Nephrol Dial Transplant (2009) 24: 2852–2859
doi: 10.1093/ndt/gfp144
Advance Access publication 15 April 2009

Cinacalcet and achievement of the NKF/K-DOQI™ recommended target values for bone and mineral metabolism in real-world clinical practice—the ECHO observational study

Pablo Ureña[1], Stefan H. Jacobson[2], Emanuel Zitt[3], Marc Vervloet[4], Fabio Malberti[5], Neil Ashman[6], Sean Leavey[7], Marianne Rix[8], Ingrid Os[9], Heikki Saha[10], Miroslav Ryba[11], Veronika Bencova[12], Ana Baños[13], Valter Zani[13] and Denis Fouque[14]

[1]Clinique du Landy, Saint Ouen, France, [2]Danderyd Hospital and Karolinska Institute, Stockholm, Sweden, [3]Academic Teaching Hospital, Feldkirch, Austria, [4]VU Medisch Centrum, Amsterdam, The Netherlands, [5]AO Istituti Ospitalieri di Cremona, Cremona, Italy, [6]The Royal London Hospital, London, UK, [7]Waterford Regional Hospital, Waterford, Ireland, [8]University Hospital, Copenhagen, Denmark, [9]Ullevål University Hospital, University of Oslo, Oslo, Norway, [10]Tampere University Hospital, Tampere, Finland, [11]Krajska Nemocnice Liberec, Liberec, Czech Republic, [12]DIA_NE sro, Nitra, Slovakia, [13]Amgen Europe GmBH, Zug, Switzerland and [14]Hôpital Edouard Herriot, University Lyon 1, France

Correspondence and offprint requests to: Pablo Ureña; E-mail: urena.pablo@wanadoo.fr

Abstract

Background. The use and effectiveness of cinacalcet in 'real-world' clinical practice was investigated in a pan-European observational study in dialysis patients with secondary hyperparathyroidism (SHPT) of varying severity.

Methods. Adult patients with chronic kidney disease on dialysis who had initiated cinacalcet treatment were enrolled. Data were collected 6 months before initiating cinacalcet, at baseline (initiation of cinacalcet) and up to 12 months after cinacalcet initiation.

Results. A total of 1865 patients [mean (SD) age 58 (15) years] were enrolled from 187 sites in 12 countries. Most patients had a dialysis vintage of ≥1 year (1–5 years, $n = 833$; >5 years, $n = 748$ versus <1 year, $n = 265$). The patients generally had severely uncontrolled intact parathyroid hormone (iPTH) serum levels (median 721 pg/ml) and elevated phosphorus (median 5.9 mg/dl) and calcium (median 9.6 mg/dl) at baseline, despite being prescribed conventional therapies. The proportions of patients achieving the recommended [NKF-K/DOQI™ (KDOQI™)] targets increased from baseline [4%, 39%, 40% and 46% for iPTH, phosphorus, calcium and calcium–phosphorus product (Ca × P), respectively] to Month 12 (28%, 48%, 51% and 68%, respectively). At Month 12, 18% of patients had achieved the combined target for iPTH + Ca × P compared with 2% at baseline. Most patients (65%) received <60 mg/day cinacalcet at Month 12. Vitamin D sterol use remained fairly stable throughout the study. There was a 13% decrease in prescribed sevelamer; use of calcium-based phosphate binders increased by 5.6%. There was no unexpected safety or tolerability concerns.

Conclusion. This analysis of current European clinical practice shows that—consistent with findings from randomized controlled trials and retrospective observational studies—cinacalcet improves attainment of KDOQI™ bone metabolism targets in dialysis patients with various stages of SHPT.

Keywords: calcimimetic; cinacalcet; clinical practice; secondary hyperparathyroidism; targets

Introduction

Patients with chronic kidney disease (CKD) can develop secondary hyperparathyroidism (SHPT) through altered metabolism of calcium, phosphorus and vitamin D [1]. Uraemic patients with SHPT exhibit persistently elevated serum parathyroid hormone (PTH) levels [2], which can deleteriously affect the function of multiple organs [3]. Cardiovascular complications may also occur [2]; these effects are associated with increased mortality and morbidity [4,5].

To improve the care of dialysis patients, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative [NKF-K/DOQI™ (KDOQI™)] recommends targets for serum intact PTH [iPTH; 150–300 pg/ml (15.9–31.8 pmol/l)], serum phosphorus [3.5–5.5 mg/dl (1.13–1.78 mmol/l)], total corrected serum calcium [8.4–9.5 mg/dl (2.10–2.37 mmol/l)] and the calcium–phosphorus product (Ca × P) [<55 mg^2/dl^2 (<4.44 $mmol^2/l^2$)] [6]. Consistent achievement of the recommended targets strongly predicts survival [7]; however, only a small proportion of dialysis patients with SHPT receiving conventional therapies (calcium salts, vitamin D sterols and phosphate binders) achieve and sustain control of KDOQI™ targets for serum iPTH, phosphorus and calcium [8]. Furthermore,

calcium salts and vitamin D sterol treatment can elevate calcium and/or phosphorus levels, causing hypercalcaemia and/or hyperphosphataemia, respectively, and a high risk of cardiovascular and soft tissue calcification. Soft tissue calcifications generally necessitate treatment interruption, potentially allowing disease progression [9–11].

The calcimimetic cinacalcet (Mimpara®/Sensipar®, Amgen Inc., Thousand Oaks, CA, USA) was approved for the treatment of SHPT in dialysis patients in 2003 (in the USA, 2004 in Europe) and it has enabled reconsideration of treatment paradigms. Cinacalcet suppresses PTH secretion by increasing the sensitivity of the parathyroid calcium-sensing receptors to extracellular calcium [12,13]. Phase III studies show that cinacalcet improves patients' likelihood of achieving the recommended KDOQI™ target for serum iPTH, phosphorus, calcium and Ca × P [14,15]. Compared with conventional therapy, treatment with cinacalcet has also been shown to give more sustained control of iPTH and Ca × P [16].

Observational studies reflect 'real-world' clinical practice and yield important information about the effectiveness of treatment regimens and their use by clinicians in daily practice. The use of less stringent inclusion/exclusion criteria in observational studies allows a closer reflection of the overall patient population than in randomized clinical trials. There is currently little information available on cinacalcet and its impact on markers of mineral bone disease in real-life clinical practice. To address this, we conducted ECHO (Evaluation of the Clinical Use of Mimpara® in Haemodialysis and Peritoneal Dialysis Patients, an Observational Study)—the first pan-European observational study to investigate the use and effectiveness of cinacalcet in dialysis patients with various stages of SHPT.

Methods

Patients

Data were collected from adult CKD patients on dialysis who had been prescribed cinacalcet; patients treated with cinacalcet in any interventional clinical trial were excluded. Where local regulations required, patients signed an informed consent form approved by an independent ethics committee/institutional review board.

Study design

This was a multicentre, multinational, part-retrospective/part-prospective, observational study. Sites with an interest in observational research and with cinacalcet prescribers were approached for inclusion in May/July 2005. The aim was to select dialysis centres and patient numbers to ensure that enrolment within each country cluster was broadly the representative of the dialysis population within that country cluster with respect to region and type of centre.

Patients were enrolled between July 2005 and October 2006 from 187 sites in 12 countries. There were two study periods: 6 months' retrospective data collection from patients receiving vitamin D sterols and/or phosphate-binding agents (before cinacalcet initiation); and 12 months' retrospective/prospective data collection (depending on the timing of study enrolment) from patients initiating cinacalcet (baseline). No treatment algorithm was provided. The decision to initiate cinacalcet was made by the treating physician, thus the study observed actual clinical practice.

No clinic visits were required other than those regularly scheduled. No laboratory or diagnostic tests were performed other than those associated with usual patient care. Medical histories, comorbidities, concurrent medication and laboratory data were collected, with data being taken from patient records, where appropriate, by investigators or designees. Variables collected were age at enrolment, gender and race; primary aetiology of CKD; medical history; dialysis start date, dialysis modality and number of hours of haemodialysis per week at enrolment; history of kidney transplantation and parathyroidectomy; site characteristics such as type of centre, centre funding, number of dialysis patients cared for by centre; prior involvement in cinacalcet clinical studies; number of dialysis patients receiving cinacalcet; PTH, P, Ca and Ca × P and albumin laboratory values; frequency of PTH, P and Ca testing; phosphate-binder usage; vitamin D usage; dialysate standard calcium concentration; hospitalizations and adverse drug reactions (ADRs).

Key measures

The key measures were the proportion of patients attaining KDOQI™ targets for serum iPTH, phosphorus, calcium Ca × P and the combination of iPTH + Ca × P at 12 months, observed by individual country (overall data rather than individual country data are presented here). Other measures included absolute values over time and percentage changes in serum iPTH, phosphorus, calcium and Ca × P; and the evaluation of practice patterns in SHPT management, assessed by the usage of cinacalcet, vitamin D sterols (IV or oral calcitriol and alfacalcidol and IV paricalcitol) and phosphate binders [calcium based (sevelamer, lanthanum carbonate) and aluminium based] alone or in combination.

Safety and tolerability were assessed in terms of the incidence of ADRs, serious ADRs and deaths. An ADR was defined as an adverse event that the investigator considered to be attributed to the use of cinacalcet.

Parathyroid hormone measurements

Biochemical markers and drug usage were assessed locally at intervals defined by local clinical practice. PTH assay information was available from 102 sites (55%). Most sites (94%) used iPTH measurements; the Elecsys PTH, Immulite and PTH Advia Centaur assays were most commonly used [81 sites (79%)]. The frequency of PTH measurements was at the discretion of the treating nephrologist. In the 6 months before cinacalcet initiation, PTH was measured <1 time/month in 80% of patients; 9–12 months after cinacalcet initiation, the PTH testing frequency increased (<1 time/month, 58% of patients; 1–<2 times/month, 42% of patients).

Statistical analyses

The study was not designed to perform formal statistical comparisons, so a sample size was selected based on the need to have sufficient data to enable the analyses to be run separately for individual countries (or country clusters). The number of participants from each country or country cluster was aimed to reflect the proportion of dialysis patients in that country or country cluster as compared with the whole European dialysis population. The number of participants was intended to range from ∼100 patients to 600 patients within each country/country cluster. The sample size calculation for each country/country cluster was based on the anticipated value and 95% confidence interval (CI) for PTH and Ca × P (primary measure). Combinations of possible scenarios were determined to provide acceptable precision of the estimate for the primary measure and to enable separate analyses for individual countries.

The analysis population comprised all enrolled patients starting cinacalcet therapy—the primary analysis set for effectiveness and safety. Analyses used observed data; percentages were calculated according to the total number of patients in the full analysis set with no missing data. Patients not reporting data on a parameter at a particular time point were excluded from the analysis at that time point. Analyses were descriptive and are presented for all continuous and categorical variables.

Serum iPTH, phosphorus, calcium and Ca × P analyses at time points before, at and following cinacalcet initiation were based on the means of all values collected within specified time frames [for achievement of target analyses, ±3 months for all parameters (−3 months at initiation) and for absolute values/percentage change analysis, ±6 weeks for PTH (−3 months at initiation) and ±2 weeks for P and Ca (−2 weeks at initiation)]. PTH levels measured by the biointact assay were converted to iPTH values by multiplying them by 1.95 [17]. Corrected calcium (mg/dl) was calculated as total calcium (mg/dl) + 0.8 [4.0 − albumin (g/dl)]. Reported ionized serum calcium values (12% of total values) were handled separately using a target of 4.4–5.2 mg/dl for ionized calcium and $<28.5\ mg^2/dl^2$ for ionized Ca × P.

To eliminate erroneous data, values outside the following ranges were excluded from analyses: calcitriol 0–15 μg/week; alfacalcidol (oral and

intravenous) 0–25 μg/week; paricalcitol 0–50 μg/week; phosphate binder 0–15 000 mg/day (0–10 000 mg/day if calcium based); dialysate calcium 0–20 mg/dl; iPTH 10–12 000 pg/ml; derived corrected or investigator-reported corrected calcium values 5–14 mg/dl; ionized calcium 4.4–5.2 mg/dl; phosphorus 2–10 mg/dl; albumin 1–20 g/dl). Information on total elemental calcium intake was not collected.

ADRs were reported from baseline. All ADRs reported were assigned a MedDRA preferred term. Other safety data (i.e. numbers and proportions of patients hospitalized, admitted to an intensive care unit, with symptomatic fractures and undergoing parathyroidectomy) were analysed before and after cinacalcet initiation. To allow analysis of discontinuations, patients completing the study were regarded as those who received their last cinacalcet dose on or after Day 330.

Results

Patients

A total of 1865 patients were enrolled from 187 centres in 12 European countries (Austria, Czech Republic, Slovakia, France, Italy, The Netherlands, Denmark, Finland, Norway, Sweden, Ireland and the UK) between July 2005 and October 2006. Of these, 1607 (86%) completed the study, 254 (14%) withdrew and 453 (24%) discontinued cinacalcet by Month 12. Completion/withdrawal data were unavailable for four patients.

The patients' mean [standard deviation (SD)] age at cinacalcet initiation (baseline) was 58 (15) years (Table 1). The majority (88%) of patients were receiving haemodialysis. At cinacalcet initiation, almost all patients were receiving conventional SHPT therapy—vitamin D sterols (62% of patients) and phosphate-binding agents (90%). iPTH was severely uncontrolled at baseline (median 721 pg/ml). Median baseline values for serum phosphorus, calcium and Ca × P (Table 1) also exceeded the KDOQI™ recommended targets.

Achievement of KDOQI™ treatment targets

Achievement of KDOQI™ targets improved for all four biochemical parameters from baseline (cinacalcet initiation) to Month 12 (Figure 1). The proportions (95% CI) of patients attaining KDOQI™ targets at Month 12 were 28% (26–31%) for serum iPTH, 48% (45–50%) for phosphorus, 51% (48–53%) for calcium and 68% (66–70%) for Ca × P, compared with 4, 39, 40 and 46% at baseline, respectively. Thirty-six percent (95% CI 33–38%) of patients had achieved a PTH level of 100–300 pg/ml by Month 12. At Month 12, 18% (95% CI 16–20%) of patients achieved the combined KDOQI™ target for iPTH and Ca × P compared with 2% at baseline. Within 3 months of starting cinacalcet, median values for serum phosphorus, serum calcium and Ca × P were reduced sufficiently to achieve KDOQI™ targets (Figure 2). The median percent changes from baseline to Month 12 were −50, −9, −6 and −17% for serum iPTH, phosphorus, calcium and Ca × P, respectively; 66% of patients achieved a reduction in iPTH of ≥30% from baseline.

When patients were stratified by baseline iPTH severity (mild: iPTH 300–<500 pg/ml; moderate: iPTH 500–800 pg/ml; severe: iPTH >800 pg/ml), achievement of KDOQI™ targets at Month 12 for serum iPTH was higher

Table 1. Patient demographics and baseline laboratory values at initiation of cinacalcet therapy

Variable	Total ($n = 1865$)
Demographic	
Mean (SD) age, years	58 (15.0)
Gender, *n* (%)[a]	
Male	1068 (57)
Female	791 (42)
Race, *n* (%)	
White	1298 (70)
Black and other	77 (4)
Not recorded	490 (26)
Dialysis modality, *n* (%)[b]	
Haemodialysis	1632 (88)
Peritoneal dialysis	229 (12)
Mean (SD) duration of dialysis (months)	
Haemodialysis	79 (78)
Peritoneal dialysis	37 (49)
Dialysis vintage, *n* (%)	
<1 year	265 (14)
1–5 years	833 (45)
>5 years	748 (40)
Awaiting renal transplantation, *n* (%)	566 (30)
Previous renal transplantation, *n* (%)	381 (20)
Previous parathyroidectomy, *n* (%)	153 (8)
History of diabetes, *n* (%)	367 (20)
Conventional drug use	
Vitamin D use, *n* (%)	1154 (62)
Phosphate binder use, *n* (%)	1683 (90)
Calcium based	774 (42)
Sevelamer	1225 (66)
Aluminium based	266 (14)
Lanthanum carbonate	13 (0.7)
Laboratory parameters	
Median (Q1, Q3) serum iPTH (pg/ml)	721 (507, 1050)
Median (Q1, Q3) serum phosphorus (mg/dl)	5.9 (4.8, 6.8)
Median (Q1, Q3) serum calcium (mg/dl)	9.6 (9.1, 10.4)
Median (Q1, Q3) serum Ca × P (mg^2/dl^2)	56 (46, 67)

Ca × P, calcium–phosphorus product; CI, confidence interval; iPTH, intact parathyroid hormone; Q, quartile; SD, standard deviation.
[a]Gender not recorded for six patients.
[b]Twelve patients started cinacalcet before dialysis. Dialysis duration was not recorded for three patients.

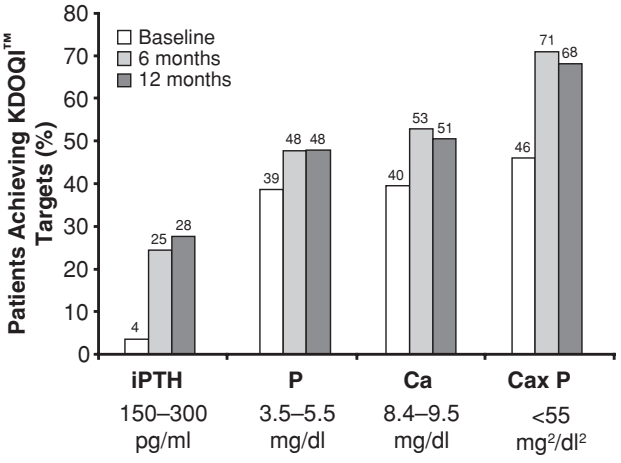

Fig. 1. Proportion of patients achieving Kidney Disease Outcomes Quality Initiative (KDOQI™) recommended targets at baseline, 6 months and 12 months. Ca, calcium; Ca × P, calcium–phosphorus product; iPTH, intact parathyroid hormone; P, phosphorus.

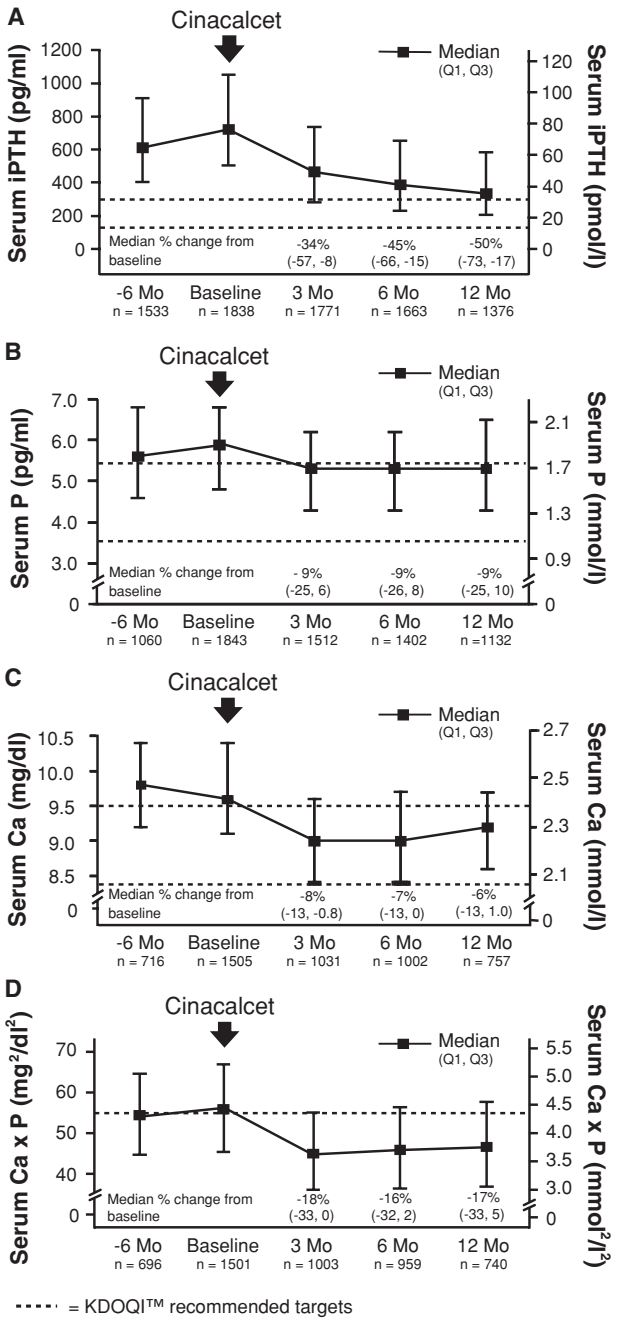

Fig. 2. Changes in serum levels of laboratory parameters over time: (**A**) iPTH, (**B**) phosphorus, (**C**) calcium, (**D**) Ca × P. Ca, calcium; Ca × P, calcium–phosphorus product; iPTH, intact parathyroid hormone; P, phosphorus; Q, quartile.

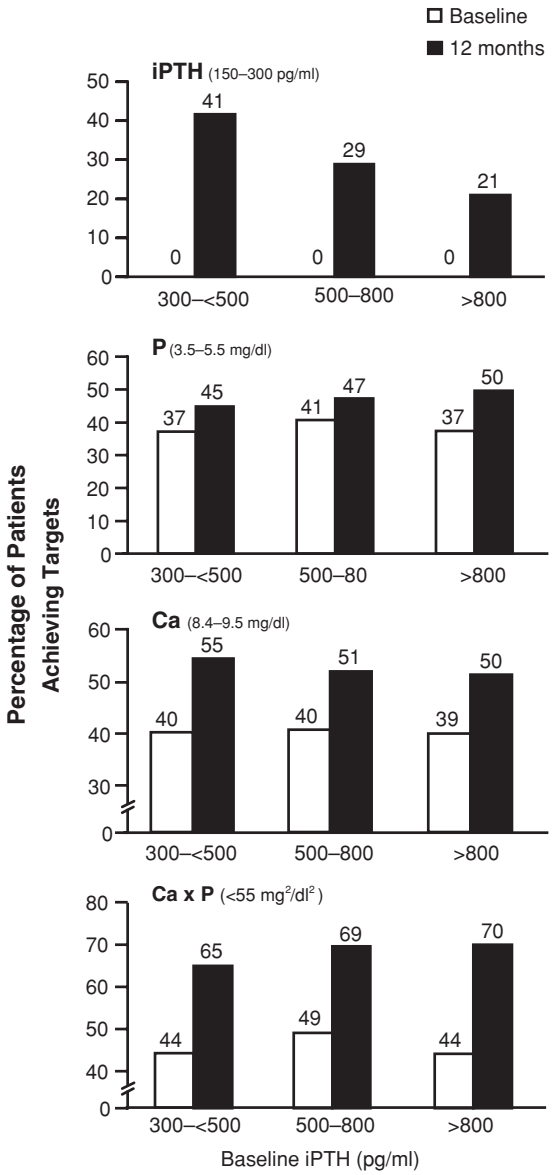

Fig. 3. Achievement of Kidney Disease Outcomes Quality Initiative (KDOQI™) recommended targets according to baseline disease severity, mild (median baseline iPTH 300–<500 pg/ml), moderate (median baseline iPTH 500–800 pg/ml) and severe (median baseline iPTH >800 pg/ml). Ca, calcium; Ca × P, calcium–phosphorus product; iPTH, intact parathyroid hormone; P, phosphorus.

for patients with mild disease (41%) versus those with moderate (29%) and severe disease (21%) (Figure 3). For all disease severities, iPTH levels were reduced after 3 months' cinacalcet treatment, with the greatest reduction seen in the severe disease subgroup (Figure 4). Patients achieving the recommended target iPTH range at 12 months also had controlled phosphorus and calcium levels (mean within recommended ranges) regardless of baseline iPTH levels (data not shown). However, in patients who failed to achieve the iPTH target range at Month 12, those with mild disease (baseline iPTH 300–<500 pg/ml) had the highest phosphorus values at Month 12 [mean (SD) phosphorus 6 (1.5) mg/dl compared with 5.6 (1.4) mg/dl and 5.4 (1.4) mg/dl in moderate and severe SHPT patients, respectively]. In contrast, serum calcium levels were within the target range in patients who did not achieve iPTH <300 pg/ml at Month 12, regardless of baseline iPTH levels.

Cinacalcet dose, vitamin D and use of phosphate binders

Twelve months after cinacalcet initiation ($n = 1574$), the mean (SD) daily dose was 50 (37) mg [median (Q1, Q3) = 30 mg (30 mg, 60 mg)] for the total study population;

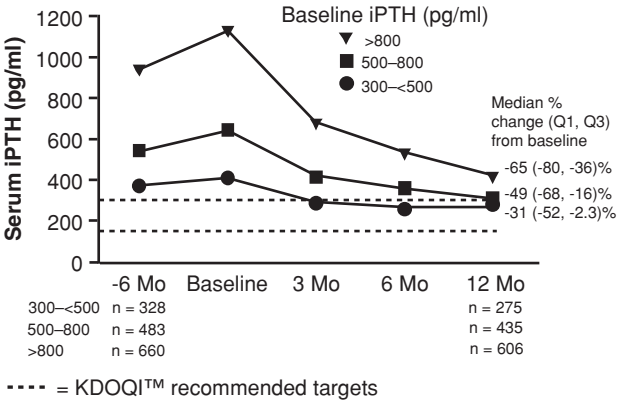

Fig. 4. Magnitude of iPTH reduction according to baseline disease severity (baseline iPTH: mild, 300–<500 pg/ml; moderate, 500–800 pg/ml; severe, >800 pg/ml). iPTH, intact parathyroid hormone; KDOQI™, Kidney Disease Outcomes Quality Initiative; Q, quartile.

Table 2. Mean cinacalcet dose (Month 12) in patients reaching/not reaching Kidney Disease Outcomes Quality Initiative (KDOQI™) target range at 12 months according to disease severity

	Mean (SD) cinacalcet dose (mg/day) [No. of patients]	
Disease severity by baseline iPTH level	150–300 pg/ml	>300 pg/ml
Mild (iPTH 300–<500 pg/ml)	34 (26) [126]	50 (35) [134]
Moderate (iPTH 500–800 pg/ml)	48 (35) [145]	55 (38) [286]
Severe (iPTH >800 pg/ml)	53 (31) [146]	64 (40) [474]

Ca × P, calcium–phosphorus product; iPTH, intact parathyroid hormone; SD, standard deviation.

patients withdrawn from cinacalcet, but continuing on the study, were listed as 0 mg. For patients remaining on treatment at Month 12 ($n = 1374$), the mean (SD) daily dose was 57 (34) mg [median (Q1, Q3) = 60 mg (30 mg, 60 mg)]. Most patients (65%) received ≤60 mg/day; doses administered included 30 mg/day (37%); 60 mg/day (28%), 90 mg/day (13%); 120 mg/day (5%); 180 mg/day (1%); other (3%) and no dose (12%). Table 2 shows the cinacalcet dose in patients with mild, moderate and severe SHPT by target achievement. Patients with baseline iPTH >800 pg/ml not reaching the target range of 150–300 pg/ml at Month 12 were receiving only a slightly higher mean dose compared with those within target [63.7 mg/day (>300 pg/ml) versus 52.7 mg/day (150–300 pg/ml)].

Overall, the proportion of patients taking vitamin D products remained relatively stable over the study period (62% at baseline, 63% at Month 6 and 58% at Month 12). Patients taking vitamin D sterols were mostly receiving alfacalcidol (35% at Month 12) or calcitriol (17% at Month 12), with only a small number taking paricalcitol (7% at Month 12). Any changes in the mean dose over time were minimal (Table 3).

Of the 90% of patients prescribed phosphate binders at baseline, most received sevelamer (66%) and/or calcium-based agents (42%). Twenty-two percent of patients received a combination of both sevelamer and calcium-based agents. Some changes in phosphate-binder use were observed during cinacalcet treatment: from baseline to Month 12, sevelamer use decreased by 13%, whereas the use of calcium-based phosphate binders increased by 5.6%. The mean sevelamer dose decreased from baseline to Month 12 (from 5099 to 4875 mg/day), and the mean dose of calcium-based phosphate binders increased (from 1794 to 1978 mg/day) (Table 3). Doses of aluminium-based phosphate binders remained relatively stable; lanthanum carbonate doses increased, but few patients received this agent (<1% at baseline; 5% at Month 12).

Table 3. Doses of vitamin D sterols and phosphate binders over time

Mean dose (SD)	−6 months Baseline	6 months	12 months
Vitamin D sterols (μg/week) (*n* at baseline)			
Alfacalcidol			
IV ($n = 247$)	5.4 (3.7)	5.6 (3.5)	5.6 (3.1)	4.9 (2.8)
Oral ($n = 474$)	3.3 (2.5)	3.5 (3.0)	3.7 (3.1)	4.0 (3.5)
Calcitriol			
IV ($n = 119$)	3.9 (1.7)	4.0 (1.9)	3.4 (1.4)	3.2 (1.5)
Oral ($n = 215$)	2.4 (1.4)	2.15 (1.3)	2.5 (1.8)	2.5 (1.6)
Paricalcitol[a]			
IV ($n = 61$)	13.9 (9.6)	18.0 (11.4)	16.2 (9.5)	16.3 (9.5)
Phosphate binders (mg/day)			
Calcium based ($n = 769$)	1810 (1287)	1794 (1268)	1942 (1355)	1978 (1420)
Sevelamer ($n = 1218$)	5010 (2645)	5099 (2618)	4995 (2562)	4875 (2560)
Aluminium based ($n = 259$)	2499 (1607)	2719 (1639)	2517 (1573)	2639 (1528)
Lanthanum carbonate ($n = 13$)	950 (577)	1692 (596)	1800 (777)	2042 (887)

IV, intravenous; SD, standard deviation.
[a]No. of patients received oral paricalcitol from baseline to Month 12.

Tolerability, safety and treatment persistence

ADRs were reported in 11% of patients; nausea (5%) and vomiting (3%) were most commonly reported. All other ADRs occurred in <1% of patients: abdominal pain (0.9%); diarrhoea (0.9%); dyspepsia (0.6%) and hypocalcaemia (0.6%). Six patients (0.3%) had serious treatment-related AEs: gastric ulcer haemorrhage (0.1%); angina pectoris (0.1%); increased blood potassium (0.1%), convulsion (0.1%); hypocalcaemia (0.1%); lung disorder (0.1%); muscular weakness (0.1%); neuralgia (0.1%) and paraesthesia (0.1%).

The mean (SD) cinacalcet therapy duration was 322 (93) days. Three-quarters of patients remained on cinacalcet at Day 330; the main reasons for discontinuation of cinacalcet were renal transplantation (5%), PTH oversuppression (4%), nausea and vomiting (3%), non-compliance (1%), parathyroidectomy (1%), AE other than nausea and vomiting or hypocalcaemia (1%), hypocalcaemia (0.6%), poor response (0.4%) and other (7%). Key reasons for withdrawal from the study comprised death (5%) and other (5%).

The numbers/proportions of patients hospitalized, admitted to an intensive care unit or experiencing symptomatic fractures remained stable throughout the study (data not shown). Before cinacalcet therapy, 8% of patients underwent a parathyroidectomy; from baseline to Month 6

and from Months 6 to 12, 0.8% and 2% of patients, respectively, were parathyroidectomized.

Discussion

This large observational study indicates that cinacalcet treatment improves attainment of the KDOQI™ recommended serum iPTH, phosphorus, calcium and Ca × P targets in a CKD dialysis population with SHPT in the real-world setting. The effectiveness of cinacalcet in clinical practice is consistent with reports in similar patients in randomized, controlled trials and in a recent observational retrospective study [14,15,18,19].

At baseline, iPTH levels were severely uncontrolled in most patients (median baseline serum iPTH level, 721 pg/ml); only 4% of patients had an iPTH level within KDOQI™ targets at baseline. Similarly, serum phosphorus, serum calcium and Ca × P were also insufficiently controlled, with median baseline levels exceeding KDOQI™ targets. These data highlight the presence of a population of dialysis patients with various stages of SHPT that require additional intervention for them to attain KDOQI™ bone metabolism targets.

Following initiation of cinacalcet treatment, beneficial effects were observed for all four parameters in these patients with severely uncontrolled disease. Cinacalcet treatment increased the proportion of patients attaining KDOQI™ targets, particularly for iPTH (28% at Month 12 versus 4% at baseline). Median serum levels were reduced by 50% for iPTH, by 17% for Ca × P, by 9% for phosphorus and by 6% for calcium at Month 12. These results are consistent with previous interventional studies of the effects of cinacalcet therapy in similar patient populations [14–16,18,20]. Furthermore, 36% of patients achieved a PTH level of 100–300 pg/ml at Month 12, the PTH range with the lowest risk of mortality [21], and two-thirds of patients experienced a reduction in iPTH levels ≥30% between baseline and Month 12.

Although the ECHO study did not contain a control group, the proportion of patients achieving KDOQI™ targets with cinacalcet was generally better than those receiving conventional therapy in the control arm of other studies [18,20]. For example, 28% of patients achieved the KDOQI™ target for iPTH with cinacalcet, compared with 10% and 17% of patients receiving conventional therapy in the studies conducted by Moe *et al*. and Messa *et al*., respectively, and 24% in a recent observational study conducted by St Peter and colleagues [19]. The improved attainment of KDOQI™ targets is an important finding, given the association between consistent control of biomarkers of bone and mineral metabolism and survival in dialysis patients [7].

The mean and median daily cinacalcet doses used in the ECHO study (50 and 30 mg/day, respectively) were markedly lower than those administered to patients in phase III, randomized, double-blind, placebo-controlled trials (mean 107 mg/day), which followed strict protocol-defined guidelines on dosing titration (iPTH ≤250 pg/ml was the primary endpoint in the phase III trials, which was implemented before publication of the KDOQI™ targets) [20]. This suggests that cinacalcet may be insufficiently uptitrated in a flexible dosing regimen in real-life clinical practice. In this study, for example, patients with baseline iPTH >800 pg/ml who were not achieving targets received only a slightly higher mean dose than those within target [63.7 mg/day (iPTH >300 pg/ml) versus 52.7 mg/day (iPTH 150–300 pg/ml)]. Slow and modest dosage titration was also observed in the observational study conducted by St Peter and colleagues [19]. Increasing cinacalcet doses at predefined time points in patients not achieving KDOQI™ targets may further improve the control of biochemical parameters in patients with SHPT, although higher doses may potentially increase the incidence of any cinacalcet-related side effects.

Cinacalcet also appears to be reserved for use in patients with more severe disease. Disease severity was indicated by patients with very high PTH levels and insufficient control of biochemical parameters at baseline, in addition to long dialysis vintage (mean duration >6.5 years for haemodialysis and >3 years for peritoneal dialysis at baseline). However, patients with mild disease at baseline (i.e. median iPTH 300–<500 pg/ml) were more likely to achieve KDOQI™ PTH targets than those with more severe disease (i.e. median iPTH >800 pg/ml). This supports the supposition that treating patients with SHPT at an earlier, less-severe disease stage may result in the prevention of more severe or therapy-resistant SHPT. Whether improved attainment of KDOQI™ targets, especially for iPTH, produces improved clinical outcomes is the leading question of the ongoing, prospective, randomized trial, EVOLVE. However, it should be noted that the magnitude of iPTH reduction increased with increasing disease severity, as defined by median baseline iPTH, indicating that cinacalcet also has an important role in improving severely uncontrolled SHPT. Interestingly, patients with more severe SHPT, and thus higher bone turnover, also had lower phosphorus levels after Month 12 versus those with less severe SHPT, suggesting that high bone turnover may be improving with cinacalcet treatment; however further studies are needed to confirm this.

The mean total dose of calcium-based phosphate binders used in the ECHO study ranged from 1794 to 1978 mg/day, which was considerably greater than the KDOQI™ recommended maximum (1500 mg/day) for patients with CKD stage 5 [6]. Indeed, both the proportion of patients receiving calcium-based phosphate binders and the mean dose increased from baseline to Month 12. However, levels of both serum calcium and serum phosphorus were reduced by Month 12, indicating that the potential calcium-increasing effect of calcium-based phosphate binders was offset by cinacalcet treatment, which lowers calcium levels. Based on expert opinion rather than evidence and published before the introduction of cinacalcet, the KDOQI™ recommendations for calcium intake aim to reduce the risk of vascular calcification caused by high calcium in the presence of high phosphorus—a common occurrence in this patient population. Recent evidence from preclinical *in vivo* studies suggests that calcimimetics may prevent soft tissue (including vascular) calcification and may increase calcium deposition in bones under calcium-loading conditions [22,23].

There were no unexpected safety or tolerability concerns during the present study. The incidence of ADRs was low, serious ADRs were rare, and there were relatively few discontinuations. Importantly, over three-quarters of patients remained on cinacalcet 12 months after treatment initiation.

When interpreting the results, limitations of observational analyses should be considered. The decision to initiate cinacalcet was made locally at the discretion of the treating physician, limiting the validity of the findings. It is possible that the knowledge that treatment practices were being observed as part of a prospective study may have influenced the nephrologists' treatment decisions. Patients and sites were not selected as being representative of Europe as a whole, and covariate analyses indicated significant interactions between countries and outcomes (data not shown). The frequency of testing was based on local clinical practice and variation was apparent across different sites, possibly influencing titration and target achievement. Missing data from some sites and at some time points could have introduced bias into the analyses.

Despite its limitations, this study provides important information on current SHPT management, highlighting unmet need in dialysis patients with moderate SHPT as well as in those with severe disease. A population of poorly controlled patients exists despite extensive use of conventional therapy. This analysis of current clinical practice across Europe has shown that cinacalcet treatment provides marked improvements in biochemical parameters, helping patients to achieve KDOQI^{TM} targets for serum levels of iPTH, phosphorus, calcium and Ca $\times$ P.

Acknowledgements. This study was sponsored by Amgen Europe. We would like to thank Chris Harris of Amgen Europe for clinical support, Tamsin Williamson and Andrew Lockley of Bioscript Stirling Limited and Antonia Panayi of Amgen Europe for providing writing support, Tracey Wheeler of Amgen Europe for the biostatistics analyses and Jason Smith for his assistance with the numerical programming. We would also like to thank all ECHO investigators: Drs Odd Aakervik, Alberto Albertazzi, Mahen Albadawy, John Alexander, Brahim Amara, Stig Arne Kjellevold, Klaus Arneitz, Hjalmar Aselius, Markku Asola, Martin Auinger, Neils Aunsholt, Lynda Azzouz, Peter Balcke, Pierre Bataille, Charlotte Bebb, Guido Bellinghieri, Pierre Benas, Michel Beruard, Erling Bjerregaard Pedersen, Chantal Bony, Pierre Bories, Jean-Louis Bouchet, Jean Bracco, Mohamed Brahim Bounab, Maurizio Brigante, Christian Broyet, Philippe Brunet, Anton Brunhofer, Petr Bucek, Agnes Caillette-Beaudoin, Silvia Carozzi, Lofti Chalabi, Moktar Chawki, Bouchra Chlih, Bruno Coevoet, Florence Cogny, Giacomo Colussi, Peter Conlon, Francis Counillon, Herve Le Monies de Sagazan, Franco della Grotta, Henrik Daugaard, Henning Danielsen, Renato Demontis, Cora Denicola, Anna Deschamps, Claude Desvergnes, Sven-Ingmar Deurell, Petra Douwes-Draaijer, Petronella Du Buf-Vereijken, Manfred Eigner, Rocco Ferrara, Henry Fitte, Jean-Louis Flavier, Terja Forslund, Johannes Fraberger, Giovanni Maria Frasca, Luc Frimat, Hacène Gaid, Martha Galli-Leslie, George Galvan, Rüdiger Ganss, Giacomo Garibotto, Janusz Goch, Helmut Graf, Nils Grefberg, Peter Smak Gregoor, Pasquale Guastaferro, Marie-Paule Guillodo, Johann Günther Loipl, Mikko Haapio, Atman Haddj-Elmrabet, Abdelkader Hadj, Ernst Hagen, Jan Hama, Mathias Haarhaus, Vlasta Havrankova, James Heaf, Maija Heiro, Olof Hellberg, Isabel Hernandez, Iveta Hofierkova, Gerhard Hofstatter, Adriaan Hollander, Herwig Holzer, Eero Honkanen, Philippe Honore, Gilles Hufnagel, Britta Hylander, Giovanni Iacono, Andrea Icardi, Risto Ikäheimo, Jean-Paul Imiela, Otmar Janko, Gert Jensen, Veronique Joyeux, Norbert Kaiser, Marcelo Kamienny, Suren Kanagasundarem, Mahzuz Karim, Krassimir Katzarski, Rateb Khayet, Heinrich Kiss, Renate Klauser-Braun, Jerzy Klefter, Richard Kogler, Dietmar Kohlhauser, Isabelle Kolb, Walter Kotzmann, Josef Kovarik, Mustafa Kurtovic, Michel Lankester, Isabelle Landru, Erland Löfberg, Luigi Lombardi, Anne Lumiaho, Stig Lykkegaard Hansen, Ghassan Maakaroun, Soren Madsen, Öyvind Mathillas, Bruno Memoli, Filippo Milione, Magdalena Mokrejsova, Francoise Moussion, Kwok Wai Mui, Janneke Mulder, Marta Nedbalkova, Peter Neudorfer, Ulrich Neyer, Finn Nielsen, Lisbet Nilsson, Emerson Nsembami, Roman Ondraschek, Sonia Osagie, Ove Ostergaard, Kjeld Erik Otte, Sergio Papagni, Benny Persson, Nathalie Pertuiset, Philippe PetitJean, Dominique Pierre, Francesco Pizzarelli, Erich Pohanka, Wolfgang Pronai, Gabriel Racz, Bernd Ramsauer, Jean-Pierre Rechke, Louis Reichert, Björn Rogland, Alexander Rosenkranz, Catherine Rouanet, Markus Rumpsfeld, Martin Saint-Georges, Kristian Selvig, Wolfgang Serininger, Elvia Sicurezza, Richard Smith, Robert Smith Pedersen, Beata Somloova, Agneta Ståhl-Nilsson, Gunnar Sterner, John Stoves, Paolo Strippoli, Ulf Strömbom, Peter Swedenborg, Petr Taborsky, Anne-Beate Tafjord, Zafer Takla, Tugduial Tanquerel, Marc Ten Dam, Martin Tidman, Lars Thorud, Frederic Tollis, Henk van Hamersvelt, Bert-Jan Potter van Loon, Rudolf Vikydal, Louis-Jean Vleming, Andreas Vychytil, Hans Waller, Bruno Watschinger, Clemens Weiser, Lars Weiss, Björn Wikström, Jan Wilske, Christine Wohlfahrt and Ulf Wrege.

Conflict of interest statement. N.A. has received honoraria from Amgen. D.F. has received speaker and consultancy fees from Amgen, Genzyme and Shire. S.J. has acted as scientific consultant for Amgen, Abbott, Genzyme and Swedish Orphan. He has also received honoraria from Amgen, Abbott, Genzyme and Swedish Orphan. I.O. has received honoraria either as a scientific consultant or as a speaker from Amgen, Abbott, Novartis, Roche, Swedish Orphan and Sanofi-Aventis. M.R. has acted as scientific consultant for Amgen. H.S. has given lectures supported by Amgen, Abbott and Genzyme. P.U. has received honoraria for scientific consulting and symposia and clinical research grants from Amgen, Shire and Roche. M.V. has received research grants from Abbott and Genzyme and has participated in advisory boards for Abbott and Genzyme. V.Z. and A.B. are employees of Amgen. The remaining authors have no conflicts of interest.

References

1. Isakova T, Gutierrez O, Shah A *et al*. Postprandial mineral metabolism and secondary hyperparathyroidism in early CKD. *J Am Soc Nephrol* 2008; 19: 615–623
2. Slatopolsky E, Brown A, Dusso A. Pathogenesis of secondary hyperparathyroidism. *Kidney Int* 1999; 56(Suppl. 73): S14–S19
3. Massry SG, Smogorzewski M. Mechanisms through which parathyroid hormone mediates its deleterious effects on organ function in uremia. *Semin Nephrol* 1994; 14: 219–231
4. Block GA, Klassen PS, Lazarus JM *et al*. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephro* 2004; 15: 2208–2218
5. Melamed ML, Eustace JA, Plantinga LC *et al*. Third-generation parathyroid hormone assays and all-cause mortality in incident dialysis patients: the CHOICE study. *Nephrol Dial Transplant* 2008; 23: 1650–1658
6. National Kidney Foundation. K/DOQI clinical practice guidelines: bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; 42(Suppl 4): S1–S201
7. Danese MD, Belozeroff V, Smirnakis K *et al*. Consistent control of mineral and bone disorder in incident hemodialysis patients. *Clin J Am Soc Nephrol* 2008; 3: 1423–1429
8. Fouque D, Roth H, London G *et al*. Achieving K/DOQI targets for phosphorus and calcium metabolism by dialysis modality among prevalent ESRD patients in France in 2006. The French Prospective Phosphorus and Calcium Observatory in Maintenance Dialysis (Abstract). *J Am Soc Nephrol* 2007; 18: 9
9. Block GA, Hulbert-Shearon TE, Levin NW *et al*. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 1998; 31: 607–617
10. Block GA, Port FK. Re-evaluation of risks associated with hyperphosphataemia and hyperparathyroidism in dialysis patient: recommendations for a change in management. *Am J Kidney Dis* 2001; 37: 1331–1333

11. Moe S, Drueke TB. Management of secondary hyperparathyroidism: the importance and the challenge of controlling parathyroid hormone levels without elevating calcium, phosphorus, and calcium-phosphorus product. *Am J Nephrol* 2003; 23: 369–379
12. Hammerland LG, Garrett JE, Hung BCP *et al*. Allosteric activation of the Ca^{2+} receptor expressed in *Xenopus laevis* oocytes by NPS 467 or NPS 568. *Mol Pharmacol* 1998; 53: 1083–1088
13. Nemeth EF, Steffey ME, Hammerland LG *et al*. Calcimimetics with potent and selective activity on the parathyroid calcium receptor. *Proc Natl Acad Sci USA* 1998; 95: 4040–4045
14. Block GA, Martin KJ, de Francisco AL *et al*. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med* 2004; 350: 1516–1525
15. Lindberg JS, Culleton B, Wong G *et al*. Cinacalcet HCl, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: a randomized, double-blind, multicenter study. *J Am Soc Nephrol* 2005; 16: 800–807
16. Frazao JM, Holzer H, Stummvoll HK *et al*. Cinacalcet (Mimpara®/Sensipar®) maintains achievement of NKF-K/DOQI treatment targets for secondary hyperparathyroidism (HPT) in patients on dialysis (Abstract). *Nephrol Dial Transplant* 2005; 20 (Suppl 5): SP209
17. Martin KJ, Juppner H, Sherrand DJ *et al*. First- and second-generation immunometric PTH assays during treatment of hyperparathyroidism with cinacalcet HCL. *Kidney Int* 2005; 68: 1236–1243
18. Messa P, Macário F, Yaqoob M *et al*. The OPTIMA study: assessing a new cinacalcet (Sensipar/Mimpara) treatment algorithm for secondary hyperparathyroidism. *Clin J Am Soc Nephrol* 2008; 3: 36–45
19. St Peter WL, Li Q, Liu J *et al*. Cinacalcet use patterns and effect on laboratory values and other medications in a large dialysis organization, 2004 through 2006. *Clin J Am Soc Nephrol* 2009; 4: 354–360
20. Moe SM, Chertow GM, Coburn JW *et al*. Achieving NKF-K/DOQI bone metabolism and disease treatment goals with cinacalcet HCl. *Kidney Int* 2005; 67: 760–771
21. Tentori F, Blayney MJ, Albert JM *et al*. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2008; 52: 519–530
22. Henley D, Shatzen E, Lott F *et al*. Distribution and elimination of ^{45}Ca after oral administration of a calcimimetic in cynomolgus monkeys under calcium loading conditions. *Nephrol Dial Transplant* 2007; 22(Suppl 6): 217 (abstract Sa0013)
23. Lopez I, Mendoza FJ, Aguilera-Tejero E *et al*. The effect of calcitriol, paricalcitol and a calcimimetic on extraosseous calcifications in uremic rats. *Kidney Int* 2008; 73: 300–307

Received for publication: 8.10.08; Accepted in revised form: 11.3.09

Nephrol Dial Transplant (2009) 24: 2859–2865
doi: 10.1093/ndt/gfp170
Advance Access publication 15 April 2009

Interaction between parathyroid hormone and the Charlson comorbidity index on survival of incident haemodialysis patients

Luigi Francesco Morrone[1], Sandro Mazzaferro[2], Domenico Russo[3], Filippo Aucella[4], Mario Cozzolino[5], Maria Grazia Facchini[6], Andrea Galfrè[7], Fabio Malberti[8], Maria Cristina Mereu[9], Maurizio Nordio[10], Giovanni Pertosa[11], Domenico Santoro[12] and CPCP Study Investigators*

[1]Renal Division, A.O. Rummo, 82100 Benevento, [2]Renal Division, Università 'Sapienza', 00161 Roma, [3]Renal Division, University Federico II, 80131 Napoli, [4]Renal Division, PO Lastaria, 71036 Lucera, [5]Renal Division, A.O. San Paolo Polo Universitario, Milano, [6]Renal Division, A.O. Sant' Orsola Malpighi, 40138 Bologna, [7]Renal Division, Dialisi Territoriale, 09100 Cagliari, [8]Renal Division, A.O. Istituti Ospitalieri, 26100 Cremona, [9]Renal Division, PO Nostra Signora di Bonaria, 09025 S. Gavino Monreale, [10]Renal Division, P.O. Campo San Piero, 35100 Padova, [11]Renal Division, Azienda Universitaria Ospedaliera Policlinico, 70124 Bari and [12]Renal Division, Università degli Studi di Messina, 98128 Messina, Italy

Correspondence and offprint requests to: Luigi Francesco Morrone; E-mail: l.morrone@fastwebnet.it
*Investigators of the CPCP ('Comorbidity–Parathormone–Calcium–Phosphate') study, belonging to the 'Mineral Metabolism and Trace Elements' study group of the Italian Society of Nephrology, are listed in the Appendix.

Abstract

Background. Haemodialysis patients are ageing and have with a high rate of comorbidities. The impact of this novel clinical setting on intact parathyroid hormone (iPTH) is not well established.

Methods. For this observational, prospective multicentre cohort study, incident haemodialysis patients were recruited in 40 Italian centres and followed up for a mean period of 18 ± 6.7 months. Clinical characteristics and biochemistry were recorded at baseline. Comorbid conditions were scored by the Charlson comorbidity index (CCI).

Results. Data of 411 patients (mean age: 66.5 ± 14.8 years; 17.3% >80 years old) were recorded. The mean CCI was 4.17 ± 2.8. In patients with CCI >0, an inverse correlation was observed between CCI (excluding age) and iPTH ($P = 0.00002$). Independently of CCI, patients with iPTH <150 pg/ml had 76% as high as the risk