 0.79	n = 108 14.2 ± 0.84	14.2 ± 0.83	13.9 ± 0.48	14.2 ± 0.87	0.16	N/A
Mean ± SD epoetin dosage,[a] IU/kg/week	n = 121 56.9 ± 35.74	n = 28 32.5 ± 18.81	n = 93 64.2 ± 36.44	64.2 ± 36.44	120.1 ± 37.69	54.3 ± 25.86	<0.001	N/A
Region, n (%)								
Australia	54 (14)	26 (13)	28 (14)	18 (19)	1 (7)	17 (22)		–
Canada	68 (17)	33 (17)	35 (18)	24 (26)	6 (43)	18 (23)		–
Europe	252 (65)	128 (66)	124 (64)	51 (55)	7 (50)	44 (56)	0.7	0.80[b] (0.26–2.48)
Israel	16 (4)	8 (4)	8 (4)	–	–	–		
Primary cause of kidney disease, n (%)							0.03	3.65[c] (1.12–11.83)
Diabetes	100 (26)	49 (25)	51 (26)	24 (26)	7 (50)	17 (22)		–
Glomerulonephritis	82 (21)	39 (20)	43 (22)	22 (24)	0	22 (28)		–
Hypertension	67 (17)	31 (16)	36 (19)	13 (14)	3 (21)	10 (13)		
Other	141 (36)	76 (39)	65 (33)	34 (37)	4 (29)	30 (38)		
Use of ACEi and/or ARB during the study; yes, n (%)	110 (28)	50 (26)	60 (31)	37 (40)	9 (64)	28 (35)	0.05	3.28 (1.001–10.739)
Mean ± SD BMI,[a] kg/m²	n = 235 27.9 ± 5.42	n = 130 27.9 ± 5.54	n = 105 28.0 ± 5.29	27.7 ± 5.20	30.3 ± 5.48	27.3 ± 5.04	0.05	N/A
Mean ± SD TSAT,[a] %	n = 202 27.0 ± 9.30	n = 111 27.5 ± 8.82	n = 91 26.4 ± 9.87	n = 77 26.9 ± 10.11	n = 11 20.3 ± 6.53	n = 66 28.0 ± 10.23	0.02	N/A
Mean ± SD iron,[a] g/l	n = 228 14.2 ± 5.22	n = 123 14.3 ± 5.09	n = 105 14.0 ± 5.40	n = 91 14.2 ± 5.40	n = 14 12.7 ± 5.62	n = 77 14.4 ± 5.36	0.3	N/A
Mean ± SD proteinuria,[a] g/day	n = 213 1.2 ± 1.70	n = 119 1.2 ± 1.71	n = 94 1.3 ± 1.70	n = 81 1.4 ± 1.78	n = 13 1.1 ± 1.45	n = 68 1.5 ± 1.84	0.5	N/A

t-Test for continuous variables.
Chi-square Wald test for categorical variables.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; N/A, not available; OR, odds ratio; SD, standard deviation; TSAT, transferrin saturation.
[a]At start of the maintenance phase.
[b]OR for combined region: Europe vs non-Europe.
[c]OR for combined cause of kidney disease: diabetes vs non-diabetes.
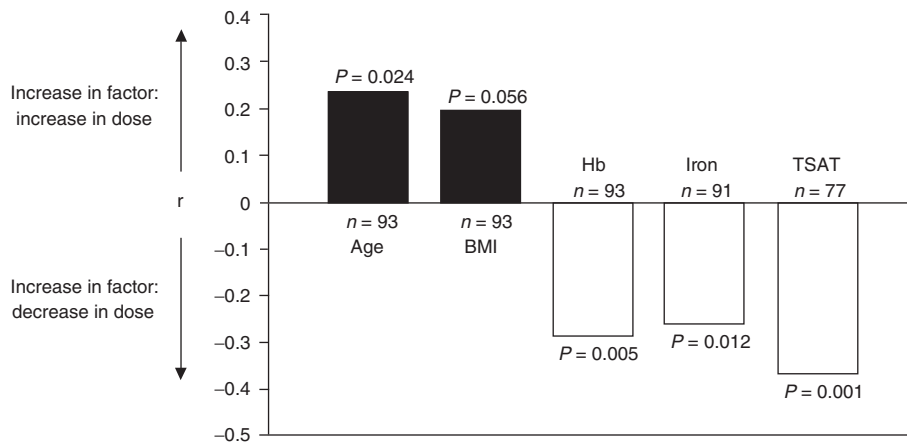
Fig. 2. Patient factors associated with epoetin dosage. Factors identified as significantly associated with epoetin dosage at the beginning of the maintenance phase by Pearson's correlation coefficient are shown. Hb level is based on values recorded at the beginning of the stabilization phase. BMI, TSAT and iron are based on values recorded at the beginning the maintenance phase.

Table 2. ANCOVA analysis with weekly epoetin dose at beginning of the maintenance phase as the dependent variable

Source of variation	df	Type III SS	Mean square	F-value	P-value
Model	11	50 591.6	4599.2	5.24	<0.0001
Error	53	46 529.1	877.9		$R^2 = 0.52$
Total	64	97 120.7			
Diabetes	1	11 079.5	11 079.5	12.62	<0.001
Diabetes•ACEi/ARB	1	8708.7	8708.7	9.92	0.003
TSAT, %	1	8521.0	8521.0	9.71	0.003
ACEi/ARB	1	4735.0	4735.0	5.39	0.024
Pre-treatment haemoglobin, g/dl	1	3713.3	3713.3	4.23	0.045
Iron at maintenance, g/l	1	3653.1	3653.1	4.16	0.046
Age, years	1	2107.8	2107.8	2.40	0.1
Proteinuria, g/day	1	1885.2	1885.2	2.15	0.1
Region[a]	2	3593.7	1796.9	2.05	0.1
BMI at maintenance, kg/m^2	1	306.4	306.4	0.35	0.6

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; df, degrees of freedom; SS, sums of squares; TSAT, transferrin saturation.
[a]Regions include Australia, Canada and Europe.

Table 3. ANCOVA analysis with weekly epoetin dose at beginning of the maintenance phase as the dependent variable, including a marker for epoetin hyporesponsiveness

Source of variation	df	Type III SS	Mean square	F-value	P-value
Model	12	66 470.7	5539.2	9.40	<0.0001
Error	52	30 650.0	589.4		$R^2 = 0.68$
Total	64	97 120.7			
Epoetin hyporesponsive	1	15 879.1	15 879.1	26.9	<0.001
Diabetes	1	5795.4	5795.4	9.83	0.003
Diabetes•ACEi/ARB	1	4063.6	4063.6	6.89	0.011
Age, years	1	2033.0	2033.0	3.45	0.069
TSAT, %	1	1959.9	1959.9	3.33	0.074
Region[a]	2	3029.7	1514.8	2.57	0.086
ACEi/ARB	1	1236.1	1236.1	2.10	0.2
Proteinuria, g/day	1	520.0	520.0	0.88	0.4
Pre-treatment haemoglobin, g/dl	1	461.6	461.6	0.78	0.4
Iron at maintenance, g/l	1	434.9	434.9	0.74	0.4
BMI at maintenance, kg/m^2	1	26.6	26.6	0.05	0.8

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; df, degrees of freedom; SS, sums of squares; TSAT, transferrin saturation.
[a]Regions include Australia, Canada and Europe.

was analysed, augmented by a binary marker for epoetin hyporesponsiveness during the stabilization phase of the study (Table 3). In the latter model, diabetes as the primary cause of kidney disease, interaction between ACE inhibitor/ARB use and diabetes, age, TSAT, region and a marker for epoetin hyporesponsiveness were all significantly (at 10% level) associated with epoetin dosage, with the overall model explaining 68% of the dosage variability. This analysis suggests that unidentified patient characteristics associated with a maximum epoetin dose >100 IU/kg/week during stabilization accounted for 24% (16%/68%) of the explained variance in the maintenance epoetin dose after adjusting for baseline demographic and disease-related factors, as well as continuous covariates.

Discussion

A maximum epoetin dose >100 IU/kg/week during the stabilization phase (defined as epoetin hyporesponsiveness) was required by a clinically significant minority of patients (15%) to achieve anaemia correction. As expected, markers for anaemia predicted higher doses of epoetin. Age, diabetes, ACE inhibitor/ARB use, BMI, pre-treatment haemoglobin level, serum iron and TSAT were identified as the most important factors contributing to variation in epoetin dosage requirements during the subsequent maintenance phase. Geographical region may be another

important factor in determining epoetin requirements and could be attributed to patients from Canada and Australia being older and having higher BMIs than patients from Europe. The statistically significant interaction between ACE inhibitor/ARB use and diabetes in the model suggests that the ESA dosage requirement is different across the subgroups of patients identified by the combination of ACE inhibitor/ARB use and history of diabetes. Although proteinuria did not correlate with epoetin dose, addition of proteinuria to the ANCOVA model increased the portion of variance of epoetin dose explained by the model. Additional unknown patient characteristics appeared to be significant predictors of the epoetin dosage requirement, as indicated by the relevant contribution (24%) of an epoetin hyporesponsiveness marker to the portion of explained variance in the epoetin dosage.

Similarly, a study of peritoneal dialysis patients identified a variety of correlations with ESA hyporesponsiveness, including age, serum creatinine, CRP, TSAT and serum albumin [18]. In a large survey of haemodialysis patients, levels of nutritional markers, pre-albumin ($P = 0.004$) and cholesterol ($P < 0.001$) were negatively correlated with ESA hyporesponsiveness [19]. Although CRP and nutritional variables were not correlated with epoetin hyporesponsiveness in the current study, higher epoetin doses were required in patients as age and BMI increased. Adipose tissue is a major source of inflammatory cytokines, and inflammatory markers, including CRP, are elevated with increasing BMI [20]. The correlation between BMI and CRP suggests that high ESA dosage requirements with increased weight may be related to increased inflammation. The relationship between inflammation/infection and hyporesponsiveness was supported by a study of 64 chronic haemodialysis patients in whom CRP correlated with ESA hyporesponsiveness ($P < 0.01$) [21].

The association of diabetes with high epoetin dosage requirements is consistent with other studies showing that erythropoietin levels are excessively low in anaemic diabetic patients compared with those without diabetes [22,23]. In addition, diabetic patients with renal failure are particularly prone to anaemia [24]. Interestingly, erythropoietin levels are low in anaemic diabetic patients with or without impaired renal function [22].

Several variables were evaluated in this analysis and others were accounted for in the ECAP study; however, not all factors reported to be associated with ESA hyporesponsiveness by the EBPG or NKF-K/DOQI were evaluated in this study [4,7]. Folate and vitamin B12 deficiency were measured in all patients and no deficiencies were identified. Patients with malignancy and patients with haemoglobinopathy were excluded from the study. Although elevated parathyroid hormone or possible aluminium intoxication were not accounted for in this study, they are unlikely to have been present in these patients. Other factors known to increase ESA dosage requirements, such as increased protein carbamylation in end-stage renal disease [25], were not evaluated in the current study.

This subgroup analysis is limited by those controversial factors inherent to *post hoc* exploratory analyses of clinical trials and by the reduced sample size of the chosen cohort. In the ECAP study, only a small number of patients treated to the high-haemoglobin target were epoetin hyporesponsive. This study defined epoetin hyporesponsiveness as an epoetin dose >100 IU/kg/ week during the stabilization phase, which was approximately twice the mean dose for the responsive patients. This is lower than the >300 IU/kg/week defined in the EBPG guidelines [4]; however, these guidelines are for haemodialysis patients and this study evaluated patients who were not on dialysis. In addition, the incidence of a higher dose of ESA and the explanatory variables associated with it were analysed only for the subgroup of patients who were treated to achieve a greater degree of anaemia correction.

This subgroup analysis is clinically relevant, highlighting the need for further study of ESA hyporesponsiveness in patients not on dialysis. This analysis also emphasizes that is it clinically important to correct iron deficiency in CKD patients requiring ESA, the most common cause of incomplete response to ESA [4], and to increase ESA dosage to higher levels to achieve anaemia correction in a significant minority of patients. In summary, correction of anaemia to a normalized haemoglobin target required doses >100 IU/kg/week in 15% of CKD patients. Higher epoetin requirements were associated with older age, higher BMI, anaemia, ACE inhibitor/ ARB use and diabetes as the primary cause of renal disease. Other unknown variables contributed to 24% of the variability in epoetin dosing. Additional studies are needed to identify which other variables are significant explanatory factors.

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