Cinacalcet Treatment for Secondary Hyperparathyroidism in Dialysis Patients: An Observational Study in Routine Clinical Practice

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Key Words

Calcimimetic • Cinacalcet • Secondary hyperparathyroidism • Dialysis • Parathyroid hormone • Calcium • Phosphorus

Abstract

Background: Cinacalcet reduces intact parathyroid hormone (iPTH), Ca and P serum levels in patients with secondary hyperparathyroidism (SHPT). **Methods:** This Spanish, multicenter, observational, retrospective study collected data from SHPT dialysis patients 12 weeks before and up to 72 weeks after starting cinacalcet in clinical practice. **Results:** Data from 428 patients with uncontrolled SHPT despite receiving standard of care (29% with baseline iPTH 501–800 pg/ml; 51% with >800 pg/ml) were collected. Percentages of patients within National Kidney Foundation Kidney Disease Outcomes Quality Initiative targets at baseline and 72 weeks were: iPTH, 0 versus 32.5% ($p < 0.05$); Ca, 40.1 versus 50% ($p < 0.05$); P, 47.7 versus 53.8% ($p = 0.162$). Vitamin D sterol use decreased from 53.3% at baseline to 36.7% at 72

weeks ($p < 0.05$). The mean $\pm$ SD cinacalcet dose at 72 weeks was 44.0 ± 25.8 , 51.7 ± 31.3 and 57.1 ± 37.0 mg for patients with baseline iPTH 301–500, 501–800 or >800 pg/ml, respectively. The main adverse reactions were nausea (5.4%), dyspepsia (5.1%) and vomiting (3.7%). **Conclusions:** The introduction of cinacalcet improved the routine clinical management of SHPT in a large cohort of Spanish dialysis patients. Cinacalcet is effective and well tolerated regardless of disease severity, and maintains its efficacy over 72 weeks.

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Introduction

Secondary hyperparathyroidism (SHPT) is a progressive disease associated with chronic kidney disease and characterized by elevated parathyroid hormone (PTH) levels and disordered mineral metabolism [1, 2].

Elevated serum PTH, P and Ca levels are independently associated with increased morbidity and mortality in dialyzed patients [3]. In their clinical practice guidelines

the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI™) [4] established treatment goals for mineral metabolism to improve dialysis patient care.

Hypercalcemia and hyperphosphatemia, as a result of either SHPT or the use of therapeutic agents, contribute to soft-tissue and vascular calcification, which might increase cardiovascular disease and mortality [5]. For these reasons, new therapeutic alternatives should be envisaged in order to reduce the risks associated with the adverse effects of traditional therapies.

The calcimimetic cinacalcet mainly increases the sensitivity of the Ca-sensing receptor to extracellular Ca [6], thus inhibiting the release of PTH [7], although, as recently shown, it also decreases PTH synthesis [8]. Calcimimetic agents and vitamin D sterols have a different mechanism of action, which not only decreases PTH synthesis but also has indirect effects that limit their efficacy (increase in intestinal Ca and P absorption and low bone turnover). Phase III clinical trials have shown that treatment of SHPT with cinacalcet simultaneously reduces PTH, Ca, P and Ca × P levels, allowing more patients to achieve KDOQI™ treatment targets [9, 10]. However, data about the effectiveness of cinacalcet in routine clinical practice are scarce [11, 12]. REHISET is a Spanish observational multicenter study intended to describe the efficacy and safety results of cinacalcet in the treatment of SHPT in a large cohort of dialysis patients in routine clinical practice and compare its results with published clinical trials.

Material and Methods

This Spanish, multicenter, observational, retrospective study was designed to collect data from dialysis patients treated de novo with cinacalcet drug after its commercialization in Spain in June 2005. Centers were distributed uniformly throughout all the Spanish regions. Main inclusion criteria were: patients who had received dialysis for >30 days before initiation of cinacalcet, aged ≥18 years, diagnosed with SHPT, with laboratory data from 12 weeks before and up to 72 weeks after starting cinacalcet treatment in routine clinical practice and with at least 16 weeks of follow-up with cinacalcet treatment. Patients were excluded if they had been included in a clinical trial of cinacalcet during the follow-up period. The study protocol was approved by all Ethics Committees of centers where it was required according to legislation on retrospective observational studies. All recruited patients started cinacalcet between June 2005 and March 2006. The day of cinacalcet initiation was considered as the baseline time point (week 0). Cinacalcet and other treatment modifications during the time of the study were performed according to the protocol of each center (in accordance with KDOQI treatment recommenda-

tions [4], which were the most accepted and best known by Spanish physicians until the recent publication of the recommendations of the Spanish Society of Nephrology (SEN) [13] and the new Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [14]). Relevant medical history, comorbidities, and laboratory data were collected and assigned (according to date of extraction) to study time points at weeks -12 ± 2 weeks, -4 ± 2 , 0 , $+4 \pm 2$, $+12 \pm 2$, $+16 \pm 2$, $+24 \pm 4$, $+48 \pm 4$ and $+72 \pm 4$. On-site monitoring was conducted in all centers to ensure quality of data. The primary endpoint was the percentage of cinacalcet-treated patients within KDOQI target for intact PTH (iPTH). Secondary endpoints included the percentage of patients within KDOQI targets for Ca and P, the changes in biochemical parameters (iPTH, Ca and P) during the study, the changes in cinacalcet utilization, the usage of vitamin D analogs and phosphate binders, and the safety profile of cinacalcet.

Statistical Analysis

Summary statistics were calculated for continuous and categorical variables. Analyses were based on observed data only. The McNemar test was applied to compare frequencies between different time points (matched-pairs analysis). Differences in mean levels between subgroups or with respect to baseline were assessed using Student's *t* tests or paired *t* tests, respectively. The effect of cinacalcet on iPTH, P and Ca with respect to disease severity was explored by calculating 95% confidence intervals for these parameters at each study point in 3 patient subgroups (defined according to their baseline iPTH): 301–500 pg/ml (31.9–53 pmol/l); 501–800 pg/ml (53.1–84.8 pmol/l) and >800 pg/ml (>84.8 pmol/l). These cut-offs were chosen according to the upper iPTH limit in the KDIGO guidelines [14] (300 pg/ml), the upper limit for a significant increase in mortality in SEN recommendations [13] (500 pg/ml), and the cut-off value for considering parathyroidectomy in KDOQI guidelines [4] (800 pg/ml). All the calculations were performed using SPSS® 14.0 (SPSS Inc., Chicago, Ill., USA).

Results

Patients

The study included 428 patients initiating cinacalcet in the clinical practice (baseline time point), from whom 150 did not complete the follow-up. Data were collected from 36 hospital nephrology services or satellite dialysis units. Figure 1 shows the data availability at each study point, based on primary endpoints, and the reasons for patient withdrawals. Forty-six patients (10.8%) were lost to follow-up during the study period (of whom 34 belonged to two centers that did not collect data after 24 weeks due to logistic problems). There were 25 deaths (5.8%) during the follow-up, none of them related to cinacalcet treatment: 15 patients (60%) died due to cardiovascular causes, 8 patients (32%), due to noncardiovascular causes, and in 2 patients (8%) we were not able to document the cause of death.

Fig. 1. Patients with data available at each study point and reasons for incomplete follow-up data.

Table 1. Baseline characteristics of 428 dialysis patients starting cinacalcet in clinical practice

Baseline characteristics	Patients
Age, years	
Mean $\pm$ SD	60.2 $\pm$ 15.7
Range	19–92
Men, n	232 (54.2%)
Diabetes, n	78 (18.2%)
Time on dialysis	
Median, months	57.6
Q1–Q3, months	28.2–119.1
Prior parathyroidectomy, n	24 (5.6%)
Previous transplantation, n	109 (25.5%)
1	73 (17.1%)
2 or >2	36 (8.4%)
Etiology of renal disease	
Diabetic nephropathy, n	42 (9.8%)
Glomerulonephritis, n	78 (18.2%)
Vascular nephropathy, n	49 (11.4%)
Polycystic kidney disease	32 (7.5%)
Chronic pyelonephritis, n	60 (14.0%)
Hereditary, n	12 (2.8%)
Other, n	55 (12.9%)
Unknown, n	100 (23.4%)
Dialysis type	
Hemodialysis, n	379 (88.6%)
Hemodiafiltration, n	35 (8.2%)
Long nocturnal HD, n	1 (0.2%)
Peritoneal dialysis, n	13 (3.0%)

Patient Characteristics at Cinacalcet Initiation

Patient characteristics at initiation of cinacalcet are summarized in table 1. Mean $\pm$ SD age was 60.2 $\pm$ 15.7 years, 54.2% were men, and most of them were undergoing hemodialysis (97%). Mean PTH, Ca and P at baseline were 941 $\pm$ 516 pg/ml (99.7 $\pm$ 54.7) pmol/l, 9.6 $\pm$ 0.8 mg/dl (2.4 $\pm$ 0.2 mmol/l) and 5.6 $\pm$ 1.4 mg/dl (1.8 $\pm$ 0.4 mmol/l), respectively. Before the initiation of cinacalcet, 80% of patients had moderate or severe SHPT (29% with baseline iPTH 501–800 pg/ml and 51% with >800 pg/ml), despite receiving standard care previously, i.e. vitamin D sterols (53.3% of patients) and phosphate binders (93%) (table 2).

The iPTH levels in the 12 weeks before the initiation of cinacalcet increased from 812 $\pm$ 510 pg/ml (86.1 $\pm$ 54.1 pmol/l) to 941 $\pm$ 516 pg/ml at baseline (median percentage change of +18.8 $\pm$ 201.8%) whereas the Ca and P levels remained unchanged, i.e. levels of 9.8 $\pm$ 0.9 mg/dl (2.4 $\pm$ 0.2 mmol/l) and 5.6 $\pm$ 1.6 mg/dl (1.8 $\pm$ 5.2 mmol/l) at week –12, respectively, with median changes of –1.6 $\pm$ 8.1 and 0 $\pm$ 34.0%.

The mean albumin levels were 3.9 $\pm$ 0.4 g/dl, and remained unchanged during the follow-up (3.8 $\pm$ 0.4 g/dl at week 72). Mean dialysate Ca concentration at baseline was 2.8 $\pm$ 0.3 mEq/l (without changes at week 72: 2.9 $\pm$ 0.3 mEq/l).

Table 2. Medications for SHPT (including cinacalcet) administered at each study point

	Baseline (n = 428)	Week 24 (n = 416)	Week 72 (n = 278)
<i>Cinacalcet</i>			
Patients, n	428 (100%)	416 (100%)	278 (100%)
Mean dose (± SD), mg/day	28.9 ± 6.0	45.9 ± 26.5*	52.3 ± 33.8*
Median dose, mg/day	30	30	45
<i>Vitamin D sterols</i> ¹			
Patients, n	228 (53.3%)	185 (44.5%)*, ²	102 (36.7%)*, ³
Oral calcitriol			
Patients, n	45 (10.5%)	37 (8.9%)	17 (6.1%)
Mean dose (± SD), µg/week	1.83 ± 0.9	1.94 ± 1.14	1.36 ± 0.6*
Median dose, µg/week	1.5	1.5	1.5
Intravenous calcitriol			
Patients, n	58 (13.6%)	30 (7.2%)*	11 (4.0%)*
Mean dose (± SD), µg/week	2.6 ± 1.9	2.1 ± 1.2*	2.0 ± 1.0*
Median dose, µg/week	2.0	2.0	2.0
Intravenous alfacalcidol			
Patients, n	47 (11.0%)	44 (10.6%)	20 (7.2%)
Mean dose (± SD), µg/week	4.3 ± 2.1	4.8 ± 2.5*	3.6 ± 1.8*
Median dose, µg/week	4.0	4.5	3.0
Intravenous paricalcitol			
Patients, n	86 (20.1%)	78 (18.8%)	53 (19.1%)
Mean dose (± SD), µg/week	10.6 ± 4.9	10.8 ± 6.1	9.6 ± 6.6*
Median dose, µg/week	10	9	9
<i>Phosphate binders</i> ⁴			
Patients, n	398 (93.0%) ⁵	370 (88.9%) ⁶	248 (89.2%) ⁷
Calcium-based			
Patients, n	193 (45.1%)	239 (57.5%)*	151 (54.3%)*
Mean dose (± SD), mg/day	2,379 ± 3,699	2,500 ± 3,416	2,195 ± 3,900
Median dose, mg/day	1,500	2,000	1,500
Sevelamer			
Patients, n	326 (76.2%)	285 (68.5%)	205 (73.7%)
Mean dose (± SD), mg/day	5,377 ± 2,579	5,046 ± 2,610	4,975 ± 2,476*
Median dose, mg/day	4,800	4,800	4,800
Aluminum-based (acetate/carbonate)			
Patients, n	84 (19.6%)	57 (13.7%)	31 (11.2%)*
Mean dose (± SD), mg/day	1,347 ± 806	1,253 ± 587	1,267 ± 713
Median dose, mg/day	1,165	1,165	932

* p < 0.05 vs. baseline.

¹ Eight, 5 and 1 patients were treated with 2 vitamin D/analogues at baseline, week 24 and week 72, respectively; 55 patients (12.9%) never used vitamin D analogues during the whole study.² One patient was receiving oral paricalcitol and 1 patient cholecalciferol.³ One patient was receiving oral paricalcitol and 1 patient cholecalciferol.⁴ 169, 186 and 114 patients were treated with 2 phosphate binders at baseline, week 24 and week 72, respectively; 19, 14 and 14

patients were treated with 3 phosphate binders at baseline, week 24 and week 72, respectively; 6 patients (1.4%) never used phosphate binders during the whole study.

⁵ One patient was receiving calcium glucobionate + calcium carbonate and 1 patient sucralfate.⁶ Two patients were receiving calcium glucobionate + calcium carbonate and 1 patient sucralfate.⁷ One patient was receiving calcium glucobionate + calcium carbonate and 2 patients were receiving sucralfate + magaldrate.

Fig. 2. Evolution of mineral metabolism parameters during the study in the overall sample. * $p < 0.05$ versus week 0 (baseline); % change is expressed as median percentage of change. Gray area = KDOQI targets.

Fig. 3. Changes in mineral metabolism parameters during the study according to baseline SHPT severity. * $p < 0.05$ versus week 0 (baseline); % change is expressed as median percentage of change. Gray area = KDOQI targets.

Fig. 4. Changes in cinacalcet doses during the study.

KDOQI Target Achievement

Figure 2 shows the change in iPTH, Ca and P levels during follow-up. The proportion of patients within KDOQI targets at baseline and following 72 weeks of cinacalcet was: 0 versus 32.5% for iPTH ($p < 0.05$); 40.1 versus 50% for Ca ($p < 0.05$) and 47.7 versus 53.8% for P ($p = 0.162$). The median percentage change in serum iPTH, Ca and P levels from baseline to week 72 was -61.7% , i.e. final mean value of 415.6 ± 349.2 pg/ml (44.0 ± 37.0 pmol/l) ($p < 0.05$ vs. baseline); -3.1% , i.e. 9.3 ± 0.8 mg/dl (2.3 ± 0.2 mmol/l) ($p < 0.05$ vs. baseline), and -7.5% , i.e. 5.1 ± 1.5 mg/dl (1.6 ± 0.5 mmol/l) ($p < 0.05$ vs. baseline), respectively (fig. 2). A total of 73% of patients had a $\geq 30\%$ iPTH reduction from baseline or achieved the iPTH target after 72 weeks and 46.9% of the patients achieved the target of iPTH ≤ 300 pg/ml at the end of the study period.

The percentage of patients with iPTH levels < 150 pg/ml at each follow-up visit was as follows: week -12 , 0.9%; week 0, 0% (as required per protocol); week $+24$, 13.4%; week $+48$, 11.5%; week 72, 11.4%.

Achievement of KDOQI Targets by Initial Severity of SHPT

During the 72 weeks of follow-up, a significant and sustained decrease in iPTH, Ca and P levels was observed, independently of baseline disease severity (fig. 3a–c). The median reduction in iPTH levels was higher for patients with baseline iPTH > 800 pg/ml ($-73.7 \pm 31.2\%$, $p < 0.05$ vs. baseline) than for patients between 301 and 500 pg/ml

($-43.1 \pm 86.4\%$, $p = \text{NS}$) or 501–800 pg/ml ($-52.3 \pm 48.0\%$, $p < 0.05$ vs. baseline), resulting in similar final levels for the three subgroups.

More patients with baseline iPTH 301–500 pg/ml (63.0%) completed the study with iPTH levels < 300 pg/ml with respect to patients with baseline iPTH 501–800 pg/ml (46.3%) or baseline iPTH > 800 pg/ml (43.8%). However, the percentages of patients achieving KDOQI targets at week 72 were similar for the three severity subgroups (34.8% with iPTH 150–300 pg/ml for patients with baseline iPTH 301–500 pg/ml; 31.3% for iPTH 501–800 pg/ml and 33.8% for iPTH > 800 pg/ml, data not shown for the other parameters).

Cinacalcet and Concomitant Medications during the Study

Table 2 presents the number of patients treated with each SHPT therapy during the 72 weeks, together with the mean and median administered doses. The cinacalcet dose was significantly increased during the first 12 weeks and continued to increase at a slower rate throughout the study (fig. 4). The dose was increased at least once in 76% of patients, and decreased at least once in 53%. No changes were performed in 15% of cases.

Vitamin D sterol use decreased throughout the study ($p < 0.05$ at weeks 24 and 72 vs. baseline; table 2), although the percentage of patients using paricalcitol remained similar. There was a statistically significant increase in the proportion of patients receiving Ca-contain-

Table 3. Doses of SHPT medications after 72 weeks of cinacalcet treatment in subgroups of patients defined by their baseline SHPT severity

	Baseline iPTH 301–500 pg/ml (n = 47)	Baseline iPTH 501–800 pg/ml (n = 69)	Baseline iPTH >800 pg/ml (n = 132)
<i>Cinacalcet</i>			
Patients, n	47 (100%)	69 (100%)	132 (100%)
Mean dose ($\pm$ SD), mg/day	44.0 $\pm$ 25.8	51.7 $\pm$ 31.2	57.2 $\pm$ 37.1
Median dose, mg/day	34.3	45.0	60.0
Range, mg/day	4.3 – 120	4.3 – 150	8.57 – 180
<i>Vitamin D sterols</i>			
<i>Oral calcitriol</i>			
Patients, n	4 (9%)	6 (9%)	6 (5%)
Mean dose ($\pm$ SD), μ g/week	1.4 $\pm$ 0.9	1.4 $\pm$ 0.5	1.2 $\pm$ 0.5
Median dose, μ g/week	1.1	1.5	1.5
<i>Intravenous calcitriol</i>			
Patients, n	0	0	10 (8%)
Mean dose ($\pm$ SD), μ g/week			1.9 $\pm$ 1.0
Median dose, μ g/week			1.7
<i>Intravenous alfacalcidol</i>			
Patients, n	6 (13%)	4 (6%)	10 (8%)
Mean dose ($\pm$ SD), μ g/week	2.4 $\pm$ 1.0	3.1 $\pm$ 2.0	4.5 $\pm$ 1.7*
Median dose, μ g/week	2.6	2.5	4.0
<i>Intravenous paricalcitol</i>			
Patients, n	8 (17%)	18 (26%)	23 (17%)
Mean dose ($\pm$ SD), μ g/week	7.1 $\pm$ 4.7	10.8 $\pm$ 9.8	9.5 $\pm$ 4.0
Median dose, μ g/week	7.9	7.5	9.0
<i>Phosphate binders</i>			
<i>Calcium-based</i>			
Patients, n	17 (36%)	34 (49%)	87 (66%)*
Mean dose (SD), mg/day	2,415 $\pm$ 2,695	1,830 $\pm$ 1,822	2,318 $\pm$ 4,855
Median dose, mg/day	1,500	1,260	1,500
<i>Sevelamer</i>			
Patients, n	37 (79%)	53 (77%)	94 (71%)
Mean dose ($\pm$ SD), mg/day	5,276 $\pm$ 2,411	4,906 $\pm$ 2,224	5,004 $\pm$ 2,635
Median dose, mg/day	4,800	4,800	4,800
<i>Aluminum-based (acetate/ carbonate)</i>			
Patients, n	3 (6%)	5 (7%)	21 (6%)
Mean dose ($\pm$ SD), mg/day	1,243 $\pm$ 749	1,445 $\pm$ 797	1,216 $\pm$ 720
Median dose, mg/day	932	1,864	932
* p < 0.05 versus baseline iPTH 301–500 pg/ml.			

ing phosphate binders ($p < 0.05$ at weeks 24 and 72 vs. baseline) and a decrease in the proportion of patients receiving aluminum-based phosphate binders ($p < 0.05$ at week 72 vs. baseline), but the overall use of phosphate binders remained stable. In general, the dose of vitamin D sterols from baseline to 72 weeks slightly decreased; the changes in the dosage of calcitriol (oral and intravenous),

alfacalcidol (intravenous) and paricalcitol (intravenous) were statistically significant. There were no important changes in the dose of phosphate binders throughout the study, except for a slight decrease in the sevelamer dose (table 2).

Despite a similar proportion of patients reaching iPTH treatment targets in the subgroups defined according to

Table 4. Adverse reactions to cinacalcet

Adverse reaction	Patients, n	Patient, %
Nausea	23	5.4
Dyspepsia	22	5.1
Vomiting	16	3.7
Epigastralgia	6	1.4
Hypocalcemia ¹	4	0.9
Abdominal pain	3	0.7
Anorexia	3	0.7
Diarrhea	2	0.5
Malaise	1	0.2
Myalgia	1	0.2
Constipation	1	0.2
Lip paresthesia	1	0.2
Gastritis	1	0.2
Pretibial ulcer	1	0.2

¹ According to investigator subjective impression.

initial severity (fig. 3a), the mean dose of cinacalcet at 72 weeks was substantially lower in patients with baseline iPTH 301–500 pg/ml (44.0 mg) than in patients with baseline iPTH 501–800 pg/ml or >800 pg/ml (51.7 and 57.1 mg, respectively) (table 3). The final doses of vitamin D sterols were also lower in the less severe subgroup (although the percentages of treated patients were similar) whereas there were no differences in the doses of phosphate binders (but a lower number of patients was being treated with Ca-based drugs in the less severe subgroup; table 3).

Treatment Discontinuations, Tolerability and Safety Profile

At least 65% of patients starting cinacalcet in regular clinical practice maintained the treatment after 72 weeks. Forty-three patients (10%) reported discontinuation of cinacalcet treatment: 5 (1.2%) due to patient's decision; 6 (1.4%) due to parathyroidectomy (a low percentage despite of the severe-SHPT population included in the study); in 22 patients (5.1%), the investigator decided to discontinue the treatment due to efficacy-related reasons (1 case due to lack of efficacy and 21 cases due to the investigator's perception of excessive control of SHPT disease), and, finally, in 10 patients (2.3%), treatment was discontinued due to poor tolerability.

In total, there were 54 patients (12.6%) that could be considered as nonresponders to cinacalcet, due to one of the following reasons: parathyroidectomy (n = 6, 1.4%);

cinacalcet discontinuation before 72 weeks due to elevated PTH levels (n = 1, 0.2%), or with PTH levels above 300 pg/ml or a reduction less than 30% versus baseline value at 72 weeks (n = 47, 11.0%, from whom 25 had PTH levels above 800 pg/ml).

Table 4 displays the adverse reactions to cinacalcet treatment in 85 patients (19.9%). The most common were nausea (5.4%), dyspepsia (5.1%) and vomiting (3.7%). None of them was considered serious, and only in 10 cases (2.3%) was treatment discontinuation needed.

Discussion

Although many data have been collected about cinacalcet in interventional trials, results in large cohorts from routine clinical practice are sparse [11, 12]. The REHISSET study constitutes the first large data collection in Spain on the use and efficacy of cinacalcet in clinical practice. Cinacalcet significantly improved the attainment of KDOQI iPTH, P and Ca targets, simultaneously reducing these parameters in all patients, independent of the degrees of initial SHPT. Thirty-two percent of patients achieved the iPTH target, and an additional 40% completed the study with more than 30% reduction of their baseline levels. It is important to note that, despite the described differences between iPTH assays, we replicated the results using validated formulas to convert PTH values to Nichols-equivalent values [15] (the assay on which the KDOQI target was based). In our study, most centers used a second-generation electrochemiluminescence method that does not excessively overestimate PTH, and no significant differences in mean PTH levels or percent of patients achieving the KDOQI target with or without correction to the Nichols values were found (data not shown). The recent 2009 KDIGO guidelines [14], to solve the problem of interassay variability, recommend maintaining iPTH levels in the range of 2–9 times the upper normal limit of each assay, although a recent European publication acknowledges that patients with iPTH, Ca and P levels within the KDOQI target ranges have the lowest risk of mortality compared with those outside the target values and thus, some patients treated following the KDIGO guidelines could be at increased risk of mortality compared with those treated to meet the KDOQI target range [16].

Since the study was conducted soon after cinacalcet commercialization in Spain, the study cohort probably includes patients with more severe forms of SHPT as reflected by their elevated baseline iPTH levels (940 pg/ml)

despite administration of classical treatments. Thus, the patients included in the current study were probably those more refractory to vitamin D sterols and phosphate binders, in whom the investigators decided to try the new drug cinacalcet before referring them for parathyroidectomy. This is confirmed by the fact that although the described cohort constitutes 2.3% of the population undergoing dialysis in Spain in 2005 [17], their demographic and clinical characteristics slightly differ from those prevalent in the overall patients [17, 18]. Our patients are about 6 years younger, with more women (male:female ratio 1.18 vs. 1.56 for the reference population) and less diabetes (18 vs. 26%), although their time on dialysis is similar (median of almost 5 years). It has previously been reported that younger age and absence of diabetes mellitus are associated with more severe SHPT [19]. The differences in these variables could also explain the low mortality rate found in our sample (5.4% in 72 weeks) compared with the annual mortality of Spanish dialysis patients in that year (13.7%) [17].

Despite this severity, the efficacy of cinacalcet in this observational study is comparable to that demonstrated in previous clinical trials. At the end of the study, almost one half of the patients (47%) achieved iPTH levels below 300 pg/ml. This figure is slightly lower than the 56–71% reported in phase III clinical trials [20–22], and in the OPTIMA [23] and SENSOR [24] studies, but the relative reduction in iPTH levels was a bit higher (62 vs. 48–57% in the aforementioned studies, which included patients with less severe disease, i.e. baseline iPTH levels between 483 and 840 pg/ml). In addition, there were notable differences in the administered doses that must be taken into account. Moe et al. [20, 21], in their combined analysis of the 3 placebo-controlled, 26-week, phase III studies with cinacalcet, found that 56% of the patients had achieved iPTH levels <300 pg/ml, but the median dose at the end of the studies was 90 mg/day, which is twice as high as the dose we administered (45 mg/day). In the 1-year, placebo-controlled trial [22], the doses administered to the entire cinacalcet group were not reported, but the subgroup with >30% reduction in the iPTH level (82%) was receiving a mean of 99 mg/day at the end of the study. Finally, the doses administered in the OPTIMA and SENSOR studies were also higher although more comparable to ours (56 and 67 mg/day in the mean, respectively). The differences are probably due to uptitration of dose per protocol in the aforementioned clinical trials, whereas, in our study, the dose increases were left to the physician's discretion.

The reductions in Ca and P were somewhat lower than those reported in 6-month clinical trials [20, 22, 23].

Mean Ca was reduced by 3.1% in our study versus a mean reduction of –8, –6.5 and –7% in the studies by Moe et al. [20], Sterrett et al. [22] and Messa et al. [23], respectively. Mean P was reduced by 7.5% versus –12% [20], –3.6% [22] and –10% [23], respectively.

With regard to other effectiveness data from routine clinical practice, a European study assessing long-term use of cinacalcet (approximately 2,000 patients on dialysis from 12 countries) [11] reported percentages of target achievement very similar to ours. They found that patients with more severe disease were less likely to achieve the iPTH target. In our cohort, similar findings were obtained when only the upper limit of 300 pg/ml was considered. However, the final percentages of patients meeting the KDOQI target for iPTH in our study did not display significant differences according to baseline severity due to a higher number of individuals with less severe disease whose iPTH levels fell below 150 pg/ml. The mean cinacalcet doses in the ECHO study were comparable (58–62 mg/day for patients with baseline iPTH 721–1,050 pg/ml and >1,050 pg/ml, respectively). As our results suggest that long-term dialysis predicts poor response to cinacalcet, the longer disease duration reported for their patients (mean of more than 6.5 years) might explain the differences between the two studies. Concerning low levels of PTH, although epidemiologic studies have been conducted on patients with SHPT mainly treated with vitamin D derivatives, and the significance of PTH values may not be the same in a cohort using calcimimetics, they should be avoided in dialysis patients [13, 14, 16]. Thus, Ca-containing phosphate binders, vitamin D derivatives and/or calcimimetics should be reduced or stopped [14].

In a large USA cohort treated with cinacalcet over 12 months [12], St. Peter et al. found worse results than those reported here, with only one quarter of patients achieving the iPTH target (from a median baseline PTH level of 577 pg/ml). Although the differences in response cannot be readily explained, their population presented important differences such as younger age and a larger number of African-American patients, but on the other hand, they were less time on dialysis and included a higher proportion of diabetics. The dose at 12 months for those patients (55 mg) was very similar to ours, with higher use of vitamin D sterols.

As expected, the mean cinacalcet dose increased according to disease severity, with 29% higher dose requirements in patients with severe disease. The final median dose in this subgroup was 60 mg/day, which suggests that cinacalcet was uptitrated – although very slowly – in the

patients with severe disease. Further studies should address the question whether the effectiveness could be improved with the use of higher doses, within the technical specifications (maximum recommended dose of 180 mg/day). Pharmacokinetic data suggest that dose response is linear over the range of 25–200 mg/day in patients on hemodialysis, and that gastrointestinal effects may be dose related [25]. In our study, treatment with cinacalcet was generally well tolerated. Dyspepsia, nausea or vomiting appeared in about 5% of patients, but led to treatment discontinuation in very few cases. These incidences are slightly lower to those reported in clinical trials [20–24, 26] (nausea: 13–32%, vomiting: 9–27%). A possible explanation could be the longer titration period in our study, but we cannot discard an underestimation of the incidence of adverse events due to the retrospective design, which is not a good way to assess tolerability. There is a probable association between the incidence of adverse events and the cinacalcet dose, but some degree of individual susceptibility also seems to be involved [20–24].

The use of cinacalcet was accompanied by a reduction in the use of vitamin D sterols, although the percentage of patients using paricalcitol remained similar. It must be noted that the number of patients on vitamin D treatment at baseline was particularly low for a SHPT cohort (less than 40%). A possible explanation could be that high Ca and/or P levels militated against the use of vitamin D sterols. After the introduction of cinacalcet, which allowed a better control of both Ca and P, we did not observe an increased use of vitamin D sterols, not even at low doses. Block et al. [27], in a clinical trial of combined therapy with cinacalcet and low doses of vitamin D sterols, found that 62% of patients refractory to conventional therapy achieved the KDOQI iPTH target in parallel with a reduction of 51% in the weekly dose of vitamin D sterols. However, it is important to emphasize that due to the increasingly recognized benefits of vitamin D in dialysis patients [28], nephrologists should be aware that the use of cinacalcet (probably irrespective of PTH levels) should not preclude the addition of native vitamin D (with pleiotropic effects beyond mineral metabolism, as recently demonstrated by Matias et al. [29]). As mentioned before, others have found an increased and more consistent use of vitamin D [12]. Thus, cinacalcet may allow treatment optimization with native or active vitamin D compounds.

Reductions in the use of some phosphate binders (especially sevelamer) [30] have also been described, although we did not observe such a trend. On the other hand, a significant increase in patients taking Ca-based phosphate binders is confirmed. It is important to em-

phasize that Ca-based phosphate binders have been associated with an increased risk of progression of vascular calcification before the calcimimetic era [31], and that they may have contributed to oversuppression of PTH in some patients. Results of prospective studies that are being currently conducted will allow more information to be gained in this relevant issue.

Almost 20% of the patients were on aluminium-based phosphate binders at baseline. Although they are not recommended for long-term use either by International or Spanish guidelines, a significant percentage of patients are still receiving them in routine practice [32, 33].

Our study included a large number of patients with a long follow-up, thus providing evidence from use of cinacalcet in routine clinical practice, in contrast to previous clinical trials. Nevertheless, there are certain limitations inherent in observational studies that should be taken into account. The included population was not entirely representative of the overall SHPT population, as they were refractory to conventional treatments. We collected data on concomitant medication use, but did not have enough patients to evaluate the effectiveness in each drug combination. For this reason, we cannot exclude that the effect of cinacalcet may differ depending on the use of concomitant agents, but previous stratified analyses from clinical and observational trials suggest that this effect is low [27, 34]. We did not control for other potential confounders as comorbidities or compliance with administered medications, which could influence the amount of delivered dose and drug effectiveness. As there was no comparator group, it is not clear whether our findings may be attributed only to cinacalcet. However, during the 12 weeks before the initiation of cinacalcet the iPTH levels of this cohort were rising despite classical treatment. Further studies assessing dose adjustments performed in clinical practice in more detail could help establishing maximal benefits of cinacalcet depending on patients' profiles (baseline severity, concomitant medications, age, time on dialysis).

Despite the improvement in biochemical parameters observed in the current and previous studies, the effect of cinacalcet on patient outcomes needs to be verified. Some combined analyses of clinical trials [35] suggest that cinacalcet is associated with significant reductions in the risk of parathyroidectomy, fracture and cardiovascular hospitalization; ongoing clinical trials have been specifically designed to answer those questions [36, 37].

In conclusion, cinacalcet in routine clinical practice allows increasing the percentage of patients achieving the treatment targets for iPTH, Ca and P, regardless of SHPT

disease severity at treatment initiation, simultaneously reducing all three laboratory parameters, and maintaining its effectiveness over a 72-week period. It must be stressed that the observed biochemical benefits were obtained with doses of cinacalcet 50% lower than those used in phase III studies. The optimal use of phosphate-binders and vitamin D in cinacalcet-treated patients needs to be addressed in future studies.

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Conflict of Interest

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