BENEFICIAL DOSE CONVERSION FROM OTHER ERYTHROPOIESIS STIMULATING AGENTS TO C.E.R.A. IN HAEMODIALYSIS AND NOT ON DIALYSIS PATIENTS WITH ANAEMIA SECONDARY TO CHRONIC KIDNEY DISEASE IN CLINICAL PRACTICE: MINERVA STUDY

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INTRODUCTION

- Methoxy polyethylene glycol-epoetin beta is a first continuous erythropoietin receptor activator (C.E.R.A.) indicated for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD).
- The efficacy of once monthly C.E.R.A. for correction of anaemia[1-4] and maintenance of stable haemoglobin (Hb) levels in CKD patients have been demonstrated in several studies, most of them performed in haemodialysis patients[5-8].
- To date, the shift from other ESAs to C.E.R.A. has not been performed by using a specific conversion factor but according to the previous erythropoiesis-stimulating agents (ESA) dose categories suggested in the conversion schedule recommended by the Summary of Product Characteristics (SPC). However, it is unknown whether this dosage schedule reflects dosing strategies adopted for haemodialysis and not on dialysis patients in routine clinical practice.

OBJECTIVE

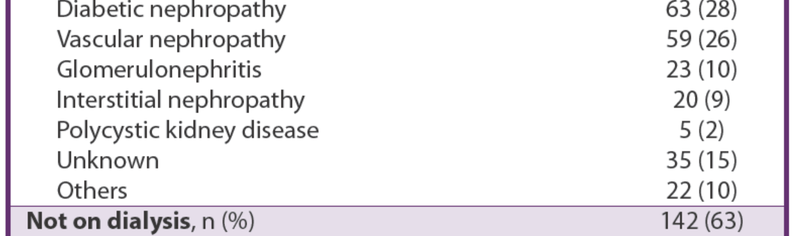
- The MINERVA study was undertaken to assess whether the correction dose was adequate, and to characterize the conversion schedule from other ESAs to C.E.R.A. used in both dialysis and not on dialysis anemic CKD patients in routine clinical practice.

METHODS

DESIGN

- This was an observational, prospective and multicenter study conducted in 13 Spanish Renal Units. Patients were followed up for one year after inclusion (baseline). Patient data collection was obtained from monthly visits in haemodialysis patients and every two months in patients not on dialysis (Figure 1). Efficacy data at baseline, month 6, and month 12 are presented.

Figure 1. Study design



PATIENTS

Inclusion criteria

- Adult anaemic CKD patients on haemodialysis and not on dialysis (stages 3-5).
- At the time of study initiation (baseline visit), patients should have received at least one dose of C.E.R.A.
- Written informed consent from all patients.

Exclusion criteria

- Renal transplant patients or peritoneal dialysis patients.

RESULTS

PATIENTS' CHARACTERISTICS

- A total of 227 patients were evaluated. Patients' baseline characteristics are detailed in **Table 1**.

Table 1. Patients' characteristics at baseline visit (N=227)

Characteristics	Value
Age, median (range), years	76 (64-81)
Male, n (%)	126 (56)
BMI, mean ± SD, kg/m²	27.1 ± 5.1
eGFR*, mean ± SD, mL/min/1.73m² (CKD not on dialysis)	24.7 ± 9.6
Etiology of CKD†, n (%)	
Diabetic nephropathy	63 (28)
Vascular nephropathy	59 (26)
Glomerulonephritis	23 (10)
Interstitial nephropathy	20 (9)
Polycystic kidney disease	5 (2)
Unknown	35 (15)
Others	22 (10)
Not on dialysis, n (%)	142 (63)
ESA-naïve	31 (22)
Converting from other ESA	111 (78)
Haemodialysis, n (%)	85 (37)
ESA-naïve	2 (2)
Converting from other ESA	83 (98)

*eGFR, estimated glomerular filtration rate in not on dialysis patients -by the MDRD-4 formula; †Multiple-choice variable; SD, standard deviation; BMI, body mass index; CKD, chronic kidney disease; ESA: Erythropoiesis stimulating agents.

- At the beginning of the study, a total of 120 patients had converted from other ESAs: 63 (53%) patients were not on dialysis and 57 (47%) on haemodialysis. Types of ESAs and mean doses received prior to C.E.R.A. initiation are detailed in **Table 2**.

Table 2. Previous ESA treatment (N=120)

ESA	n (%)	Dose (mean ± SD)
Not on dialysis		
Epoetin beta	51 (81)	5,292.5 ± 5,989.3*
Darbepoetin alfa	12 (19)	38.8 ± 32.4†
Haemodialysis		
Epoetin beta	38 (66)	8,574.6 ± 6,083.3*
Darbepoetin alfa	19 (33)	28.7 ± 33.1†

*IU/week; †mcg/week. ESA, erythropoiesis-stimulating agents; SD, standard deviation.

RESULTS

TREATMENT WITH C.E.R.A.

Naïve patients

- Naïve patients not on dialysis had been under C.E.R.A. treatment for a mean time of 1.7 ± 0.7 months when the study was initiated. The **initial mean dose of** C.E.R.A. was not significantly different from the recommended starting dose by the **SPC**. The **median C.E.R.A. dose** was maintained stable throughout the **12-month period**, without significant changes from that recommended (**Table 3**).

Table 3. Mean doses of C.E.R.A. in naïve patients

	Real doses (µg/kg/month)		Dose per SPC (µg/kg/month)	p-value (mean dose vs. SPC)
	Mean ± SD	Median (range)		
Baseline	1.19 ± 0.49	1.14 (0.86-1.54)	1.2	0.906
12-month follow-up	1.19 ± 0.49	1.12 (0.86-1.44)	1.2	0.914

Patients switched from other ESAs

- Patients switched from other ESAs had been under C.E.R.A. treatment for 7.0 ± 5.4 months at the study initiation. Both haemodialysis and not on dialysis patients received **lower starting C.E.R.A. doses** at switching than those recommended by the SPC according to the previous ESA dose categories. **Dose conversion factors** estimated were more favourable to C.E.R.A. at higher doses of previous ESA in both dialysis and not on dialysis patients (**Tables 4A y 5A**).
- The **mean C.E.R.A. dose** administered during the **12-month follow-up** did not significantly vary from the dose at conversion neither in haemodialysis patients nor in those patients not on dialysis (**Tables 4B y 5B**).

Table 4. C.E.R.A. dosing schedule according to the previous ESA dose category in CKD not on dialysis patients

A

Previous darbepoetin alfa dose (µg/week)	Previous epoetin beta dose (IU/week)	C.E.R.A. dose (µg/month) SPC	MINERVA Study		
			Conversion factor (95% CI)	C.E.R.A. dose at conversion (µg/month) (mean ± SD)	p-value vs. SPC
<20	<4000	120	28.4 (24.3-32.4)	72.5 ± 16.5	<0.001
20-40	4000-<8000	120	46.9 (37.0-56.7)	100.0 ± 46.3	0.116
40-80	8000-16000	200	67.4 (52.0-82.8)	143.7 ± 64.7	<0.01
>80	>16000	360	80.0 (0-166.1)	300.0 ± 173.2	0.609

B

Previous darbepoetin alfa dose (µg/week)	Previous epoetin beta dose (IU/week)	Mean dose study follow-up (µg/month) (mean ± SD)	p-value vs. dose at conversion
<20	<4000	82.3 ± 33.7	0.211
20-40	4000-<8000	117.0 ± 66.1	0.152
40-80	8000-16000	143.7 ± 65.9	0.625
>80	>16000	328.3 ± 215.8	0.285

SD, standard deviation; SPC, summary of product characteristics.

Table 5. C.E.R.A. dosing schedule according to the previous ESA dose category in haemodialysis patients

A

Previous darbepoetin alfa dose (µg/week)	Previous epoetin beta dose (IU/week)	C.E.R.A. dose (µg/month) SPC	MINERVA Study		
			Conversion factor (95% CI)	C.E.R.A. dose at conversion (µg/month) (mean ± SD)	p-value vs. SPC
<40	<8000	120	25.3 (19.1-31.5)	104.1±39.1	0.180
40-80	8000-16000	200	56.9 (43.8-70.1)	155.0±66.2	<0.01
>80	>16000	360	95.1 (37.4-152.7)	195.8±71.4	<0.005

B

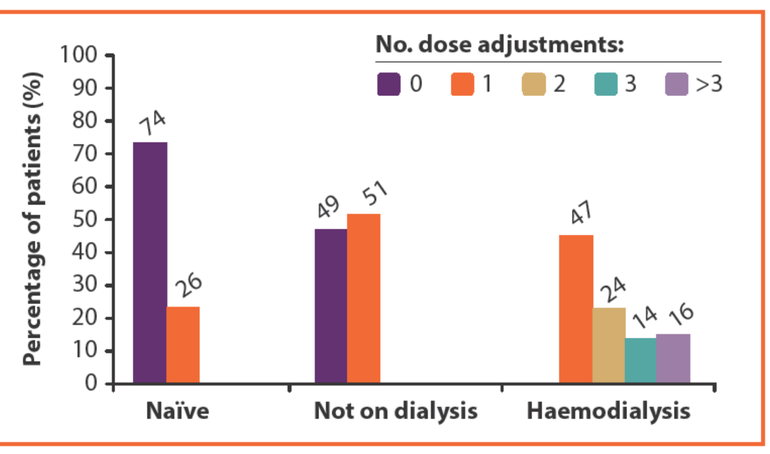
Previous darbepoetin alfa dose (µg/week)	Previous epoetin beta dose (IU/week)	Mean dose study follow-up (µg/month) (mean ± SD)	p-value vs. dose at conversion
<40	<8000	128.2±79.44	<0.05
40-80	8000-16000	179.0±83.5	0.078
>80	>16000	133.2±98.8	0.116

SD, standard deviation; SPC, summary of product characteristics.

C.E.R.A. dose modifications

- Twenty-three (74%) **naïve patients** did not require any dosage adjustment. Among **patients switched from other ESA**, 49% of patients not on dialysis did not needed any dosage modification while 85% of haemodialysis patients required at least one dose adjustment, with a mean of 2.2 ± 1.5 dose changes. Distribution of patients according to the number of dose adjustments of C.E.R.A. is shown in **Figure 2**.

Figure 2. Distribution of patients according to the number of dose adjustments of C.E.R.A. during the follow-up period



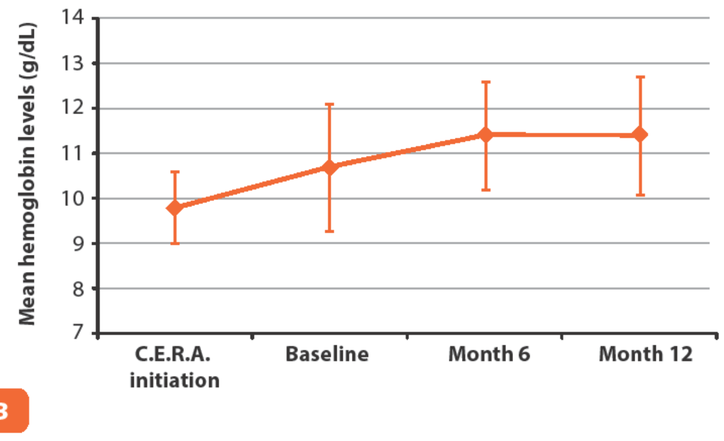
EFFECTIVENESS OF C.E.R.A.

- **ESA-naïve patients** experienced a gradual increase in Hb levels from initiation of C.E.R.A. therapy to month 12 (**Figure 3A**) with 76% and 57% of patients reaching the Hb target range (11-13 g/dL) at months 6 and 12 (**Figure 4**).
- Mean Hb concentration and the proportion of patients with Hb levels within the target range were maintained stable without significant changes during the 12-month follow-up period in **patients switched from other ESAs** both on haemodialysis and not on dialysis (**Figure 3B and Figure 4**).

Figure 3. Evolution of haemoglobin levels and C.E.R.A. doses during the follow-up period in naïve patients (A) and those switched from other ESAs (haemodialysis and not on dialysis) (B)

A

C.E.R.A. dose (µg/month), mean ± SD			
C.E.R.A. initiation	Baseline	Month 6	Month 12
82.4 ± 31.6	82.4 ± 31.6	106.8 ± 62.5	104.1 ± 77.8



B

C.E.R.A. dose (µg/month), mean ± SD			
	Baseline	Month 6	Month 12
Not on dialysis	99.0 ± 60.7	99.5 ± 82.5	92.8 ± 93.8
Haemodialysis	171.4 ± 106.6	173.5 ± 104.8	167.3 ± 114.6

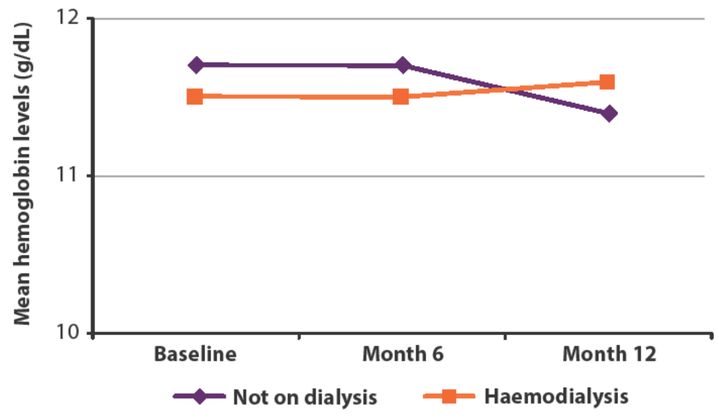
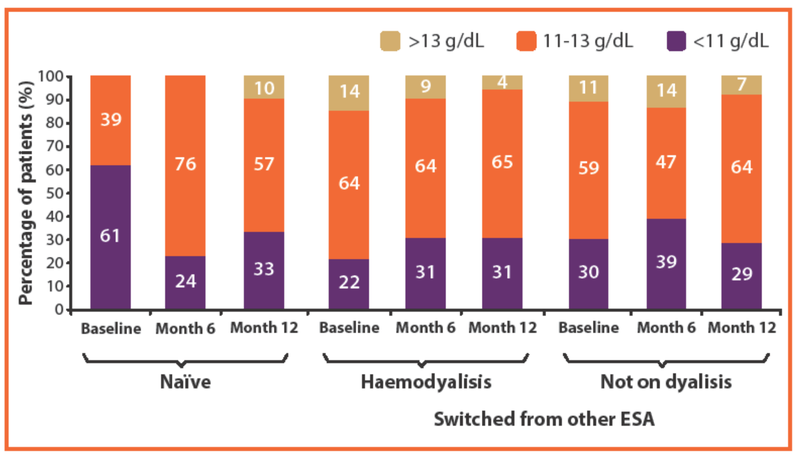


Figure 4. Distribution of patients with haemoglobin levels within the target range during the follow-up period



SAFETY

- No C.E.R.A.-related adverse events were reported during the study period.

CONCLUSIONS

- The recommended monthly dose of C.E.R.A. for ESA-naïve CKD patients seems to be adequate for correction and maintenance of stable haemoglobin levels in routine clinical practice.
- However, conversion from a previous shorter-acting ESA requires lower doses of C.E.R.A. than those recommended by the SPC, particularly when higher doses of previous ESAs are required. Thus, conversion to C.E.R.A. allows achieving Hb levels with lower doses of ESA, in agreement with guidelines' indications, which have clinical and economic implications.

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