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Study of the non-modifiable causes of poor response to erythropoietin treatment in emodialysis patients

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SUMMARY

Patients receiving recombinant human erythropoietin (rHuEPO) therapy show wide variability in their responsiveness to the drug. Variables that affect rHuEPO dose requirements can be broadly divided into modificable and immutable characteristics. Most of the scientific research on rHuEPO hyporesponsiveness has focused on modificable variables (iron status, dialysis adequacy), while immutable variables such as gender, etiology of chronic renal failure (CRF) and age have been insufficiently explored. A cross sectional study was performed in order to evaluate if immutable patient characteristics determine rHuEPO dose requirements among 215 patients (52% males; mean age 66 ± 14 years) on hemodialysis (HD) for more than twelve months. Data were collected at 10 hemodialysis units in Aragon. Patients were divided into three groups according to their gender, their cause of CRF (diabetic nephropathy, vascular nephropathy, tubulointerstitial nephropathy and primary glomerulonephritis) and their age (younger than 60 years, from 60 to 75 years, older than 75 years). Despite a similar dose of rHuEPO, women had lower mean hemoglobin (11.1 ± 1.5 versus *11.6 ± 1.7 g/dl; p = 0.0258) than men. The greater hemoglobin in men than women may be attributed to greater serum albumin in men (3.5 ± 0.3* versus *3.7 ± 0.3 mg/dl; p = 0.0001). Requirements of rHuEPO were higher in the patients with etiology of primary glomerulonephritis compared with those with the other etiologies, even those with diabetic nephropathy (p = 0.0374). The rHuEPO doses required to obtain similar hemoglobin levels were higher in patients younger than 60 years (p = 0.0249). We conclude that women, patients with primary glomerulonephritis as cause of CRF, and patients younger than 60 years showed the highest requirements of rHuEPO doses.*

Key words: ***Erythropietin. Hemodialysis. Hemoglobin. Glomerulonephritis. Age. Albumin.***

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ESTUDIO DE CAUSAS NO MODIFICABLES DE POBRE RESPUESTA AL TRATAMIENTO CON ERITROPOYETINA EN PACIENTES EN HEMODIÁLISIS

RESUMEN

Los pacientes en tratamiento con eritropoyetina humana recombinante (rHuEPO) presentan una amplia variabilidad en su respuesta al medicamento. Las variables que afectan a los requerimientos de dosis de rHuEPO se pueden dividir de una forma amplia en modificables y no modificables. La mayoría de los estudios realizados sobre la capacidad de respuesta a la rHuEPO se han centrado en las variables modificables (déficit de hierro, dosis de diálisis), mientras que las variables no modificables como el sexo, la etiología de la insuficiencia renal crónica y la edad han sido insuficientemente estudiadas. Se realiza un estudio transversal entre 215 pacientes con una permanencia en hemodiálisis superior a doce meses (hombres 52%, edad media 66 ± 14 años) con la finalidad de valorar si características no modificables de los pacientes influyen sobre los requerimientos de rHuEPO. Los datos se obtuvieron de las diez unidades de hemodiálisis de Aragón. Los pacientes se dividieron en grupos para su comparación de acuerdo con el sexo, las causas de insuficiencia renal crónica (IRC) (nefropatía diabética, nefropatía vascular, nefropatía intersticial y glomerulonefritis primaria) y la edad (< 60 años, entre 60-75 años y > 75 años). Las mujeres presentaban una hemoglobina significativamente más baja que los hombres (11,1 ± 1,5 versus *11,6 ± 1,7 g/dl; p = 0,0258) a pesar de recibir dosis similares de rHuEPO. La mayor hemoglobina en los hombres puede estar en relación con unos niveles séricos de albúmina más elevados que en las mujeres (3,7 ± 0,3* versus *3,5 ± 0,3 mg/dl; p = 0,0001). Los requerimientos de rHuEPO fueron significativamente más elevados en los pacientes con glomerulonefritis primaria como causa de su IRC que en los otros grupos etiológicos, incluso que aquellos con nefropatía diabética (p = 0,0374). Las dosis requeridas de rHuEPO para conseguir unos niveles similares de hemoglobina fueron más elevadas en los pacientes menores de 60 años (p = 0,0249). En conclusión, las mujeres, los pacientes con glomerulonefritis primaria como causa de su IRC, y los menores de 60 años son los grupos de enfermos con mayores requerimientos de rHuEPO.*

Palabras clave: ***Eritropoyetina. Hemodiálisis. Hemoglobina. Glomerulonefritis. Edad. Albúmina.***

INTRODUCTION

The recent publication of the European Guideline review for anemia management in patients with chronic renal failure (CRF) recommends to assure a minimum hemoglobin concentration (Hb) higher than 11.0 g/dL, independently of age, gender or race.[1] The target hemoglobin level to be reached, always higher than 11 g/dL, should be individualized in each patient, considering the patient's age, gender, race, activity, and associated co-morbidity factors.[1] To achieve this goal, it is important to know the factors that determine the response sensibility to erythropoiesis-stimulating agents.[2] Most of the studies carried out on factors that lead to a poor response to treatment with stimulating-stimulating agents have focused on those that may be modified (appropriate treatment with iron, dialysis dose, *secondary hyperparathyroidism)*,[3,4] whereas factors that cannot be modified, such as gender, CRF etiology, and age have been insufficiently studied.[5-6]

The aim of the present study was to analyze whether the non-modifiable characteristics of hemodialysis (HD) patients, such as gender, etiology of CRF, and age, may condition a lower response to recombinant human erythropoietin (rHuEPO).

MATERIAL AND METHODS

This is a cross-sectional study carried out on prevalent patients, during the year 2001, in the Hemodialysis Units of the Aragón province. Data gathering system was based on a questionnaire sent to all

10 HD Units of Aragón. The questionnaire was sent in November of 2000 and data gathering ended up in May of 2001.

The questionnaire asked about patients' characteristics: birth date, gender, cause of renal disease, date of HD initiation, percentage of urea reduction (PUR), duration (in minutes) of each HD session, membranes used, type of vascular access, and blood flows used (mL/min). Data on anemia control with hemoglobin (Hb) levels (g/dL), rHuEPO dose (IU/kg of body weight/week), erythropoietin response index (ERI) calculated by the ratio rHuEPO dose (IU/ kg of body weight/week) and mean Hb (g/dL), ferritin serum levels (ng/mL), and transferrin saturation index (TSI) (%) were also gathered. With regards to renal osteodystrophy and calcium-phosphorus metabolism control, information was asked on calcium serum levels (mg/dL), phosphorus (mg/dL), intact parathyroid hormone (iPTH) (pg/mL), and aluminum (_g/L). Nutritional status was assessed by serum creatinine (mg/dL), albumin (g/dL) and transferrin (mg/dL) levels.

PATIENTS

Data on 215 patients (112 men and 103 women) from the 10 HD units in Aragón were selected. *The only inclusion criteria were: being on dialysis program for longer than a year and on treatment with subcutaneous rHuEPO*. The decision of selecting patients with a HD duration longer than one year was based on the knowledge that HD duration is correlated with dialysis dose received, with a better anemia management, and with greater serum albumin levels.[7] Distribution of patients according to CRF etiology was as follows: diabetic nephropathy (DN) 47 cases, interstitial nephropathy (IN) 44 cases, vascular nephropathy (VN) 37 cases, primary glomerulonephritis (GM) 33 cases, polycystic renal disease 16 cases, systemic disease 5 cases, other causes 10 cases, and unknown origin 23 cases.

For analysis of the influence of the cause of CRF, we selected the 161 patients that represented the four etiology groups with the greatest number of patients with a known cause of CRF (DN, IN, VN, and GM), and since they included a similar number of patients in each group it allowed for comparison between them.

STATISTICAL ANALYSIS

Results are expressed as mean ± standard deviation (SD). Besides descriptive statistics, a comparison was done between quantitative variables by Student's t test for non-paired data and Chi squared for qualitative variables. *For mean comparison between more than two subgroups, ANOVA test was used, with post-hoc analysis by Fisher's test.*

Potential predictors for Hb level and rHuEPO dose were analyzed by linear regression. Included variables in the analysis were: age, gender, creatinine, PUR, Hb, rHuEPO dose, ferritin, TSI, serum calcium level, serum phosphorus level, iPTH, serum aluminum level, albumin, transferrin, and years on HD. Those independent variables that correlated with Hb level and rHuEPO dose with a $p < 0.20$ were included in a step-wise linear regression model. A p value < 0.05 was considered as significant. Statistical analyses were done with Statview software (Abacus Concept Inc, Berkeley, CA.)

Table I. Clinical and biochemistry data of the 215 patients in the study

Age (years)	66.0 ± 14.1
Time on HD (years)	3.7 ± 3.6
Hemoglobin (g/dL)	11.4 ± 1.7
rHuEPO (IU/kg/week)	111.8 ± 65.1
ERI	10.3 ± 6.6
Creatinine (mg/dL)	8.8 ± 2.4
Albumin (g/dL)	3.6 ± 0.3
Transferrin (mg/dL)	178.5 ± 39.6
Ferritin (ng/dL)	335.6 ± 256.6
TSI (%)	28.6 ± 11.5
Serum calcium (mg/dL)	9.6 ± 0.9
Serum phosphorus (mg/dL)	5.5 ± 1.6
iPTH (pg/mL)	310.4 ± 380.5
Seum aluminum (ng/mL)	28.1 ± 19.0
PUR (%)	66.5 ± 8.2

Data expressed as mean ± SD.

RESULTS

Clinical and biological characteristics of the studied population are summarized in Table I. Mean duration of HD session was 228 ± 22 minutes. *Of the studied patients, 183 were dialyzed through an autologous arterial-venous fistula (AVF), 11 through a provisional catheter, 12 through a permanent catheter, and 9 through a graft. The mean for blood flows was 287 ± 43 mL/min. Thirty-one percent of the patients were dialyzed with high-permeability membranes.* Sixty-five percent of the patients reached a target hemoglobin of 11.0 g/dL.

When categorizing the population by gender, female patients presented a lower Hb level than male patients ($p = 0.0258$), in spite of receiving similar rHuEPO doses (table II). Creatinine ($p = 0.0006$) and

Table II. Comparison of clinical and biochemistry data of the 215 patients in the study, by gender

	Male pts (n = 112)	Female pts (n = 103)	p
Age (years)	64.5 ± 14.7	67.6 ± 12.3	0.1085
Time on HD (years)	2.9 ± 2.5	4.6 ± 4.4	0.0011
Hemoglobin (g/dL)	11.6 ± 1.7	11.1 ± 1.5	0.0258
rHuEPO (IU/kg/week)	108.1 ± 56.8	115.8 ± 69.5	0.3722
ERI	9.7 ± 6.0	10.9 ± 7.3	0.2189
Creatinine (mg/dL)	9.3 ± 2.5	8.2 ± 2.0	0.0006
Albumin (g/dL)	3.7 ± 0.3	3.5 ± 0.3	0.0001
Transferrin (mg/dL)	183.2 ± 44.6	173.1 ± 32.8	0.0814
Ferritin (ng/dL)	324.5 ± 296.3	348.0 ± 204.0	0.5168
TSI (%)	28.4 ± 10.9	28.8 ± 12.2	0.7847
Serum calcium (mg/dL)	9.5 ± 0.9	9.6 ± 1.0	0.3929
Serum phosphorus (mg/dL)	5.5 ± 1.6	5.5 ± 1.5	0.7883
iPTH (pg/mL)	272.4 ± 333.8	351.9 ± 423.5	0.1357
Serum aluminum (ng/mL)	29.4 ± 21.2	26.7 ± 16.4	0.3311
PRU (%)	65.1 ± 8.1	67.9 ± 8.3	0.0125

Data expressed as mean± SD.

albumin (p = 0.0001) levels were also decreased in women, whereas time on dialysis (p = 0.0011) and PUR (p = 0.0125) were higher than those observed in men (table II). The remaining analyzed parameters did not show significant differences between both genders.

Since women presented greater anemia and hypoalbuminemia than men, and in order to know whether dialysis dose (PUR) could induce a greater response to rHuEPO in patients with hipoalbuminemia, we selected those cases with albumin levels lower than 3.5 g/dL (n = 61) out of the total population. These patients were categorized by gender, and subgroups were compared based on whether they reached a Hb level > 11.0 g/dL or not. In the female subgroup (n = 36), it was observed that those with a Hb level > 11.0 g/dL (n = 16) presented a PUR significantly higher than female patients with a Hb level < 11.0 g/dL (n = 20), 72.3 ± 7.4 *vs* 64.7 ± 9.8% (p = 0.0155). By contrast, in the male subgroup (n = 25), those with a Hb level > 11.0 g/dL (n = 16) had a PUR similar to those with a Hb level < 11.0 g/dL (n = 9), 66.0 ± 8.8 *vs* 64.9 ± 9.0% (p = 0.7657).

In table III, four comparison groups are established by CRF etiology. The group of patients with CRF due to GM was characterized by being younger (p = 0.0001), having greater creatinine levels (p = 0.0052), requiring higher rHuEPO doses (p = 0.0374), and higher ERI (p = 0.0469) than the three other groups. However, the former presented higher albumin levels and higher TSI than the latter three, although not reaching statistical significance. Besides, both in the group of patients with a history of GM and in the VN group, a greater proportion of male patients was noticed (p = 0.0075), a characteristic that is associated with greater Hb levels, as we have observed. The negative parameter in the GM group was a greater tendency to high phosphorus serum levels as compared to the three other groups, although not reaching statistical significance. Lastly, patients with CRF secondary to GM or IN were for longer time on HD than those with DN or VN (p = 0.0018) (table III).

Table III. Comparison of clinical and biochemistry data of 161 patients, by etiology of chronic renal failure: diabetic nephropathy (DN), vascular nephropathy (VN), interstitial nephropathy (IN) and primary glomerulonephritis (GM)

	DN (n = 47)	VN (n = 37)	IN (n = 44)	GM (n = 33)	p
Age (years)	67.1 ± 11.7	70.6 ± 9.8	68.8 ± 14.0	57.6 ± 14.2[a]	0.0001
Gender (M/F)	20/27	28/9[b]	20/24	21/12	0.0075
Time on HD (years)	2.6 ± 1.7	2.5 ± 1.8	4.8 ± 4.5[c]	4.8 ± 5.3[d]	0.0018
Hemoglobin	11.3 ± 1.3	11.9 ± 1.7	11.7 ± 1.7	11.3 ± 1.4	0.2233
rHuEPO (IU/kg/week)	108 ± 58	100 ± 59	102 ± 54	139 ± 85[a]	0.0374
ERI	9.7 ± 5.6	8.9 ± 5.8	9.1 ± 5.5	12.8 ± 8.8[a]	0.0469
Creatinine (mg/dL)	7.7 ± 2.0[e]	8.7 ± 2.1	8.6 ± 2.4	9.5 ± 2.1	0.0052
Albumin)g/dL)	3.5 ± 0.4	3.6 ± 0.3	3.6 ± 0.2	3.7 ± 0.3	0.1626
Transferrin (mg/dL)	170 ± 37	183 ± 57	177 ± 32	184 ± 40	0.4325
Ferritin (ng/dL)	328 ± 205	276 ± 147	344 ± 211	376 ± 471	0.5251
TSI (%)	26.7 ± 8.9	27.1 ± 10.1	28.6 ± 12.7	32.8 ± 13.3	0.136
Serum calcium (mg/dL)	9.4 ± 0.9	9.7 ± 1.0	9.7 ± 1.0	9.4 ± 0.8	0.1841
Serum phosphorus (mg/dL)	5.4 ± 2.1	5.6 ± 1.6	5.3 ± 1.2	6.0 ± 1.1	0.2334
iPTH (pg/mL)	265 ± 359	224 ± 218	367 ± 393	347 ± 414	0.2568
Serum aluminum (ng/mL)	22.5 ± 12.4	33.3 ± 23.8	30.3 ± 17.9	26.3 ± 18.3	0.062
PUR (%)	67.3 ± 9.2	65.6 ± 8.4	65.9 ± 7.7	65.9 ± 7.7	0.8109

Data expressed as mean ± SD.
[a] p < 0.05 GM *vs* DN, VN and I; [b] p < 0.05 VN *vs* DN and IN; [c] p < 0.05 IN *vs* DN and VN; [d] p < 0.05 GM *vs* DN and VN; [e] p < 0.05 DN *vs* VN, IN and GM.

Table IV. Comparison of clinical and biochemistry data of the 215 patients, by age groups: < 60 years, 60-75 years and > 75 years

	< 60 (n = 53)	60-75 (n = 107)	> 75 (n = 55)	p
Gender (M/F)	31/22	56/51	25/30	0.3979
Time on HD (years)	4.9 ± 5.4[a]	2.9 ± 2.5	4.0 ± 2.9	0.0048
Hemoglobin (g/dL)	11.1 ± 1.8	11.5 ± 1.7	11.3 ± 1.5	0.3146
rHuEPO (IU/kg/week)	129.8 ± 67.1[a]	101.4 ± 59.3	114.9 ± 63.5	0.0249
ERI	12.4 ± 8.0[a]	9.1 ± 5.9	10.5 ± 6.1	0.0114
Creatinine (mg/dL)	10.1 ± 2.7[b]	8.4 ± 2.1	8.4 ± 2.0	0.0001
Albumin (g/dL)	3.7 ± 0.3	3.6 ± 0.4	3.5 ± 0.3	0.1421
Transferrin (mg/dL)	185.5 ± 52.1	178.2 ± 35.7	172.8 ± 33.5	0.2969
Ferritin (ng/dL)	368.8 ± 405.3	322.2 ± 188.7	332.3 ± 197.9	0.5859
TSI (%)	30.3 ± 12.4	27.7 ± 10.7	28.7 ± 12.2	0.4483
Serum calcium (mg/dL)	9.3 ± 1.0[b]	9.6 ± 0.9	9.7 ± 0.9	0.0403
Serum phosphorus (mg/dL)	6.1 ± 1.7[b]	5.4 ± 1.6	5.1 ± 1.2	0.0035
iPTH (pg/mL)	345.6 ± 417.2	302.7 ± 338.9	292.0 ± 423.2	0.7448
Serum albuminum (ng/mL)	28.8 ± 19.0	27.7 ± 19.0	28.4 ± 19.5	0.9413
PUr (%)	65.3 ± 7.4	65.9 ± 8.5	68.6 ± 8.1	0.074

Data expressed as mean ± SD
[a] p < 0.05 < 60 years *vs* 60-75 years; [b] p < 0.05 < 60 years *vs* 60-75 years y > 75 years.

Table IV depicts three groups of patients for comparison according to age. Patients younger than 60 years represent the group that requires higher rHuEPO doses (p = 0.0249) and present a higher ERI (p = 0.0114). These significant differences are observed compared to the group of patients with age between 60-75 years, but with those older than 75 years. Hb levels were similar in the three groups, although patients younger than 60 had the lowest Hb levels and had higher rHuEPO requirements (Table IV). Patients older than 60 were characterized by having the greatest serum phosphorus levels (p = 0.0035) and the lowest serum calcium levels (p = 0.0403), as compared to the two other groups. In addition, in younger patients serum creatinine levels were higher than in the two other groups (p = 0.0001). Besides, it was the group presenting the highest serum albumin levels and the longest duration on HD, the latter parameter reaching significant differences as compared to patients aged 60-75 years (p = 0.0048). Parameters for iron metabolism and serum aluminum levels were similar in the three groups.

An interesting data that should be highlighted is that, when selecting patients older than 80 (n = 20) among the group of patients older than 75, we observe that the former need higher rHuEPO doses as compared to the group 60-75 years (n = 107) and break the tendency for the older the age, the lesser the need of rHuEPO, 131.4 ± 72.3 vs. 101.4 ± 59.3 IU/kg of body weight/week, (p = 0.0225). This subgroup of patients older than 80, together with those younger than 60, are the ones that present higher rHuEPO requirements.

In the univariant linear regression analysis, on the total studied population, the best predictive variables (p < 0.20) for Hb level were albumin (p = 0.0001), rHuEPO dose (p = 0.0001), transferrin (p = 0.0066), ferritin (p = 0.0281), gender (p = 0.0258), phosphorus (p = 0.0693), TSI (p = 0.1153), age (p = 0.1772), and calcium (p = 0.1826). As for rHuEPO dose, the best predictive variables were: Hb (p = 0.0001), aluminum (p = 0.0157), calcium (p = 0.0132), age (p = 0.0225), transferrin (p = 0.0348), and ferritin (p = 0.0884).

In the step-wise linear regression model, the only three predictive variables for Hb level were: albumin (R = 0.32; coefficient = 1.666), rHuEPO dose (R = 0.411; coefficient = -0.008), and calcium (R = 0.464; coefficient = -0.375). When rHuEPO dose was used as a dependent variable, the independent predictive variables were: calcium (R = 0.255; coefficient = -18.791), Hb (R = 0.364; coefficient = -10.341), and aluminum (R = 0.398; coefficient = -0.549).

DISCUSSION

Appropriate anemia management in HD patients requires paying attention to a wide range of factors, including the dose of erythropoiesis-stimulating agents, the presence of inflammation, iron deficiency, *secondary hyperparathyroidism,* and dialysis dose. However, there are other factors that we cannot modify and that affect anemia management, such as gender, etiology of CRF, and age. One of the findings of the present study is that women on HD have

lower Hb levels than men, in spite of receiving similar rHuEPO doses. This observation has already been noticed in other studies,[5] and in deed, in the recently published DOPPS study on anemia management in HD in twelve countries indicated that patients with a greater tendency to present Hb levels > 11.0 g/dL were male patients, patients with older age, those with a history of polycystic renal disease, and those with higher serum albumin or calcium levels, and higher TSI.[8] Besides, it was indicated that the administration of higher rHuEPO doses was associated with the following patient's characteristics: being young or being woman, those with higher body weight, those that did not have polycystic renal disease as a cause of CRF, those with the lowest TSI, Hb or serum albumin.[8] However, the reasons why these different characteristics induced higher Hb levels or higher rHuEPO requirements were not analyzed. In this sense, the reason for a lower response of women on HD to rHuEPO is not fully understood.[6] It has been discussed the possibility to extrapolate to patients on HD the higher response to androgen-induced erythropoiesis in healthy men than in healthy women. It is likely that there exist differences among genders, because of sexual hormones, in iron release from reticuloendothelial cells to bone marrow in order to improve erythropoiesis, and that would explain the differences in Hb levels observed between male and female patients on HD.[9] Another possibility, not confirmed, is that red blood cells half-life would be shorter in women than in men.[6] Ifudu *et al*.[5] posed that if higher rHuEPO requirements in women on HD were due to some modifiable cause, this cause ought to be determined. In our study, we have observed that decreased Hb levels were accompanied in women by significant decreases also in albumin levels. *And, since in the step-wise regression analysis serum albumin was the most important independent predictive factor for Hb levels, this could be one of the reasons for a lower erythropoiesis response in women,* because women received higher dialysis doses and had similar iron and calcium-phosphorus metabolism to that in men of the study. Until now, lower albumin levels had not be proposed as a likely explanation for the observed differences in anemia management between both genders in the HD population.[6] Insisting in the amelioration of the nutritional status of female patients on HD and knowing that they will require higher rHuEPO doses than men would prevent to excessively increase intravenous iron supplementation as the only measure to reduce rHuEPO dose, which in many patients leads to an unnecessary iron overload.[5] An effective measure would be to increase as much as possible the dialysis dose, since it has been shown in women that the higher the PUR, the lower the mortality is.[10-11] The implementation in women of higher dialysis doses would probably allow reducing rHuEPO requirements. In deed, in our female patients with serum albumin < 3.5 g/dL, a significant difference in the PUR was detected between those that reached a Hb level > 11.0 g/dL and those that did not. *These results suggest that in women, particularly in those with hypoalbuminemia, increasing the dialysis dose may improve the response to rHuEPO.*

With regards to the etiology of CRF and response to rHuEPO, as evidenced in the DOPPS study,[8] patients with a history of polycystic renal disease are the ones requiring the lowest dose. In the epidemiological study on anemia management in Spain,[12] it was only indicated that the mean rHuEPO dose varied according to CRF etiology, being significantly higher for multiple myeloma, hereditary, tubulointerstitial, and post-renal transplantation nephropathies, but not providing additional information. In our study, although we have not included in the comparison patients with polycystic renal disease, we have observed as the most relevant finding that patients with a history of GM are the ones requiring the highest rHuEPO doses as compared to patients with DN, IN, and VN. We have not found this datum published in the literature, likely because comparisons have not been established between these etiologic groups. One possible explanation to this observation is that the use of cytotoxic drugs for a period of time in patients with GM may condition a lower response capability of bone marrow to erythropoiesis-stimulating agents.[13] Another possibility to take into account is the younger age of patients with GM as compared to the other etiologic groups, which conditions higher rHuEPO requirements, as seen from the DOPPS study results.[8] On the other hand, it does have been described that diabetic patients with or without CRF have a more severe anemia than non-diabetic individuals.[14-16] This phenomenon is attributed to a lower capability of generating endogenous erythropoietin, among other reasons because of the autonomic neuropathy that some diabetic patients present, as well as because of a lower capability to respond to it.[17-19] Based on this hypothesis, it has been inferred that rHuEPO requirements in diabetic patients on HD are higher. However, there are studies, such us Frankenfield's *et al.*,[20] that find that diabetic patients on HD require lower rHuEPO doses than non-diabetics to reach the target hematocrit. Ifudu *et al*.[5] did not find significant differences in rHuEPO requirements between diabetics and non-diabetics in a population on HD. In the diabetic patients of our study, similar rHuEPO

needs are observed between patients with VN and IN, which are lower than those of patients with a history of GM.

Finally, the subgroup analysis by age of our study patients clearly shows that those younger than 60 years are the ones with the highest rHuEPO requirements and with a higher ERI. Besides, in the simple regression analysis age is one of the parameters that significantly correlate with rHuEPO requirements. The observation that younger patients require higher rHuEPO doses has been described in the DOPPS study,[8] although not analyzing the reasons for this correlation. In some studies, it have been observed that anemia in chronic renal failure is more severe in children than in adults,[21-22] and that, with the same renal failure degree, children tend to have a more severe anemia than adults.[21] One possible explanation is that cellular density of the bone marrow in children is lower than in adults.[22] However, the causes that influence on these different rHuEPO requirements by age are not fully understood. In our study, higher serum phosphorus and lower calcium levels are observed in the group of patients younger than 60 years, as compared to the other age groups. We have recently described this association between higher rHuEPO requirements and poor control of calcium-phosphorus metabolism,[23] and it could be an explanation for higher rHuEPO requirements observed in younger patients. *In fact, in step-wise regression analysis, serum calcium level has been the most important independent predictive factor for rHuEPO dose*. Considering that rHuEPO-dependent erythropoiesis modulation is conditioned by calcium concentration within the cytoplasm of the bone marrow erythroid precursors, and that this concentration is modified by serum calcium levels, an adequate control of calcium-phosphorus metabolism may modulate the response to rHuEPO.[24,25]

Another interesting issue is the observation that patients older than 80 years require higher rHuEPO doses than patients in the 60-75 years age group. This finding would argue against the consideration that the older the patient, the lower the dose needed of rHuEPO, as it is suggested by the DOPPS study outocomes.[8] In this advanced age population, the greater rHuEPO requirements would be indicating that, from 80 years, the older age may not be a factor favoring a better response to rHuEPO. Further studies analyzing whether response capacity to rHuEPO may be reduced in advanced age patients that as it is the case in younger patients, may present a lower cellular density of the bone marrow.

In conclusion, the present study results indicate that there exist non-modifiable characteristics in patients on HD that may condition a lower response to rHuEPO treatment, and that we should take them into account when analyzing the efficacy of the dose of erythropoiesis-stimulating agents that we are prescribing. Notwithstanding, these results correspond to a small number of patients population, and therefore it would of interest to carry out further studies with the aim of identifying the true causes of the lower erythropoiesis response in women, in patients with primary glomerulonephritis as the cause of CRF, and in younger patients.

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