Pharmacotherapy quality and patient safety in haemodialysis patients treated with erythropoiesis-stimulating agents

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Abstract

Objective: To assess an interdisciplinary programme for the improvement of pharmacotherapy quality and patient safety in patients with chronic renal disease who are treated with erythropoiesis-stimulating agents.

Method: Observational, longitudinal study. Retrospective analysis (*period A*) and prospective analysis (*period B*) following implementation of the programme for haemoglobin values and monthly erythropoiesis-stimulating agent dosage. The proportion of patients with haemoglobin values within the target range (10-5-12.5 g/dL) and those with values above the safety limit (≥12.5 g/dL) were compared every 4 months and the average percentage of time with haemoglobin values within the target range and above the safety limit were compared during periods A and B.

Results: Fifty-nine patients were included in the study. The proportion of patients with haemoglobin levels within the target range increased from 28.8% to 65.4% (RR=2.27; 95% CI, 1.56-3.30) and the value in patients with haemoglobin levels above the safe level reduced from 57.6% to 19.2% (RAR=0.39; 95% CI, 0.19-0.55). The time with haemoglobin levels in the target range increased 15.7% (95% CI, 7.1-24.2) and the time with values above the safe level reduced 26.9% (95% CI, −35.1 to −18.6). The number of patients included to avoid one reaching a haemoglobin value above the safe range was 2.6 (95% CI, 2.5-2.7).

Conclusions: The implementation of an improvement programme for the quality of pharmacotherapy with erythropoiesis-stimulating agents in patients with haemodialysis significantly increases the proportion of patients with haemoglobin values within the recommended ranges of effectiveness and safety.

Key words: Renal anaemia. Chronic renal disease. Erythropoiesis-stimulating agents. Patient safety. Quality improvement.

Resumen

Calidad de la farmacoterapia y seguridad de los pacientes en hemodiálisis tratados con estimulantes eritropoyéticos

Objetivo: Evaluar un programa interdisciplinario de mejora de la calidad de la farmacoterapia y la seguridad de los pacientes con enfermedad renal crónica tratados con estimulantes eritropoyéticos.

Método: Estudio observacional longitudinal. Análisis retrospectivo *(período A)* y prospectivo tras implantar el programa *(período B)* de valores de hemoglobina y dosis de estimulantes eritropoyéticos mensuales. Se compararon, cada 4 meses, la proporción de pacientes con valores de hemoglobina dentro del ámbito objetivo (10,5-12,5g/dl) y superiores al límite de seguridad (≥ 12,5g/dl), y el porcentaje medio de tiempo con valores de hemoglobina dentro del ámbito objetivo y superiores al límite de seguridad, respectivamente, durante los períodos A y B.

Resultados: Se incluyeron 59 pacientes. La proporción de éstos con hemoglobina dentro del ámbito objetivo se incrementa de un 28,8 a un 65,4% (riesgo relativo = 2,27; intervalo de confianza [IC] del 95%, 1,56-3,30) y la de pacientes con hemoglobina superior al límite de seguridad se reduce de un 57,6 a un 19,2% (reducción abso-

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luta del riesgo = 0,39; IC del 95%, 0,19-0,55). El tiempo con hemoglobina en el ámbito objetivo se incrementa un 15,7% (IC del 95%, 7,1-24,2) y el tiempo con valores superiores al límite de seguridad se reduce un 26,9% (IC del 95%, –35,1 a –18,6). El número de pacientes que hay que incluir para evitar que uno alcance un valor de hemoglobina superior al límite de seguridad fue 2,6 (IC del 95%, 2,5-2,7).

Conclusión: La implantación de un programa de mejora de la calidad de la farmacoterapia con estimulantes eritropoyéticos en pacientes en hemodiálisis aumenta significativamente la proporción de pacientes con valores de hemoglobina dentro del ámbito de efectividad y seguridad recomendados.

Palabras clave: Anemia renal. Enfermedad renal crónica. Factores estimulantes eritropoyéticos. Seguridad del paciente. Mejora de calidad.

INTRODUCTION

Anaemia is one of the most frequent complications in patients with chronic renal disease (CRD), especially in advanced stages, and it affects approximately 60%-80% of patients. Among the factors that cause or contribute to renal anaemia, a deficit in the production of endogenous erythropoietin in the kidney stands out, which leads to a decrease in haemoglobin levels (Hb) and affects the tissue use of oxygen in the organism. The consequences in these patients are diverse and of different degrees of severity, in general, anaemia usually worsens the prognosis of patients with CRD. Therefore, aside from affecting quality of life, alterations are produced in the immune system, the nervous system (including the reduction of cognitive and concentration capacities) and, especially, the cardiovascular system (left ventricular hypertrophy), which has been associated in various studies with an increase in morbidity and mortality of patients with CRD in haemodialysis. The erythropoiesis-stimulating factors (ESF), such as the recombinant human erythropoietin (α and β) and darbepoetin-α, are administered to patients with CRD in haemodialysis to treat anaemia and prevent its complications. Therefore, treatment with ESF is usually initiated when the Hb of the patients is <10 g/dL in 2 consecutive determinations, spaced at least 2 weeks apart, as long as other possible causes of the anaemia are discarded and iron levels are normalised.

The benefits of the treatment of renal anaemia with ESF is currently being considered in terms of improved quality of life for the patient—especially concerning tolerance to exercise and functional capacities—and reduce or avoid blood transfusions and their associated risks, including iron overloads, the potential transmission of diseases or sensibilisation to future transplants. However, the individualised benefit-risk balance must take into consideration the presence of cardiovascular diseases, diabetes mellitus, and other cardiovascular risk factors, as recently published studies have reopened the date regarding Hb values that are considered optimal and the safety of ESF in patients with CRD.

Therefore, in the CHOIR study, a randomised, open clinical trial (n=1432), a greater cardiovascular risk and a risk to be hospitalised for patients with elevated Hb values (13.5 g/dL) compared to those that presented lower values (11.3 g/dL), without demonstrating improvements in quality of life. In the CREATE study, a randomised clinical trial (n=603), the authors concluded that the early and complete correction of anaemia does not reduce the risk of cardiovascular episodes. A recently published meta-analysis demonstrates an increase in the risk of adverse serious episodes, including death, when HB levels reach Hb levels over 12.0-16.0 g/dL in these patients. From these findings, not only the regulating agencies but also the professional societies have taken on the revision of scientific evidence concerning the effectiveness and safety of ESF, to provide explicit recommendations to improve their use and the results of treatment in patients. These analyses have led to modifications in the authorised conditions of use of the ESF and the updating of the clinical guides of the treatment of anaemia in CRD, however, certain discrepancies have been observed (Table 1).

This situation generates an elevated variability in the treatment of renal anaemia and reveals the opportunities to improve treatment with ESF in these patients. This study is proposed in this context, whose objective is to evaluate the results of an interdisciplinary programme to improve pharmacotherapy quality and the safety of patients with CRD in haemodialysis treated with ESF, based on the co-responsible participation of the pharmacist in the individualisation of the treatment and follow-up of the patient, through his or her integration in the interdisciplinary team of a dialysis centre.

METHOD

Observational, longitudinal study, where all patients were included with CRD treated with ESF and undergoing haemodialysis in a dialysis centre linked to a general public and university hospital. The study has been divided in 2 periods: *period A*, before the implementation of the program, where the data corresponding to the months of February 2005 to February 2006 (13 months) was analysed in a retrospective manner, and *period B*, where the results corresponding to the first 20 months of the implementation of the program (from March 2006 to October 2007) were analysed in a prospective manner. For the implementation of the program, a normalised work procedure (NWP) was designed, agreed upon between the medical team and the nursing team of the dialysis centre and the pharmacists of the pharmacy department of the hospital that was responsible for the disbursement of ESF, where, the following parameters, among others, were established: target range for Hb, limit safety value for Hb, follow-up, and monitoring frequency analysis parameters, as well as recommendations to modify doses and/or dose intervals in different situations (Table 2). The pharmacists participated in the pharmacotherapeutic and clinical follow-up of patients through periodical visits to the dialysis centre every 2-4 weeks, in order to come to an agreement

Table 1. Summary of the guidelines from professional societies and warnings from the regulating agencies that modify the authorised conditions of use of erythropoiesis-stimulating factors in patients with chronic renal disease

	NICE 2006	KDOQI 2007	FDA 2007	EMEA 2007
Target Hb	10.5-12-5 g/dL	11-12 g/dL; not above 13 g/dL	10-12 g/dL	10-12 g/dL; not above 12 g/dL, especially in patients with ischemic coronary diseases or CCF
Initiate ESF	Hb ≤11 g/dL	Not specified	Hb <10 g/dL	Not specified
Initial dose	Not specified	Depending on initial Hb, target Hb and clinical situation	EPO: 50-100 UI/kg/week DARBE: 0.45 µg/kg/week	EPO: 3×40 UI/kg/week DARBE: 0.45 µg/kg/week
Monitoring frequency	Increase Hb ≤1 g/dL in 1 month, every 4 weeks increase Hb >1 g/dL in 1 month, every 2 weeks	At least once a month	Every 2-6 weeks	At the beginning, very 1-2 weeks, elater periodically
Increase in dose	If Hb <11 g/dL ↑ dose/frequency 25% in spite of increase Hb >1 g/dL/month	Not specified Review bibliography	If Hb <10 g/dL or an increase of Hb <1 g/dL in 1 month ↑ dose 25% (wait at least 4 weeks for new increases)	If increase of Hb <1 g/dL in 1 month ↑ dose 25% (wait at least 4 weeks for new increases)
Reduction of dose	If Hb 12-15g/dl ↓ dose/frequency 25%. If Hb >15 g/dL stop ESF or ↓ dose/frequency 50% and monitor in 2 weeks	Not specified Review bibliography	If Hb is close to 12 g/dL or increases >1 g/dL in 2 weeks ↓ dose 25%. If Hb continues to increase, interrupt until it drops and reintroduce with dose reduced by 25%	If increase of Hb >2.5 g/dL in 1 month ↓ dose 25%-50%. If Hb >13 g/dL stop ESF until Hb <13 g/dL and reintroduce with a reduction of the dose by 25%

CCF indicates congestive cardiac failure; ESF, erythropoietin-stimulating factors; Hb, haemoglobin; ↑, increase; ↓, decrease.

Table 2. Normalised work procedure for patients with chronic renal disease in haemodialysis treated with erythropoiesis-stimulating factors

Target Hb: 10.5-12.5 g/dL				
Safety limit: Hb ≤12.5 g/dL				
Type of ESF and initial dose	Erythropoetin-b: 50-100 UI/kg/week, 3 times/week Darbepoetin-a: 0.45 µg/kg, once per week			
Response (Hb) and evaluation time	Situation 1 Increase of Hb >1 g/dL in 4-8 weeks and/or Hb <10.5 g/dL	Situation 2 Increase of Hb >1 and <2 g/dL in 4-8 weeks and/or Hb = 10.5-12.5 g/dL	Situation 3 Increase of Hb >2 g/dL in 4-8 weeks and/or Hb >12.5-13 g/dL	Situation 4 Hb >13.0 g/dL
Dosage parameters	**Recommendation**			
1. Dose	↑ 25%	→	↓ 25%-50%	Stop until Hb <12.5 g/dL Later → or ↓ 25%-50%
2. Interval	→	→	→ If various Hb >12.5 g/dL ↑ the interval	Suspend until Hb <12.5 g/dL; later ↑
3. Monitoring frequency for Hb	Every 4 weeks	Every 4 weeks	Every 4 weeks	2 weeks after stopping treatment
Other monitored parameters: hematocrit, ferritin, index of saturation of transferrin				

ESF indicates erythropoiesis-stimulating factors; Hb, haemoglobin; →, maintain; ↑, increase; ↓, decrease.

with the interdisciplinary team the decisions regarding the personalisation of the treatment with ISF, depending on the response obtained. The disbursement of ESF was done monthly, after the individualised request per patient of the dialysis centre to the pharmacy department.

The Hb values (g/dL) and the doses of ESF per patient were the result variables collected monthly and analysed every 4 months during periods A and B. These times were established based on the recommendations give to evaluate the response in Hb values after initiating or modifying the doses prescriptions with ESF.

The improvement of the pharmacotherapy quality with ESF was evaluated using the following indicators: proportion of patients with Hb values within the target range (10.5-12.5 g/dL), obtained every 4 months during period A and B, and average percentage of follow-up time where the patients presented stable Hb values within this range in each period. The improvement of patient safety was evaluated using the proportion of patients with Hb values above the established safety limit (≥12.5 g/dL), obtained every 4 months during periods A and B, and the average percentage of follow-up time where the patients presented stable Hb values over said limit in each period.

The statistical treatment was realised using the SPSS v.12.0 computer program. The Kolmogorov-Smirnov test was used on all of the quantitative variables. The Hb values, the average weekly doses of ESF per patient and the average percentage of follow-up time with optimal Hb and above the safety limit were compared between the 2 groups using the analysis of averages, with the Student *t* test. The difference in the proportion of patients within the target Hb range and above the safety limit, the absolute risk reduction (ARR) of presenting Hb values above the recommended safety limit and the relative risk (RR), with their respective 95% confidence intervals (CI), between the final result (measured in the 20th month of period B) and the initial (measured in the 1st month of period A) were calculated. The number of needed patients to be treated (NNT) was also calculated, as the inverse of the ARR and its 95% CI. The signification level was established at $P<.05$.

RESULTS

The number of patients evaluated in period A was 59 and in period B, 52; the reasons for the loss of patients between both periods were: death (4 patients; 6.8%), kidney transplant (2; 3.4%), or transfer to other dialysis centres (1; 1.7%). The characteristics of the population of patients studied are presented in Table 3, following a distribution of the studied variables, demographic as well as clinical, similar to other studies.

Average Hb levels of the patients in period A was 12.4 (1.5 g/dL) (95% CI, 12.3-12.5) and in period B it was 11.6 (1.4 g/dL) (95% CI, 11.5-11.7) ($P<.01$). In Figure 1 the evolutions of the proportion of patients with Hb values in the optimal target range is shown as well as those above the safety limit, analysed every 4 months in periods A and B.

Table 3. Characteristics of the population of patients studied (n=59)

Variables	
Sex (% males/% females)	58.8/41.2
Age, y[a]	67.1 (13.1) (64.3-69.9)
Weight, kg[a]	66.7 (15.7) (63.3-70.1)
Plasma creatine, mg/dL[a]	9.1 (2.6) (8.5-9.7)
Ferritin, ng/mL[a]	512.8 (415.6) (420.3-605.2)
Transferrin saturation, %[a]	23.6 (12.8) (20.1-27.2)
Transferrin, mg/dL[a]	180.4 (48.1) (169.6-191.1)
Aetiology of CRD, %	
High blood pressure	12 (20.3)
Diabetic nephropathy	14 (23.7)
Glomerulonephritis	5 (8.5)
Pyelonephritis	5 (8.5)
Interstitial nephritis	4 (6.8)
Polycystic kidneys	4 (6.8)
Unknown	15 (25.4)
Comorbidities, %	
High blood pressure	42 (71.2)
Ischemic cardiopathy, thromboembolism	30 (50.8)
Diabetes mellitus	25 (42.4)
Dyslipidemia	14 (23.7)
COPD, asthma	16 (27.1)
Time in haemodialysis, y[a]	5.1 (4.0) (4.2-6.1)

COPD indicates chronic obstructive pulmonary disease; CRD, chronic renal disease.
[a]Average (standard deviation) (95% confidence interval).

To evaluate the results of the programme, the proportions were first compared of patients with Hb values in the target range and above the safety limit obtained in month 1 of period A and month 20 of period B, that are shown in Table 4 as initial and final results, respectively. As observed, before the programme, 28.8% of the patients had Hb values within the target range, and this proportion significantly increased up to 65.4% with the interdisciplinary programme (RR=2.27; 95% CI, 1.56-3.30). At the same time, the proportion of patients with Hb values over the safety limit was initially 57.6% and it was significantly reduced to 19.2%.

Next, the indicators of average time were obtained, measured in percentages compared to the total of months of follow-up, that the patients presented stable Hb values within the target range and above the safety limit, respectively. Indeed, in Table 4, it is evident that before the programme the patients presented an average of 41.0% of the time with Hb values in the target range and 52.1% with values above the recommended safety limit. This situation was modified with the programme, increasing the time with Hb values in the target range to 56.7% and reducing the time with Hb values that could affect the safety of patients to 23.3%.

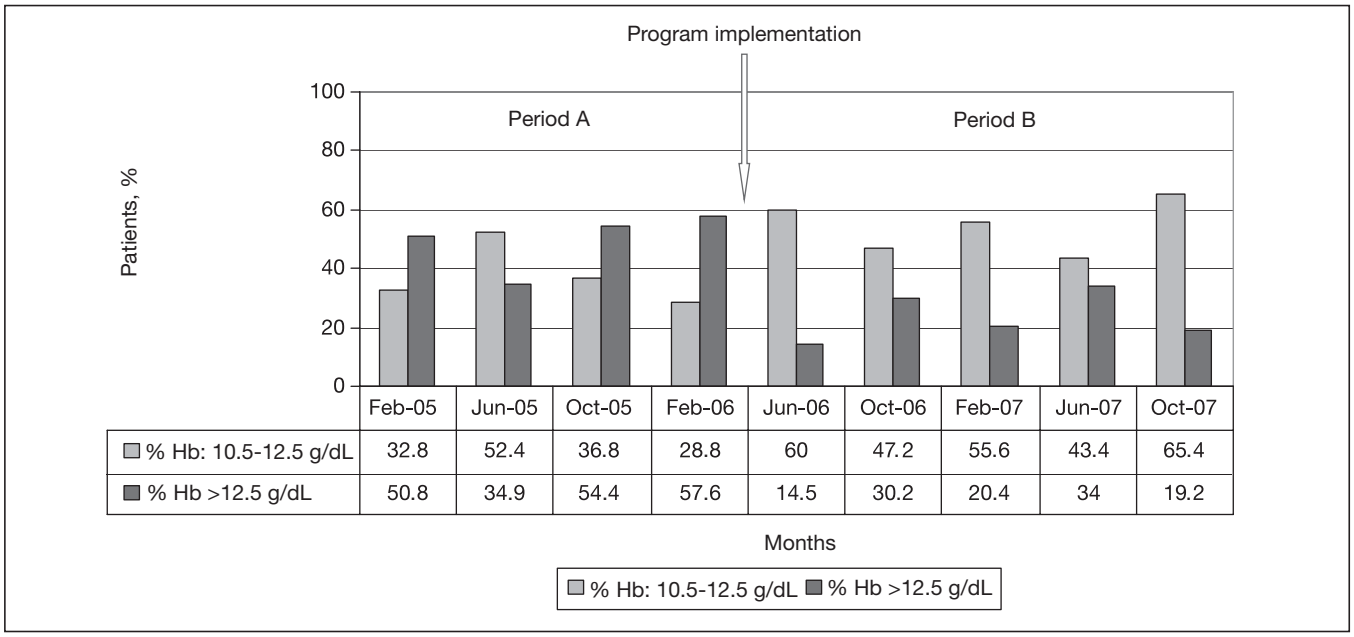

Figure 1. *Evolution of the proportion of patients with haemoglobin (Hb) values within the optimal target range (10.5–12.5 g/dL) and above the safety limit (12.5 g/dL) in periods A and B.*

In Figure 2 the evolution of the average weekly dose of ESF is shown in periods A and B, for erythropoietin-β (above) and darbepoetin-α (below). The difference in doses between both periods is illustrated in Table 5.

DISCUSSION

The potential complications of renal anaemia in patients with CRD and the variability observed in their treatment reveal the opportunities to improve pharmacotherapy with ESF and the safety of these patients. The results obtained with this study demonstrate how using an interdisciplinary follow-up programme that confirms and adapts the recommendations of scientific societies and regulating agencies to the healthcare environment, the general guidelines are established for the individualisation of treatment with ESF, in order to obtain maximum benefits and reduce risks for patients with CRD in haemodialysis.

However, there is still a good amount of controversy regarding the optimal target range Hb values and, especially, the maximum

Table 4. Comparison of the quality indicators of the pharmacotherapy and safety of patients with chronic renal disease treated with erythropoiesis-stimulating factors in periods A and B

Indicator	Initial result	Final Result	Comparison
Proportion of patients (95% CI) with Hb in the target range (10.5-12.5 g/dl)[a]	28.8 (16.8-40.4)	65.4 (52.4-78.4)	DP: 36.6% (95% CI, 22.0-51.1) RR: 2.27 (95% CI, 1.56-3.30)
Proportion of patients (95% CI) with Hb above the safety limit (≥12.5 g/dL)[a]	57.6 (45.0-70.2)	19.2 (8.5-29.9)	DP: 38.4% (95% CI, 24.5-52.3) RR: 0.34 (95% CI, 0.20-0.55) ARR: 0.39 (95% CI, 0.19-0.55)
Percentage of average time (SD) and (95% CI) of follow-up with Hb in the target range (10.5-12.5 g/dL)[b]	41.0 (22.7) (33.6-48.5)	56.7 (23.3) (49.1-64.4)	DA: 15.7% (95% CI, 7.1-24.4)
Percentage of average time (SD) and (95% CI) of follow-up with Hb above safety limit (≥12.5 g/dL)[b]	52.1 (24.6) (44.1-60.0)	23.3 (23.4) (15.6-31.0)	DA: –26.9% (95% CI, –35.1 to –18.6)

ARR indicates absolute risk reduction; CI, confidence interval; DA, difference of averages; DP, difference of proportions; Hb, haemoglobin; RR, relative risk; SD, standard deviation.
[a]The initial result corresponds to the first month of period A and the 20th month of period B.
[b]The initial result corresponds to the entire period A (13 months) and the B result to the entire period B (20 months).

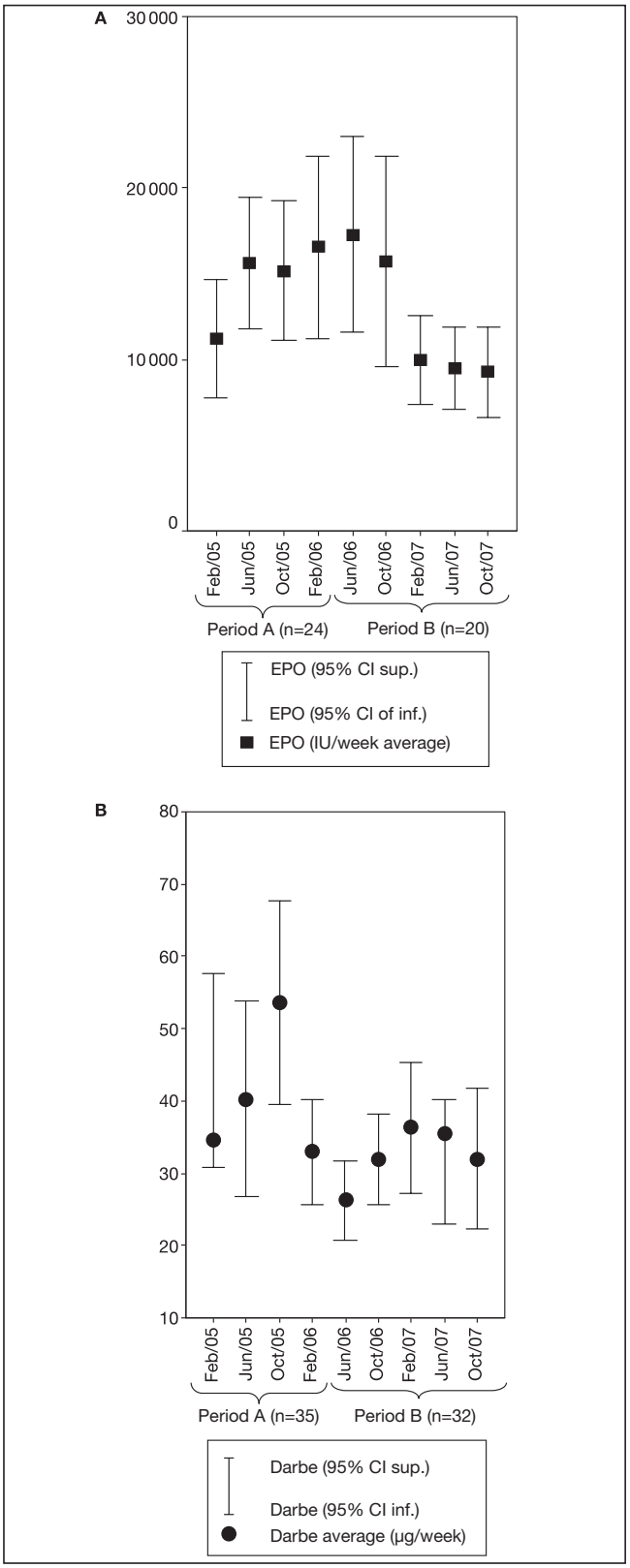

Figure 2. *Evolution of the average weekly dose of erythropoietin-β (EPO) (A) and darbepoetin-α (darbe) (B) during periods A and B. CI indicates confidence interval.*

safety limit that should not be surpassed. After the analysis of the available scientific evidence and the safety alerts issued by the medication regulating agencies, the interdisciplinary group agreed to establish the target Hb value range between 10.5-12.5 g/dL and the safety limit at 12.5 g/dL. Although the recommendations of the most representative scientific societies establish the target Hb range between 11.0-12.0 g/dL, this interval is considered to be excessively narrow given the intra-individual variability of Hb in these patients, which would have required a greater number of possibly unjustified dose changes from the clinical perspective. At the same time, considering the recommendation of the K-DOQI guides to not surpass 13 g/dL and the alerts issued by the FDA and the EMEA, that establish that the HB values should not surpass 12 g/dL, the PNT proposed considered the safety limit to be 12.5 g/dL.

The improvement in pharmacotherapy quality with ESF and patient safety has been evaluated using 2 types of indicators (Table 4): those that provide a specific measurement taken every 4 months during periods A and B—proportion of patients with Hb values within the target range and above the safety limit—and those that consider the entire follow-up period of the patients—average time (%) of follow-up where patients presented stable Hb values within the target range and outside of the safety limit during all of periods A and B—. Therefore, this last indicator take into account not only the isolated Hb values but also their intra-individual variability and, thus, the percentage of time that the patients presented Hb values within the effective and safe ranges, which may have a greater impact on the associated risks, for therapeutic failure as well as for the toxicity of the ESF. With both types of indicators, an improvement in pharmacotherapy and patient safety were confirmed for patients treated with ESF.

Indeed, as observed in Figure 1, before the programme, between 28.8% and 52.4% of the patients presented Hb values in the target range, while after the implementation of the programme, these proportions were increased to values between 43.4% and 65.4%: for the safety limit, before the programme, 34.9% to 57.6% of the patients had higher Hb values and afterwards, this proportion was reduced to values between 19.2% and 34.0%. The differences obtained in these proportions oscillated according to the months in question, but the tendencies remained stable confirming (Table 4) the fact that the percentage of patients that reached Hb values in the target range were almost doubled, and the average percentage of time within this range increased 15.7% (95% CI, 7.1-24.4).

On the other hand, the impact of the programme on the improvement of patient safety was greater, as an RAR was obtained that presented Hb values above the recommended limit of 0.39 (95% CI, 0.19-0.55). In this regard, the number of patients to be included in the programme to avoid one presenting Hb values that could potentially affect their safety was between 2 and 3 (NNT=2.6; 95% CI, –35.1 to –18.6) in the average time that the patients presented Hb values above the safety limit potentially associated with the risk of cardiovascular morbidity.

As a secondary variable, the difference in the ESF doses used by patients in periods A and B was also compared, and it was

Table 5. Difference of average weekly dose of erythropoiesis-stimulating factors in periods A and B

	ESF	Period A	Period B	Statistical significance
Dose[a]	Erythropoetin-β, IU/week	15 215.0 (8832.1) (14 199.5-16 230.5)	13 429.7 (10 420.7) (12 384.1-14 475.3)	*P*=.019
	Darbepoetin-α, µg/week	44.7 (38.8) (44.9-48.5)	31.8 (21.9) (30.1-33.6)	*P*=.001

ESF indicates erythropoiesis-stimulating factors.
*Average (standard deviation) (95% confidence interval).
*Media ± desviación estándar (intervalo de confianza del 95%).

confirmed that the improvement of the quality and safety indicators of pharmacotherapy with ESF was accompanied by a reduction of the average doses, of both erythropoietin-β (28.9%) (Table 5), with a corresponding reduction in treatment costs. Although the economic evaluation exceeds the objectives defined in this study, the results obtained may act as a first step to establish a cost-effective or cost-benefit relationship for interdisciplinary programs to improve pharmacotherapy quality in these patients.

The effectiveness of the different algorithms proposed for the treatment of renal anaemia to reach the objectives established in clinical guides is difficult to evaluate, given the limited availability of clinical results obtained with their use. Also, it is difficult to compare them with other authors, fundamentally because of their variability in the in the Hb target range and in the safety limit established, as well as the successive changes that have been produced in the last few years. A study with a similar focus, obtained a significant increase of the percentage of patients with optimal Hb values (Hb >11 g/dL) from the initial 42.2% to 60% after 21 months of follow-up. Another recent study evaluates the use of ESF during 9 months in 40 patients, obtaining 46% of the patients with determinations of Hb within the target range (Hb: 11-13.5 g/dL for patients under 60 years of age and 11-12 g/dL for patients over 60 years of age or patients with a history of cardiovascular diseases). In observational studies, the wide variety of how to handle renal anaemia has been revealed in patients in haemodialysis, as the proportion of patients with Hb <11 g/dL is found, according to different countries, among 23% to 77% and the proportion of patients with Hb >11 g/dL varies between 19% and 76%, and the data that is relevant to Spain are 31%-67%, respectively, although without establishing a maximum limit for the recommended Hb values.

An important limitation to this study is the derivation of the use of Hb values as a principal result variable, as a subrogated indicator of cardiovascular risk, as well as for the potential benefits of treatment with ESF. However, it is widely accepted that renal anaemia is a morbidity risk factor—for each gram lower in the Hb values, the risk increases for left ventricular hypertrophy (6%), cardiac dilatation (46%), and death (14%)—and diverse studies suggest that an increase in the risk of adverse cardiovascular episodes, including death, with Hb values above the limit yet to be permanently established, but could still be located between 12.0 and 14.0 g/dL. The measurement of cardiovascular episodes would have required a much larger sample size and, above all, a much longer follow-up period, which exceeds the possibilities of a healthcare programme to improve pharmacotherapy quality. At the same time, diverse studies and clinical guides recognise the potential benefits of treatment with ESF in patients with CRD in terms of improving the quality of life of these patients, to create a greater tolerance to exercise and to avoid blood transfusions.

To conclude, the implementation of a programme to improve pharmacotherapy quality with erythropoiesis-stimulating agents in patients with CRD in haemodialysis significantly increases the proportion of patients with haemoglobin levels within the recommended ranges of effectiveness and safety. Also, this improvement is obtained with a reduction in the average monthly doses per patient, and, consequently, a lower treatment cost. Fundamentally, the greatest benefit of the program is demonstrated in the significant reduction of the risk of patients to present Hb values above the recommended safety limits to prevent cardiovascular morbidity and mortality.

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