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Anaemia management with C.E.R.A. in routine clinical practice: OCEANE (Cohorte Mircera patients non-dialysés), a national, multicenter, longitudinal, observational prospective study, in patients with chronic kidney disease not on dialysis

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ABSTRACT

Objective: The aim of this study was to describe the management of anaemia with a continuous erythropoietin receptor activator (C.E.R.A., methoxy polyethylene glycol epoetin-β), in patients with chronic kidney disease (CKD) not on dialysis, naïve or non-naïve to treatment with erythropoiesis-stimulating agents (ESAs) at inclusion.

Design: National, multicentre, longitudinal, observational prospective study.

Setting: 133 nephrologists practicing in France selected patients during their routine follow-up visits. The study was non-interventional.

Participants: They were adult CKD patients not on dialysis or kidney transplant patients, naïve or not to ESA treatment: 524 patients not on dialysis (48% ESA-naïve) and 92 kidney transplant patients (24% ESA-naïve) were included and followed up every 3 months during 1 year.

Outcome measures: The two main endpoints were the percentage of patients who achieved target haemoglobin (Hb) levels as per European Medicines Agency guidelines (10–12 g/dl) around 6 months of treatment and modalities of treatment.

Results: Approximately one in two patients had an Hb level within 10–12 g/dl at baseline, and around 6 and 12 months of treatment. Ninety per cent of ESA-naïve patients achieved at least +1 g/dl increase over baseline Hb levels or had Hb within 10–12 g/dl around 6 and 12 months. The Hb level remained at approximately 11.5 g/dl during the 12 months of follow-up. Around 6 months: almost all patients were receiving a once-monthly subcutaneous dose of C.E.R.A. (patients not on dialysis: 95±54 µg; kidney transplant patients: 121±70 µg); approximately half the patients did not require a change in C.E.R.A. dose. Adverse effects related to C.E.R.A. were observed in less than 5% of patients and led to modification or discontinuation of treatment in 2%.

ARTICLE SUMMARY

Article focus

- This pharmaco-epidemiological non-interventional study was initiated in France in 2009 at the request of the French National Authority for Health (Haute Autorité de Santé, or HAS), 9 months after a continuous erythropoietin receptor activator (C.E.R.A.) was first licensed in France.
- We aimed to provide an overview of anaemia management with C.E.R.A. in patients with chronic kidney failure (CKD) not on dialysis, with or without previous kidney transplantation.
- A cohort was created to evaluate the proportion of patients with Hb levels at the 2007 European Medicine Agency target (10–12 g/dl) in routine practice.

Key messages

- The efficacy and safety of C.E.R.A. in anaemia management were confirmed in CKD patients not on dialysis, with or without previous kidney transplantation.
- The gap between European guidelines and routine practices of anaemia management of non-dialysis CKD patients still existed in 2009.
- We highlighted the importance of personalised anaemia management based on the patient's profile.

Strengths and limitations of this study

- A major strength of our study is its design (real life).
- The representativeness of the cohort is difficult to evaluate since there are no recent epidemiological data for patients not on dialysis.
- The C.E.R.A. doses used in this study were different from those in the product labelling (starting dose lower than that recommended in the Summary of Product Characteristics).

Conclusions: The efficacy and safety of C.E.R.A. in CKD patients not on dialysis, with or without kidney transplantation, were confirmed in routine clinical practice.

INTRODUCTION

Despite the introduction of erythropoiesis-stimulating agents (ESA), anaemia management in chronic kidney disease (CKD) remains a complex situation for nephrologists. All the randomised clinical trials that attempted to demonstrate the benefits of normalising haemoglobin (Hb) levels in CKD patients not on dialysis gave negative results, leading to frequent revisions of the guidelines for anaemia management.[1–4] In 2005, Afssaps recommended a target Hb level within 11–13 g/dl;[5] since 2007, the European Medicine Agency (EMA) has recommended a range 10–12 g/dl,[1] and since 2009, the European Renal Best Practice (ERBP) guidelines recommend a range 11–12 g/dl without intentionally exceeding 13 g/dl.[2] ERBP also acknowledges the difficulty of maintaining patients in a narrow target window because of Hb variability. It notes that nephrologists must accept that Hb excursions above and below the target will occur from time to time.[2 3] These frequent changes, together with the multitude of reference data and the lack of harmony between different guidelines, create confusion and make it difficult for the clinician to adhere to the guidelines.

Another major difficulty for nephrologists arises from the occurrence of intercurrent events, presence of numerous comorbidities and main ESA-resistance factors (such as iron deficiency) in CKD patients.[2 4 6] Large clinical trials have highlighted the existence of patients who respond poorly to ESA therapy as well as higher risk populations such as diabetics, with or without prior stroke, cancer patients and those with ischaemic heart disease.[2 7 8] The use of high ESA doses, which is generally necessary for patients who respond poorly or not at all, has been associated with adverse cardiovascular events. As a result, nephrologists must tailor ESA therapy to the patient's profile by using the smallest possible dose to control anaemia symptoms and achieve Hb target level. They must also jointly and adroitly manage both iron supplementation and ESA therapy, all while ensuring treatment adherence in patients who self-administer their ESA. Frequent revisions of guidelines, modifications of ESA's Summary of Product Characteristics (SPC) and concerns about the safety of ESAs raised by major clinical trials are gradually modifying practices. However, the improvement in anaemia management has remained quite modest. The proportion of non-dialysis CKD patients with an Hb level within 10–12 g/dl increased from 59% to 63% between 2005 and 2009 in the USA.[9]

At the same time, trends in anaemia management are oriented towards simplifying treatment by allowing a longer interval between doses.[10] Methoxy polyethylene glycol-epoetin-β (MIRCERA; F. Hoffmann-La Roche, Basel, Switzerland) is a continuous erythropoietin receptor activator (C.E.R.A.) with a long half-life allowing once-monthly dosing.[10 11] Its efficacy and safety have been demonstrated in clinical trials in patients not on dialysis[12–17] and in kidney transplant patients.[18]

The OCEANE (*C*ohorte Mir*cera* patients *n*on dialysé*e*s) study was initiated in 2009 with the aim of describing anaemia management with C.E.R.A. in CKD patients not on dialysis and in kidney transplant patients in France. This pharmaco-epidemiological study was carried out in conditions of routine clinical practice. Nine months after C.E.R.A. was licensed in France, a cohort was created to evaluate the proportion of patients with Hb levels at the 2007 EMA target, and to describe the practical aspects of anaemia management with C.E.R.A., with a starting hypothesis that 50% of patients would achieve this target after 6 months of treatment, in agreement with current epidemiological data,[9] and considering that clinicians were in the learning curve for this new drug.

PATIENTS AND METHODS

OCEANE was a national, multicenter, longitudinal, observational study in a cohort of patients with CKD not on dialysis initiating C.E.R.A. treatment in the correction or maintenance phase. This study took place between May 2009 and January 2011. Each patient was followed for a maximum of 12 months.

Screening of participating physicians

The physicians were selected from an exhaustive list of 800 specialists practicing in France who manage CKD patients, as identified by an independent company. We retained all specialists who were involved in the management of CKD patients not on dialysis, potential prescribers of C.E.R.A. and those interested in participating in the study.

Screening of patients

As the study was non-interventional and conducted therefore in respect of the physician's usual medical practices, patients fulfilling inclusion criteria were selected during their routine follow-up visits. Each physician had to include a maximum of 10 consecutive patients.

Patients meeting the following inclusion criteria were to be included in the study: adult CKD patients not on dialysis (with or without previous kidney transplantation), naïve or not to ESA treatment and for whom the physician has decided to initiate a C.E.R.A. treatment at the inclusion visit. Patients participating in another clinical study at the time of inclusion were not included.

Data collection

Medical history and patient characteristics were collected at baseline along with the following data at baseline and

approximately every 3 months during the 12-month study period: characteristics of C.E.R.A. treatment (route of administration, dose, dosing schedule, any treatment changes during the study), concomitant treatments, Hb levels, adverse effects and reasons for premature study withdrawal.

Ethics statement

The study was conducted in accordance with ethical guidelines and good epidemiological practices established by the Association Des Epidémiologistes de Langue Française.[19] No French ethics committee oversight was required as the design of the study was strictly observational.[20]

According to the French regulations concerning observational studies,[20] each patient was fully informed orally and in writing about the aim and the course of the study and had to raise no objection to data collection. A patient's written consent was not therefore necessary for this kind of study based on the strict respect of usual medical practice and physician–patient relationship.

Anonymity was guaranteed. Data processing was under the modified law of 6 January 1978 relating to the protection of data subjects regarding the processing of personal data.

Statistical analyses

As the main endpoint was the percentage of patients with an Hb level within 10–12 g/dl (as per 2007 EMA guidelines) around 6 months of C.E.R.A. treatment, the sample size determination was based on estimation of a proportion. On the basis of previous studies and the fact that this study described routine clinical practice, the percentage of patients with Hb levels in the 10–12 g/dl target range was estimated at 50% around 6 months of C.E.R.A. treatment. With a relative precision of 9% and α risk of 5% (Type I Error), the sample size was calculated at 500 patients, allowing for 5% of non-evaluable patients.

Therapeutic modalities for treating anaemia (dose, route of administration, conditions of administration) until the follow-up visit around 6 months were also part of the main endpoint.

Secondary endpoints were the percentage of patients with Hb levels within 10–12 g/dl around 12 months of C.E.R.A. treatment, change in Hb levels, haematocrit and laboratory parameters used to monitor anaemia and CKD and tolerability of C.E.R.A.

Statistical analyses were carried out with SAS software (release V.9.1.3), and were only descriptive. Two subgroups were studied: patients not on dialysis and kidney transplant patients. Each subgroup was further divided into patients ESA-naïve at baseline and patients currently treated with an ESA before initiation of C.E.R.A. An adjusted χ^2 test was used to compare the characteristics of nephrologists who enrolled patients with those of the general nephrologist population. The α risk was set at 5% for a two-sided situation to calculate CIs and for the χ^2 test.

RESULTS

Nephrologist data

Of 328 nephrologists who gave their provisional agreement to participate in the study, 197 confirmed their participation in writing. Finally, 133 nephrologists enrolled at least one patient, and they were representative of the general nephrologist population with the exception of gender ($p<0.05$) and geographical location ($p<0.05$). In comparison with the general nephrologist population, there was a larger proportion of men (79% vs 68%), fewer practiced in Ile de France (10% vs 17%) and more practiced in northeast France (33% vs 23%).

Description of cohort

Altogether, 616 patients were analysed: 524 patients not on dialysis (85%) and 92 kidney transplant patients (15%). Premature study withdrawals occurred in 25% of patients not on dialysis (n=134) and 21% of kidney transplant patients (n=19) for the following reasons (there could be several reasons for one patient): conversion to dialysis (46% of all reasons), death (22%), definitive discontinuation of treatment (13%), lost to follow-up (8.5%), patient moved or changed medical team (6.5%), others (6%), patient no longer wanted to participate in the study (4%), adverse events (3%) and kidney transplantation (2%).

Patients not on dialysis

Among the 524 patients not on dialysis, 253 (48%) were ESA-naïve at baseline. Baseline characteristics are shown in table 1. At baseline, 82% of patients had at least one comorbidity or cardiovascular risk factor other than hypertension (table 1). Almost all the patients (90%) had hypertension and were on antihypertensive therapy, often with two or three different drugs (57%). Angiotensin II receptor antagonists (ARAII) were prescribed in 45% of these patients and ACEIs in 32%. A minority received a blood transfusion in the 3 months preceding initiation of C.E.R.A. (ESA-naïve 5%; ESA-treated 2%).

Kidney transplant patients

Among the 92 transplant patients, 22 (24%) were ESA-naïve at baseline. Baseline characteristics are shown in table 1. At baseline, 77% of patients had at least one comorbidity or cardiovascular risk factor other than hypertension (table 1). Almost all the patients (96%) had hypertension and were on antihypertensive therapy, often with two or three different drugs (62%). ARAII were prescribed in 47% of these patients and ACEIs in 43%. All were receiving immunosuppressive therapy, the majority (87%) with two or three drugs. The most commonly used immunosuppressive drugs were mycophenolic acid (75%), cyclosporine (48%), tacrolimus (41%), sirolimus (11%), azathioprine (5%). Twenty-five per cent of patients were on corticosteroids. Two transplant patients (one ESA-naïve; one ESA-treated) had received a blood transfusion in the 3 months preceding initiation

Table 1 Characteristics of patients at baseline

	Patients not on dialysis (n=524)			Kidney transplant patients (n=92)		
	Initial ESA treatment			Initial ESA treatment		
	Naïve (n=253)	ESA-treated (n=471)	Total (n=524)	Naïve (n=22)	ESA-treated (n=70)	Total (n=92)
Age (years)*	71.1±14.5	72.1±13.4	71.6±13.9	58.8±10.2	50.5±13.9	52.5±13.5
Men (n (%))	131 (51.8)	146 (53.9)	277 (52.9)	10 (45.5)	30 (42.9)	40 (43.5)
BMI* (kg/m^2)	26.8±5.4	26.9±5.7	26.9±5.6	25.6±5.2	24.5±4.2	24.7±4.5
SBP* (mm Hg)	137.6±17.4	137.7±20.1	137.6±18.8	140.7±12.8	138.6±15.8	139.1±15.1
DBP* (mm Hg)	74.2±10.4	75.3±10.6	74.7±10.5	77.6±11.5	77.3±10.9	77.3±11.0
Duration of CKD* (years)	3.6±5.3	4.7±4.7	4.2±5.0	19.2±12.3	15.7±10.6	16.6±11.1
Cause of CKD† (n (%))						
Vascular nephropathy	120 (47.4)	122 (45.0)	242 (46.2)	2 (9.5)	9 (12.9)	11 (12.1)
Diabetic nephropathy	71 (28.1)	69 (25.5)	140 (26.7)	1 (4.8	3 (4.3	4 (4.4)
Glomerular nephropathy	27 (10.7)	30 (11.1)	57 (10.9)	7 (33.3)	28 (40.0)	35 (38.5)
Interstitial nephritis	26 (10.3)	26 (9.6)	52 (9.9)	4 (19.0)	7 (10.0)	11 (12.1)
Hereditary nephropathy	14 (5.5)	15 (5.5)	29 (5.5)	5 (23.8)	11 (15.7	16 (17.6)
Not defined	24 (9.5)	32 (11.8)	56 (10.7)	1 (4.8)	8 (11.4)	9 (9.9)
Other causes	13 (5.1)	21 (7.7)	34 (6.5)	2 (9.5)	5 (7.1)	7 (7.7)
CKD stage‡,§ (n (%))						
Stage 1	0	1 (0.4)	1 (0.2)	0	0	0
Stage 2	2 (0.8)	2 (0.8)	4 (0.8)	0	3 (4.3)	3 (3.3)
Stage 3	71 (29.6)	74 (28.0)	145 (28.8)	15 (71.4)	30 (43.5)	45 (50.0)
Stage 4	133 (55.4)	143 (54.2)	276 (54.8)	5 (23.8)	34 (49.3)	39 (43.3)
Stage 5	34 (14.2)	44 (16.7)	78 (15.5)	1 (4.8)	2 (2.9)	3 (3.3)
Cardiovascular risk factors/comorbidities						
Hypertension	224 (88.5%)	248 (91.5%)	472 (90.1%)	22 (100.0%)	66 (94.0%)	88 (95.7%)
Dyslipidaemia¶	140 (55.8%)	160 (60.4%)	300 (58.1%)	18 (81.8%)	44 (64.7%)	62 (68.9%)
Type 2 diabetes**	92 (37.6%)	109 (41.4%)	201 (39.6%)	1 (4.5%)	6 (8.6%)	7 (7.6%)
Myocardial infarction/angina††	56 (22.3%)	74 (27.4%)	130 (25.0%)	3 (13.6%)	7 (10.0%)	10 (10.9%)
Heart failure‡‡	56 (22.2%)	62 (23.0%)	118 (22.6%)	1 (4.5%)	1 (1.4%)	2 (2.2%)
Stenosis/thrombosis/aneurysm§§	49 (19.9%)	57 (21.2%)	106 (20.6%)	1 (5.3%)	9 (13.6%)	10 (11.8%)
Stroke¶¶	30 (12.0%)	26 (9.6%)	56 (10.7%)	1 (4.5%)	5 (7.1%)	6 (6.5%)
Hb*,*** (g/dl)	10.0±0.9	11.3±1.4	10.7±1.4	9.9±1.0	10.7±1.3	10.5±1.3
Hb (10–12) g/dl (n (%))	128 (51.6)	146 (54.3)	274 (53.0)	10 (45.5)	40 (57.1)	50 (54.3)
Hematocrit* (%)	30.5±2.8	34.5±4.4	32.6±4.2	30.7±3.6	33.4±4.7	32.8±4.5
Platelets* (10^3/mm^3)	248.1±75.2	247.2±92.8	247.6±85.0	246.8±73.0	249.0±74.8	248.5±74.0
Serum ferritin level* (ng/ml)	233.3±256.1	220.7±206.3	226.8±231.8	270.8±218.6	230.1±170.9	241.9±185.0
Transferrin saturation coefficient*,††† (%)	24.7±12.3	23.7±11.2	24.2±11.7	29.5±21.1	27.4±10.3	27.9±13.7
Adequate iron status‡‡‡,§§§ (n (%))	54 (46.6)	61 (45.2)	115 (45.8)	7 (63.6)	18 (58.1)	25 (59.5)
Serum creatinine* (µmol/l)	257.3±117.6	256.5±111.5	256.9±114.4	181.3±56.8	214.3±74.7	206.3±72.0

Continued

Table 1 Continued

	Patients not on dialysis (n=524)			Kidney transplant patients (n=92)		
	Initial ESA treatment			Initial ESA treatment		
	Naïve (n=253)	ESA-treated (n=471)	Total (n=524)	Naïve (n=22)	ESA-treated (n=70)	Total (n=92)
eGFR*,¶¶¶ (ml/min/1.73 m^2)	25.2±11.1	25.2±11.9	25.2±11.5	36.1±13.5	31.6±13.1	32.6±13.2
C reactive protein*, **** (mg/l)	10.9±15.0	10.3±16.4	10.6±15.7	9.7±12.4	7.8±10.8	8.2±11.1
≤5 mg/l (n (%))	73 (51.0)	77 (54 0.6)	150 (53.0)	9 (60.0)	32 (68.1)	41 (66.1)
(5–10) mg/l (n (%))	34 (23.8)	29 (20.6)	63 (22.2)	3 (20.0)	5 (10.6)	8 (12.9)
(10–20) mg/l (n (%))	14 (9.8)	17 (12.1)	31 (10.9)	0	4 (8.5)	4 (6.5)
(20–30) mg/l (n (%))	7 (4.9)	8 (5.7)	15 (5.3)	2 (13.3)	3 (6.4)	5 (8.1)
>30 mg/l (n (%))	15 (10.5)	10 (7.1)	25 (8.8)	1 (6.7)	3 (6.4)	4 (6.5)
Folate deficiency†††† (n (%))	8 (12.9)	6 (11.3)	14 (12.2)	0	1 (5.9)	1 (3.4)
Vitamin B_{12} deficiency‡‡‡‡ (n (%))	5 (8.2)	2 (4.5)	7 (6.7)	0	1 (6.7)	1 (3.7)

*Mean±SD.
†One missing data for kidney transplant patients.
‡Stage 1 (GFR (90–120) ml/min/1.73 m^2), Stage 2 (GFR (60–90(ml/min/1.73 m^2), Stage 3 (GFR (30–60(ml/min/1.73 m^2), Stage 4 (GFR (15–30) ml/min/1.73 m^2), Stage 5 (GFR <15 ml/min/1.73 m^2).
§20 Missing data for non-dialysis patients and 2 missing data for kidney transplant patients.
¶Eight missing data for non-dialysis patients and two missing data for kidney transplant patients.
**16 Missing data for non-dialysis patients.
††Three missing data for non-dialysis patients.
‡‡Two missing data for non-dialysis patients.
§§Nine missing data for non-dialysis patients and seven missing data for kidney transplant patients.
¶¶Three missing data for non-dialysis patients.
***Seven missing data for non-dialysis patients.
†††Transferrin saturation coefficient.
‡‡‡Serum ferritin >100 ng/ml and TSAT >20%.
§§§273 Missing data for non-dialysis patients and 50 missing data for kidney transplant patients.
¶¶¶Estimation of glomerular filtration rate (Cockcroft and Gault formula).
****240 Missing data for non-dialysis patients and 30 missing data for kidney transplant patients.
††††409 Missing data for non-dialysis patients and 63 missing data for kidney transplant patients.
‡‡‡‡419 Missing data for non-dialysis patients and 65 missing data for kidney transplant patients.
BMI, body mass index; CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; TSAT, transferrine saturation; eGFR, estimated glomerular filtration rate.

of C.E.R.A. Laboratory parameters at baseline for patients not on dialysis and transplant patients are shown in table 1.

Anaemia management

Before initiation of C.E.R.A.

A total of 271 patients not on dialysis (52%) were already treated with an ESA for a median duration of 2 years (0–15). Among them, 129 (48%) were on darbepoetin-α, 106 (40%) on epoetin-β and 31 (12%) on epoetin-α by the subcutaneous route. For the 129 patients on darbepoetin-α, the dosing schedule was once a week for 34%, once every 2 weeks for 47% and once every 4 weeks for 16%. For the 106 patients on epoetin-β, the dosing schedule was 2–3 times a week for 12%, once a week for 55%, once every 2 weeks for 31% and once every 4 weeks for 2%. The median weekly dose was 20 µg (5–100) for darbepoetin-α and 4000 IU (500–20 000) for epoetin-β.

A total of 70 kidney transplant patients (76%) were already treated with an ESA for a median duration of 4 years (0–12). Among them, 33 (48%) were on darbepoetin-α, 32 (46%) on epoetin-β and 4 (6%) on epoetin-α by the subcutaneous route. For the 33 patients on darbepoetin-α, the dosing schedule was once a week for 32%, once every 2 weeks for 42% and once every 4 weeks for 23%. For the 32 patients on epoetin-β, the dosing schedule was 2–3 times a week for 23%, once a week for 52% and once every 2 weeks for 26%. The median weekly dose was 30 µg (5–150) for darbepoetin-α and 5000 IU (2000–20 000) for epoetin-β.

C.E.R.A. treatment

C.E.R.A. was administered at home by the subcutaneous route for almost all the patients (99%). The dosing schedule was once a month for 49% of ESA-naïve patients and 80% of ESA-treated patients (table 2). When treatment was given once a month, the starting

Table 2 Anaemia management during the study

	Patients not on dialysis (n=524)			Kidney transplant patients (n=92)		
	Initial ESA treatment			Initial ESA treatment		
	Naïve (n=253)	ESA-treated (n=271)	Total (n=524)	Naïve (n=22)	ESA-treated (n=70)	Total (n=92)
At baseline						
C.E.R.A.						
Dose schedule (n (%))						
Once a month	123 (48.6)	230 (84.9)	353 (67.4)	12 (54.5)	44 (62.9)	56 (60.9)
Once every 2 weeks	130 (51.4)	41 (15.1)	171 (32.6)	10 (45.5)	26 (37.1)	36 (39.1)
Initial monthly dose* (µg)	86.8±32.9	108.9±67.0	98.2±54.4	108.0±45.2	133.9±75.5	127.7±70.1
First injection given by†(n (%))						
Home nurse	217 (87.5)	209 (78.3)	426 (82.7)	10 (45.5)	15 (21.7)	25 (27.5)
Patient	23 (9.3)	46 (17.2)	69 (13.4)	11 (50.0)	48 (69.6)	59 (64.8)
Family member	8 (3.2)	12 (4.5)	20 (3.9)	1 (4.5)	6 (8.7)	7 (7.7)
Other treatments						
Iron (n (%))	114 (45.1)	90 (33.2)	204 (38.9)	11 (50.0)	31 (44.3)	42 (45.7)
Folic acid‡(n (%))	43 (17.1)	38 (14.0)	81 (15.5)	8 (36.4)	24 (34.3)	32 (34.8)
Vitamin B_{12}‡(n (%))	10 (4.0)	4 (1.5)	14 (2.7)	0	0	0
Around 6 months						
Number	175	208	383	18	50	68
C.E.R.A.						
Dose schedule (n (%))						
Once a month	143 (81.7)	188 (90.4)	331 (86.4)	14 (77.8)	41 (82.0)	55 (80.9)
Once every 2 weeks	29 (16.6)	19 (9.1)	48 (12.5)	4 (22.2)	9 (18.0)	13 (19.1)
Monthly dose*(µg)	87.5±50.9	113.4±77.7	101.5±68.0	94.7±47.8	135.4±81.0	124.6±75.5
During first 6 months						
Number	249	270	519	21	68	89
At least one dose adjustment (n (%))	143 (57.4)	132 (48.9)	275 (53.0)	8 (38.1)	39 (57.4)	47 (52.8)
Type of dose adjustment (n (%))						
Dose increase	55 (22.1)	57 (21.1)	112 (21.6)	4 (19.0)	15 (22.1)	19 (21.3)
Increase and decrease	19 (7.6)	17 (6.3)	36 (6.9)	0	8 (11.8)	8 (9.0)
Dose decrease	69 (27.7)	58 (21.5)	127 (24.5)	4 (19.0)	16 (23.5)	20 (22.5)

*Mean±SD.
†Two missing data in non-dialysis patients.
‡One missing data in non-dialysis patients.
C.E.R.A., continuous erythropoietin receptor activator; ESA, erythropoiesis-stimulating agent.

dose was lower than the recommended dose in the SPC, which indicates a starting dose of 120, 200 or 360 µg/month based on the dose of the previously administered ESA. In fact, 70% of patients who were supposed to receive 120 µg, 61% of patients not on dialysis who were supposed to receive 200 µg and 57% who were supposed to receive 360 µg actually received a lower dose than that in the SPC. The mean monthly C.E.R.A. dose in patients not on dialysis was 98±54 µg. The same was true for kidney transplant patients: 59%, 50% and 50% received a dose lower than 120, 200 or 360 µg, respectively. The mean monthly C.E.R.A. dose in transplant patients was 128±70 µg (table 2). When treatment was administered once every 2 weeks, the starting dose was 0.61±0.25 µg/kg in ESA-naïve patients not on dialysis and 0.78±0.29 µg/kg in ESA-naïve transplant patients (the SPC from 2009 recommends a dose of 0.6 µg/kg once every 2 weeks in ESA-naïve patients not on dialysis).

After 6 months of treatment, C.E.R.A. was administered in the same conditions as at baseline, but with a monthly dosing schedule for the majority of patients (table 2). The mean monthly C.E.R.A. dose was 102±68 and 125±76 µg in patients not on dialysis and transplant patients, respectively (table 2). Forty-seven per cent of patients did not require a C.E.R.A. dose adjustment during the first 6 months (table 2). Among those who had at least one dose adjustment, the most frequent situation was a single dose adjustment in more than one-third of the patients (not on dialysis 37%; transplant patients 36%), two dose adjustments in 13% of patients and three or four dose adjustments in less than 5%. The proportion of patients with a dose increase or a dose decrease was similar during this period (table 2). In patients not on dialysis, the median dose increase was +50 µg (10; 380) and the median decrease was −25 µg (−360; −4) during this period. In transplant patients, the median dose increase was +50 µg (25; 360) and the median decrease was −50 µg (−360; −20) during this period. The main reason for dose adjustment (98%) was the Hb level. C.E.R.A. was temporarily withdrawn in 16% of patients not on dialysis and 21% of transplant patients. In two-thirds of these cases, the temporary discontinuation was due to the Hb level or to non-adherence to treatment. Permanent treatment discontinuations occurred in 16% of patients not on dialysis and 14% of transplant patients, and were due to conversion to dialysis.

After 12 months of treatment, the proportion of patients on a monthly dosing schedule of C.E.R.A. increased slightly (not on dialysis 89%; transplant 85%). During the 12-month follow-up, the C.E.R.A. monthly dose remained stable (figure 1); 40% of patients not on dialysis and 42% of transplant patients did not require C.E.R.A. dose adjustment; the majority of dose adjustments (95%) occurred because of the Hb level; 25% of patients not on dialysis and 21% of transplant patients temporarily discontinued C.E.R.A., mainly for reasons related to the Hb level (not on dialysis 72%; transplant 88%) or non-adherence to treatment.

Regarding adherence to C.E.R.A. treatment, less than 10% of patients with at least one available self-questionnaire declared to have forgotten or postponed the C.E.R.A. injection at least once during follow-up (patients not on dialysis 6%, 18 patients out of 291; kidney transplant patients 7.5%, 4 patients of 53). Additionally, 17% of not on dialysis patients and 21% of transplanted patients stopped C.E.R.A. temporarily over the 6 months following the first injection (only one temporary discontinuation per patient in most cases). The main causes were Hb concentration value (68% of cases) and non-compliance with treatment (14%). Over the 1-year follow-up, the main reasons for temporary discontinuation were due to Hb levels (72% of cases among not on dialysis patients and 88% of cases among transplanted patients) and patient non-compliance with treatment (28% of cases among not on dialysis patients and 12% of cases in transplanted patients).

Other treatments of renal anaemia

Before the first injection of C.E.R.A., approximately half the patients had an adequate iron status (table 1). The proportion of patients with folic acid or vitamin B_{12} deficiency is also shown in table 1. At baseline, patients received iron supplementation, primarily by the oral route, as well as folate and vitamin B_{12} supplementation (table 2).

During 6 months of treatment, the majority of patients with iron supplementation at baseline had no change in their prescription (not on dialysis 75%; transplant 81%). The percentage of patients with an adequate iron status increased during the 12-month follow-up (not on dialysis from 44% to 52%; transplant from 60% to 67%). No change was observed for patients receiving folic acid or vitamin B_{12}. Several patients not on dialysis (11 ESA-naïve; 14 ESA-treated) had a blood transfusion during the first 6 months.

Change in Hb levels

Patients not on dialysis

Before initiating C.E.R.A. treatment, the Hb level was 10.7±1.4 g/dl in patients not on dialysis (ESA-naïve 10.0±0.9; ESA-treated 11.3±1.4 g/dl). Around 6 months, the Hb level was 11.7±1.5 g/dl (ESA-naïve 11.6±1.4; ESA-treated 11.7±5.0 g/dl). Around 12 months, the Hb level was 11.6±1.4 g/dl (ESA-naïve 11.5±1.2; ESA-treated 11.7±1.5 g/dl). Figure 2A illustrates the change in Hb levels during the study.

Before the first C.E.R.A. injection, approximately half the patients had an Hb level within 10–12 g/dl (table 1). Around 6 months, the percentage of patients with an Hb level within 10–12 g/dl (main endpoint) was 45% (95% CI 41% to 50%), of which 48% were ESA-naïve (95% CI 41 to 55) and 43% were ESA-treated (95% CI 37 to 50). Among ESA-naïve patients with a

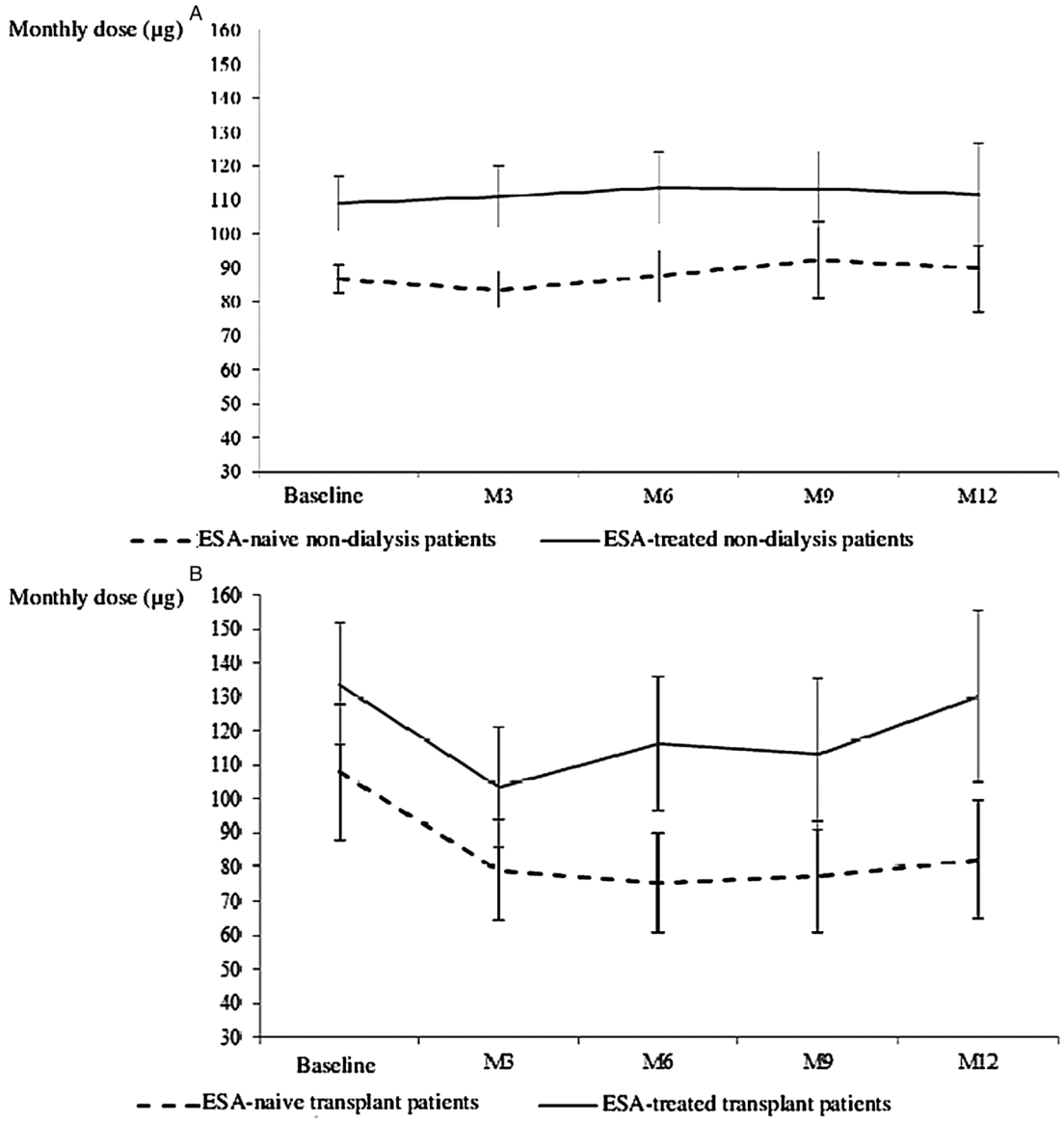

Figure 1 Change in continuous erythropoietin receptor activator dose during the study (A) in patients not on dialysis (mean ± SEM) SEM ($T_{0.025}$×SE with $T_{0.025}$ = quantile 2.5% of Student law at n—1°s of freedom) and (B) in kidney transplant patients.

baseline Hb<10 g/dl, 53% (95% CI 43% to 64%) achieved the target of 10–12 g/dl.

The proportion of patients at EMA target Hb levels remained fairly stable during the 12-month follow-up: about half the patients had Hb levels in this range (figure 3A); 68% and 80% had Hb levels within 10–12.5 and 10–13 g/dl, respectively.

Around 6 and 12 months, 80% and 97% of ESA-naïve patients, respectively, had an increase in Hb of at least +1 g/dl from baseline or reached the target range 10–12 g/dl.

Kidney transplant patients

Before initiating C.E.R.A. treatment, the Hb level was 10.5±1.3 g/dl in kidney transplant patients (ESA-naïve 9.9±1.0; ESA-treated 10.7±1.3 g/dl). Around 6 months, the Hb level was 11.5±1.3 g/dl (ESA-naïve 11.4±1.2; ESA-treated 11.5±1.4 g/dl). Figure 2B illustrates the change in Hb levels during the study.

Before the first C.E.R.A. injection, approximately half the transplant patients (54%) had an Hb level within 10–12 g/dl (table 1).

Around 6 months, the percentage of patients with Hb levels within 10–12 g/dl (main endpoint) was 47% (95% CI 36% to 58%), of which 61% were ESA-naïve (95% CI 39 to 84) and 42% were ESA-treated (95% CI 30 to 55). Among 10 transplant patients with a baseline Hb<10 g/dl, 7 achieved the target of 10–12 g/dl around 6 months.

The proportion of patients at EMA target Hb levels remained fairly stable during the 12-month follow-up: about half the patients had Hb levels in this range (figure 3B); 76% and 87% had Hb levels within 10–12.5 and 10–13 g/dl, respectively.

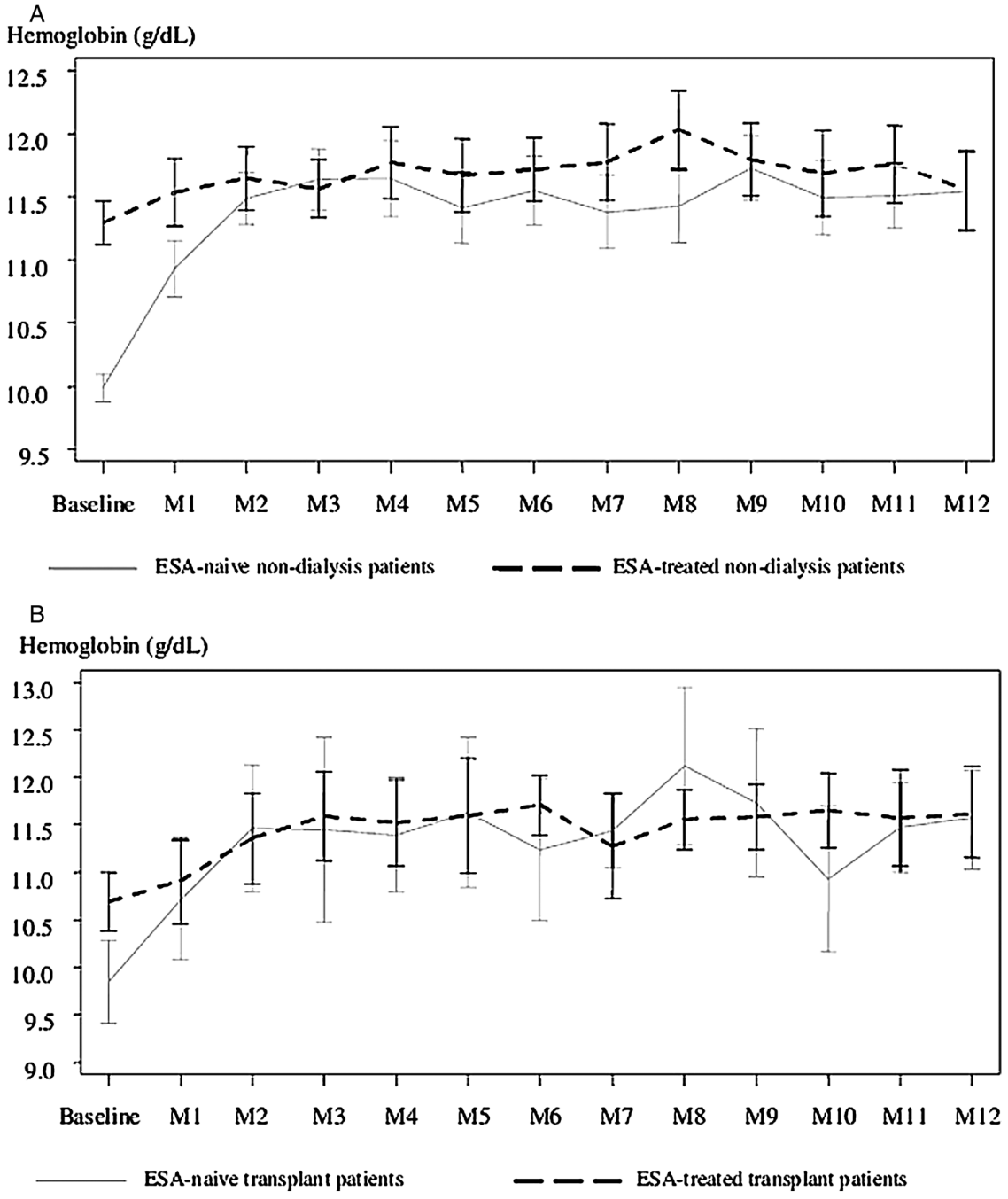

Figure 2 Change in haemoglobin levels during the study (mean ± SEM) (A) in non-dialysis patients and (B) in kidney transplant patients erythropoiesis-stimulating agent.

Around 6 and 12 months, 94% and 100% of ESA-naïve patients had an increase in Hb of at least 1 g/dl from baseline or reached the target range 10–12 g/dl.

Adverse effects

Less than 5% of patients (n=29) had adverse effects related to C.E.R.A., of which 2% (n=11) modified or discontinued treatment. Four patients not on dialysis had six serious adverse effects (SAEs) related to C.E.R.A. treatment (table 3).

The most common adverse event was a decreased platelet count/thrombocytopenia (16 cases in 14 patients), but it was considered non-serious in 87% of cases. In these 14 patients, the median platelet count was 118 500/mm^3 (79 000–188 000). Only five patients, that is, 1% of the OCEANE cohort, had a platelet count below 100 000/mm^3. After collecting additional information, only nine of these effects were ultimately considered to be related to C.E.R.A. Two patients discontinued treatment for this reason.

Nine other targeted adverse effects were reported: one gastrointestinal bleeding, four unexplained loss of efficacy and four thromboembolic effects (deep vein thrombosis, pulmonary embolism, cerebral infarction

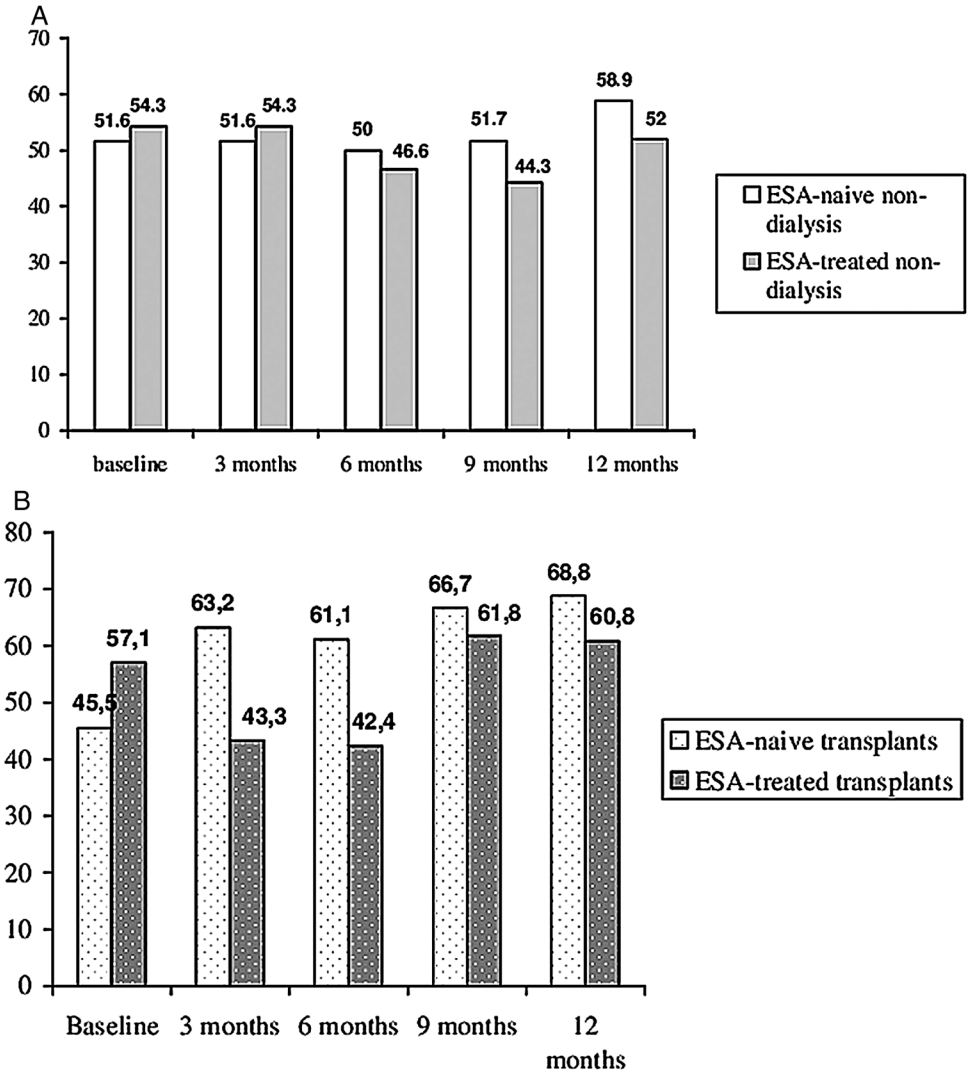

Figure 3 Change in percentage of patients with haemoglobin (Hb) level within 2007 European Medicine Agency target (Hb level within 10–12 g/dl without exceeding 12 g/dl) during the 12 months of continuous erythropoietin receptor activator treatment. (A) In patients not on dialysis, percentage of patients in target range (10–12)g/dl. (B) In kidney transplant patients, percentage of patients in target range (10–12)g/dl.

and arterial thrombosis in limb). No cases of pure red cell aplasia were reported.

Six SAEs occurred in four patients (one patient had three SAE). Four targeted adverse effects were reported as SAE in three patients (two thrombocytopenia, one gastrointestinal bleeding and one stroke). The thrombocytopenia led to treatment modification in one patient and permanent discontinuation in the other.

Another two non-targeted adverse effects described as serious occurred in two patients (one in a state of confusion and one with suspected lymphoma).

A total of 33 patients (5%) died during the study. The cause of death was reported for 25 patients (24 patients not on dialysis including 11 ESA-naïve and 1 ESA-naïve transplant patient). Causes of death were cardiovascular disorders (n=12), respiratory disorders (n=4), septicaemia (n=3), cancer (n=2), gastrointestinal haemorrhage (n=1), fall (n=1), metabolic coma (n=1) and suicide (n=1). For eight patients not on dialysis (three ESA-naïve and five ESA-treated), the cause of death was unknown. None of the deaths was related to C.E.R.A. treatment.

DISCUSSION

The results of the OCEANE study provide an overview of anaemia management with C.E.R.A. in CKD patients not on dialysis and kidney transplant patients. The study began in 2009, 9 months after C.E.R.A. was first licensed in France, at the request of the French National Authority for Health (Haute Autorité de Santé, or HAS).[21] The OCEANE study confirmed the efficacy and safety of C.E.R.A. in anaemia management in CKD patients not on dialysis, with or without previous kidney transplantation.

The proportion of patients with Hb levels within the EMA recommended target range remained stable

Table 3 Adverse effects (AE) related to continuous erythropoietin receptor activator (C.E.R.A.)

	Patients not on dialysis (N=524)			Kidney transplant patients (N=92)		
	Initial ESA treatment			Initial ESA treatment		
	Naïve (N=253)	ESA-treated (N=271)	Total (N=524)	Naïve (N=22)	ESA-treated (N=70)	Total (N=92)
At least 1 AE*	15 (5.9%)	10 (3.7%)	25 (4.8%)	1 (4.5%)	3 (4.3%)	4 (4.3%)
Blood and lymphatic system disorders	9 (3.6%)	4 (1.5%)	13 (2.5%)	–	2 (2.9%)	2 (2.2%)
Thrombocytopenia	*9 (3.6%)*	*3 (1.1%)*	*12 (2.3%)*	–	*2 (2.9%)*	*2 (2.2%)*
Thrombocythemia	–	1 (0.4%)	1 (1.02%)	–	–	
General disorders and administration site conditions	1 (0.4%)	2 (0.7%)	3 (0.6%)	–	1 (1.4%)	1 (1.1%)
Treatment ineffective	*1 (0.4%)*	*2 (0.7%)*	*3 (0.6%)*	–	*1 (1.4%)*	*1 (1.1%)*
Vascular disorders	1 (0.4%)	3 (1.1%)	4 (0.8%)	–		–
Arterial thrombosis	–	*1 (0.4%)*	*1 (0.2%)*	–		–
Venous thrombosis	*1 (0.4%)*	–	*1 (0.2%)*	–		–
Hypertension		1 (0.4%)	1 (0.2%)	–		–
Hypotension	–	1 (0.4%)	1 (0.2%)	–		–
Gastrointestinal disorders	2 (0.8%)	–	2 (0.4%)	1 (4.5%)	–	1 (1.1%)
Gastrointestinal disorder	1 (0.4%)	–	1 (0.2%)	–	–	–
Gastrointestinal bleeding	*1 (0.4%)*	–	*1 (0.2%)*	–	–	–
Oedema, tongue	–	–	–	1 (4.5%)	–	1 (1.1%)
Infections and infestations	–	2 (0.7%)	2 (0.4%)	–	–	–
Flu	–	1 (0.4%)	1 (0.2%)	–	–	–
Urinary tract infections	–	1 (0.4%)	1 (0.2%)	–	–	–
Nervous system disorders	1 (0.4%)	1 (0.4%)	2 (0.4%)	–	–	–
Headache	–	1 (0.4%)	1 (0.2%)	–	–	–
Ischaemic stroke	*1 (0.4%)*	–	*1 (0.2%)*	–	–	–
Skin and subcutaneous tissue disorders	1 (0.4%)	1 (0.4%)	2 (0.4%)	–	–	–
Dry skin	–	1 (0.4%)	1 (0.2%)	–	–	–
Pruritus	1 (0.4%)	–	1 (0.2%)	–	–	–
Metabolism and nutrition disorders	–	1 (0.4%)	1 (0.2%)	–	–	–
Diabetes poorly controlled	–	1 (0.4%)	1 (0.2%)	–	–	–
Neoplasms, benign, malignant and unspecified (including cysts and polyps)	1 (0.4%)	–	1 (0.2%)	–	–	–
Lymphoma	1 (0.4%)	–	1 (0.2%)	–	–	–
Psychiatric disorders	1 (0.4%)	–	1 (0.2%)	–	–	–
Confusional state	1 (0.4%)	–	1 (0.2%)	–	–	–
Respiratory, thoracic and mediastinal disorders	1 (0.4%)	–	1 (0.2%)	–	–	–
Pulmonary embolism	*1 (0.4%)*	–	*1 (0.2%)*	–	–	–

One patient could have had more than one AE.
*Eleven led to modification or discontinuation of treatment (non-dialysis n=9; transplant n=2).
Italics represent targeted AEs.
ESA, erythropoiesis-stimulating agent.

during the study. Approximately half the patients had an Hb level within 10–12 g/dl at baseline and around 6 and 12 months of treatment. The proportion of patients with an Hb level within 10–12 g/dl after 6 months of treatment with C.E.R.A. (main endpoint) also agreed with our starting hypothesis that 50% of patients would achieve this target, considering that physicians were in the learning curve of this new drug 9 months after it came to the market, and in the light of current epidemiological data. As a matter of fact, the improvement in the management of ESA-treated patients was modest whatever the stage of CKD. In 2003, the European PRESAM study showed that 32% of ESA-treated patients not on dialysis achieved the Hb target recommended at the time (Hb >11 g/dl).[22] In 2003, Lacson *et al*[23] showed that only 58% of end-stage renal disease patients converting to dialysis had an Hb level within 10–12 g/dl. Despite a slight progression, one in two patients overall reached the recommended target, as witnessed by the change in the percentage of CKD patients not on dialysis with an Hb level within 10–12 g/dl, which increased from 59% to 63% between 2005 and 2009 in the USA.[9]

The results of the OCEANE study are a perfect reflection of the difficulties nephrologists face when they try to adhere strictly to the narrow target range such as that recommended by the EMA (10–12 g/dl) or recently by

the ERBP (11–12 g/dl). This difficulty might arise in part from the overly frequent revision of guidelines and the absence of a consensus on the target Hb level to aim for. Furthermore, ERBP acknowledges the difficulty of maintaining patients in a narrow range because of the variability of Hb values, and notes that the nephrologist has to accept the fact that Hb excursions above and below this target value will occur from time to time.[2 3] An Hb target of 10–13 g/dl, without exceeding 13 g/dl, would probably be more pragmatic and clinically acceptable for patients.

The difficulty might also be explained by the complex clinical profile of CKD patients, who tend to be fairly elderly and present cardiovascular comorbidities as well as well-known resistance factors to ESA treatment.[3] Iron deficiency, the main resistance factor to ESA treatment,[4 5] was also present in patients in the OCEANE study and could have had a negative impact on the efficacy of C.E.R.A. Fewer than half of the patients, whether ESA-naïve or treated, had an adequate iron status at baseline. After 1 year of C.E.R.A. treatment, 52% of patients not on dialysis and 67% of transplant patients had an adequate iron status. The proportions observed in the OCEANE study are higher than the 36% reported in the PRESAM study and reflect an improvement in anaemia management since 2003.[22] European guidelines note that iron supplementation is an important factor contributing to the efficacy of ESAs to attain target Hb levels with the lowest possible ESA dose. They state that iron supplementation should be initiated first in patients with inadequate iron status and that ESA therapy should only be started after iron reserves are sufficient.[4] Another important cause of ESA resistance in anaemia management in CKD is inflammation.[4 24] In the OCEANE cohort, inflammation, defined as a C reactive protein >5 mg/l or even >30 mg/l in certain patients at baseline, might also explain the difficulty in maintaining these patients within the narrow 10–12 g/dl target range. Additionally, the other causes of hyporesponsiveness to ESAs, in particular high plasma intact parathyroid hormone concentrations, were not reported in the OCEANE study.[4] Nonetheless, the representativeness of the OCEANE cohort is difficult to evaluate since there are no recent epidemiological data for patients not on dialysis. However, the demographic characteristics of the OCEANE cohort are similar to those of patients on dialysis in the REIN report published in 2009 and in a recent Spanish prospective study;[25 26] and the characteristics of kidney transplant patients are similar to those of the patients in the ANEMIATRANS retrospective analysis.[18]

The findings from the OCEANE study highlight the importance of personalised anaemia management based on the patient's profile, taking into account the patient's characteristics and symptoms, as indicated in the latest European guidelines.[2]

Another observation that emerged from the OCEANE study is that approximately 50% of ESA-naïve patients were within the 10–12 g/dl target range at baseline. Initiation of C.E.R.A. treatment in patients with Hb >10 g/dl was probably based on the anaemia symptoms and not on the Hb level. Indeed, the SPCs of the different ESAs specify that these agents are indicated in the treatment of symptomatic anaemia associated with CKD. C.E.R.A. was therefore prescribed to these patients on the basis of clinical and not laboratory criteria. It should also be noted that when C.E.R.A. treatment was initiated, one ESA-naïve patient in two started directly on a monthly C.E.R.A. dosing schedule. This was several months ahead of the revised C.E.R.A. labelling, which now allows this dosing schedule in ESA-naïve patients, attesting in passing to the need felt by nephrologists to have a true once-monthly ESA for anaemia management before the dialysis stage. In ESA-naïve patients, the C.E.R.A. starting dose conformed to the recommendations for non-dialysed patients. However, this dose was higher in transplant patients and can be explained by a lower Hb level at baseline.

Our study has several limitations. First, the selection process should have introduced a selection bias, affecting the data in a positive fashion, as no patient with cancer and a relatively low proportion of CKD patients with cardiovascular comorbidities were enrolled in our study. As OCEANE was a non-interventional study, each physician had to consecutively include patients fulfilling inclusion criteria during routine follow-up visits without any selection guided by comorbidities. Additionally, patients with cancer or with severe cardiovascular comorbidities are more likely to be followed up by oncologists or cardiologists, respectively, rather than nephrologists. Second, although the majority of ESA-treated patients were switched to once monthly C.E.R.A. according to the dosing schedule in the product labelling, the C.E.R.A. starting dose was lower than that recommended in the SPC. This is probably due to the fact that nephrologists were not yet familiar with this new, long-acting ESA and exercised caution when switching from multiple ESA injections to once-monthly C.E.R.A. However, C.E.R.A. treatment practices progressed during the study as the physicians familiarised themselves with the once-monthly schedule during the maintenance phase.

The OCEANE study demonstrates that anaemia management with C.E.R.A. is less restrictive than with other ESAs. During the first 6 months of C.E.R.A. treatment, half the patients did not require any dose adjustment and approximately 40% of patients did not have a dose adjustment during the entire 12-month follow-up. Dose changes are one of the leading causes of Hb variability, a phenomenon which is associated with increased morbidity and mortality.[27] The fairly small proportion of patients who had a dose adjustment, previously observed in other studies,[28] was thereby confirmed in routine clinical practice in the OCEANE study.

The OCEANE study also confirmed the known safety profile of C.E.R.A.[29]

CONCLUSION

This study, conducted in routine clinical practice, followed a cohort of CKD patients not on dialysis and kidney transplant patients representative of the patient population seen in nephrology and kidney transplant centres in France.

The results confirm the efficacy and good safety profile of C.E.R.A. in CKD patients not on dialysis and in kidney transplant patients, naïve to or previously treated with ESA.

The study also shows that the gap between European guidelines and routine practices of anaemia management of non-dialysis CKD patients still existed in 2009.

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