

Cinacalcet HCl, an Oral Calcimimetic Agent for the Treatment of Secondary Hyperparathyroidism in Hemodialysis and Peritoneal Dialysis: A Randomized, Double-Blind, Multicenter Study

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Management of secondary hyperparathyroidism is challenging with traditional therapy. The calcimimetic cinacalcet HCl acts on the calcium-sensing receptor to increase its sensitivity to calcium, thereby reducing parathyroid hormone (PTH) secretion. This phase 3, multicenter, randomized, placebo-controlled, double-blind study evaluated the efficacy and safety of cinacalcet in hemodialysis (HD) and peritoneal dialysis (PD) patients with PTH ≥ 300 pg/ml despite traditional therapy. A total of 395 patients received once-daily oral cinacalcet (260 HD, 34 PD) or placebo (89 HD, 12 PD) titrated from 30 to 180 mg to achieve a target intact PTH (iPTH) level of ≤ 250 pg/ml. During a 10-wk efficacy assessment phase, cinacalcet was more effective than control for PTH reduction outcomes, including proportion of patients with mean iPTH levels ≤ 300 pg/ml (46 versus 9%), proportion of patients with $\geq 30\%$ reduction in iPTH from baseline (65 versus 13%), and proportion of patients with ≥ 20 , ≥ 40 , or $\geq 50\%$ reduction from baseline. Cinacalcet had comparable efficacy in HD and PD patients; 50% of PD patients achieved a mean iPTH ≤ 300 pg/ml. Cinacalcet also significantly reduced serum calcium, phosphorus, and Ca \times P levels compared with control treatment. The most common side effects, nausea and vomiting, were usually mild to moderate in severity and transient. Once-daily oral cinacalcet was effective in rapidly and safely reducing PTH, Ca \times P, calcium, and phosphorus levels in patients who received HD or PD. Cinacalcet offers a new therapeutic option for controlling secondary hyperparathyroidism in patients with chronic kidney disease on dialysis.

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Secondary hyperparathyroidism (HPT) is a common complication of chronic kidney disease (CKD) that is characterized by increased levels of parathyroid hormone (PTH) and abnormalities in bone and mineral metabolism (1,2). The traditional therapeutic approach for managing secondary HPT includes administration of vitamin D sterols and phosphate binders. However, treatment with vitamin D sterols may lead to hypercalcemia and hyperphosphatemia (3–6), particularly when used with large doses of calcium-containing phosphate binders (7). Elevations in the calcium-phosphorus product (Ca \times P) are associated with soft-tissue

and cardiovascular calcification and increased mortality and morbidity (8–11).

Recognizing that adverse clinical outcomes are associated with elevated PTH, Ca \times P, calcium, and phosphorus levels, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Clinical Practice Guidelines for Bone Metabolism and Disease recommend more stringent targets for these parameters (12). Studies of dialysis patients have reported that PTH levels were greater than three times the upper limit of normal in 50% of hemodialysis (HD) patients and 47% of peritoneal dialysis (PD) patients (1,2). Approximately 25% of patients in each study had abnormally low PTH levels, and elevated calcium and phosphorus levels were common. A more recent observational study of approximately 4000 dialysis patients found that achievement of the NKF-K/DOQI targets remained poor with traditional care (13). Eleven percent of these patients had PTH values that averaged 150 to 300 pg/ml during 12 mo of follow-up, and only 1% of these patients had

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average values of PTH, calcium, phosphorus, and $\text{Ca} \times \text{P}$ over 12 mo that were within all four target ranges.

Treatment of secondary HPT is difficult in PD patients. The use of intravenous vitamin D sterols is impractical in these patients. High dialysate calcium concentrations and administration of oral vitamin D sterols may lead to increased calcium balance, increased risk for hypercalcemia, and adynamic bone disease through oversuppression of PTH (2,14). Lower dialysate calcium concentrations (1.25 to 1.35 mmol/L), however, may exacerbate secondary HPT by suppressing calcium levels and increasing PTH (2). Ideally, therapies to control secondary HPT in PD patients should lower PTH while simultaneously reducing the risk for hypercalcemia.

The calcium-sensing receptor located on the surface of chief cells in the parathyroid gland is the principal regulator of PTH secretion and therefore is an ideal target for therapies to treat secondary HPT (15–17). Calcimimetics are positive allosteric modulators of the calcium-sensing receptor that increase its sensitivity to extracellular calcium by lowering the threshold for activation by extracellular calcium ions (16–18). This causes a shift to the left in the sigmoidal curve that describes the relationship of blood ionized calcium to PTH, lowering the calcium set point and resulting in reductions of PTH secretion (16). In clinical trials of HD patients with secondary HPT, oral administration of the newly Food and Drug Administration–approved calcimimetic cinacalcet HCl $\{(\alpha\text{R})-(\text{---})\text{-}\alpha\text{-methyl-N-[3-[3-[trifluoromethylphenyl]propyl]-1-naphthalenemethanamine hydrochloride; Sensipar, hereafter referred to as cinacalcet}\}$ decreased PTH with concurrent reductions in $\text{Ca} \times \text{P}$, calcium, and phosphorus (19–22). The efficacy of cinacalcet in PD patients with secondary HPT was not evaluated in those studies. This study assessed the ability of cinacalcet treatment to lower PTH, $\text{Ca} \times \text{P}$, serum calcium, and serum phosphorus in patients who have secondary HPT and receive HD or PD.

Materials and Methods

This randomized, placebo-controlled, double-blind study was designed to evaluate the efficacy and the safety of cinacalcet compared with control among patients who have secondary HPT and were on PD or HD and receiving traditional therapy. PD and HD patients with poorly controlled secondary HPT were recruited from 60 study centers in the United States, Canada, and Australia. The major inclusion criteria were age ≥ 18 yr; mean of two plasma intact PTH (iPTH) values ≥ 300 pg/ml and mean of two serum calcium values ≥ 8.4 mg/dl during the screening phase; and treatment with HD, continuous ambulatory PD, or automated PD for at least 1 mo before beginning study medication. Patients who were receiving vitamin D therapy must have been treated with a stable dose for at least 30 d before enrollment. Patients were excluded from the study when they had an unstable medical condition or when they had undergone parathyroidectomy or experienced a myocardial infarction within 3 mo before the study began. The study was conducted in accordance with the Declaration of Helsinki. Each center's Institutional Review Board approved the study design, and each patient signed an informed consent document before the initiation of any study-related procedures.

Enrollment was initiated in May 2002, and the study was completed in March 2003. Of the 662 patients who were recruited and screened for participation, 395 patients were randomly assigned in a 3:1 ratio to

receive cinacalcet ($n = 294$) or placebo ($n = 101$; Figure 1). The most common reasons for exclusion were PTH < 300 pg/ml, serum calcium < 8.4 mg/dl, changes in vitamin D doses in the 30 d before study day 1, and withdrawal of informed consent before randomization. Randomization was stratified with respect to dialysis modality (HD or PD). Patients who were receiving HD were further stratified by severity of HPT during the screening phase: mild (iPTH 300 to 500 pg/ml), moderate (iPTH 501 to 800 pg/ml), or severe (iPTH > 800 pg/ml). Patient randomization and dosing were determined by a programmatic algorithm using an interactive voice-response system to maintain the blinded nature of the study design. Thirty-eight percent of enrolled patients were women, the mean age was 52 yr, and a similar percentage of black and white patients participated (Table 1). Twelve percent of patients were treated with PD. At enrollment, 93% of patients were using phosphate binders and 66% of patients were prescribed vitamin D sterols. Thirty-five percent of the HD patients who were enrolled in this study had severe secondary HPT (iPTH > 800 pg/ml).

Study Design

The study consisted of a screening phase (up to 30 d), followed by a 16-wk dose-titration phase and a 10-wk efficacy assessment phase. Study visits occurred every 2 wk during the dose-titration and efficacy assessment phases.

Intervention with Oral Cinacalcet

Sequential titration of cinacalcet (or matching placebo) from a 30-mg starting dose to 60, 90, 120, and 180 mg once daily was permitted at 4-wk intervals when iPTH was > 200 pg/ml, serum calcium was ≥ 7.8 mg/dl, symptoms of hypocalcemia were not present, the highest study dose had not been reached, and an adverse event that precluded a dose increase had not occurred. Patients were instructed to take cinacalcet with or shortly after a meal. Compliance with study medication was 87% in each treatment group as determined by pill counts and patient diaries. Placebo and cinacalcet tablets were identical in appearance at the same dose strength.

Patients continued to receive their previously prescribed therapy for secondary HPT (phosphate binders and/or vitamin D) during the study. Changes in the dose or type of phosphate-binding agent were not restricted after the screening phase. The vitamin D dose could be reduced or withheld if the serum calcium value was ≥ 11 mg/dl, serum phosphorus was ≥ 6.5 mg/dl, or $\text{Ca} \times \text{P}$ was ≥ 70 mg^2/dl^2 . When it was withheld, vitamin D therapy could be resumed at the investigator's discretion. The dose of vitamin D could be increased if a patient had symptoms of hypocalcemia or a serum calcium < 8.4 mg/dl that did not respond to changes in calcium supplements and/or phosphate binders.

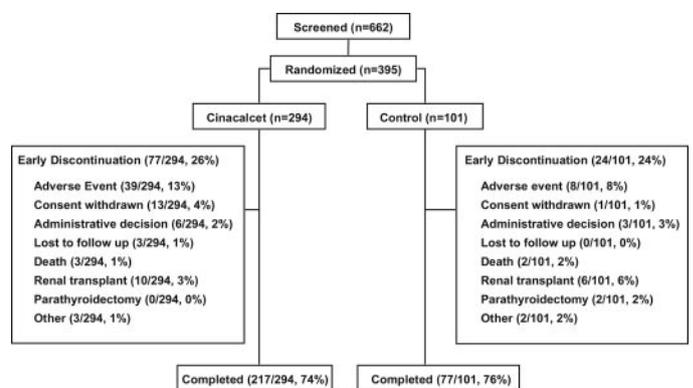


Figure 1. Patient disposition during the study.

Table 1. Baseline demographics and laboratory values^a

| | Control (n = 101) | Cinacalcet (n = 294) | Cinacalcet Randomization Strata | | | | | Peritoneal Dialysis (n = 34) |
|---|----------------------|-------------------------|------------------------------------|---------------------|-------------------|------------------|---------------|------------------------------------|
| | | | Hemodialysis/Baseline iPTH (pg/ml) | | | | | |
| | | | 300–500 (n = 74) | 501–800 (n = 84) | >800 (n = 102) | All (n = 260) | | |
| Female gender (n [%]) | 37 (37%) | 113 (38%) | 24 (32%) | 35 (42%) | 36 (35%) | 95 (37%) | 18 (53%) | |
| White race (n [%]) | 39 (39%) | 115 (39%) | 29 (39%) | 37 (44%) | 32 (31%) | 98 (38%) | 17 (50%) | |
| Black race (n [%]) | 35 (35%) | 114 (39%) | 26 (35%) | 32 (38%) | 44 (43%) | 102 (39%) | 12 (35%) | |
| Age (yr; mean [SD]) | 53.5 (13.9) | 51.8 (14.0) | 55.9 (12.9) | 53.6 (14.2) | 46.3 (13.3) | 51.4 (14.0) | 54.8 (13.0) | |
| Duration of dialysis (mo; mean [SD]) | 63.6 (65.0) | 56.4 (53.1) | 47.1 (54.5) | 50.8 (49.3) | 74.1 (55.5) | 58.8 (54.4) | 39.3 (39.4) | |
| iPTH (pg/ml; mean [SE]) | 832.1 (48.4) | 847.9 (40.1) | 418.1 (9.0) | 641.5 (11.7) | 1290.1 (49.9) | 832.2 (30.9) | 966.7 (254.8) | |
| Serum calcium (mg/dl; mean [SE]) | 10.01 (0.09) | 9.79 (0.05) | 9.60 (0.09) | 9.69 (0.10) | 9.89 (0.08) | 9.74 (0.05) | 10.21 (0.10) | |
| Serum phosphorus (mg/dl; mean [SE]) | 6.10 (0.14) | 6.10 (0.10) | 5.73 (0.17) | 5.81 (0.19) | 6.90 (0.16) | 6.21 (0.11) | 5.28 (0.25) | |
| Ca × P (mg ² /dl ² ; mean [SE]) | 60.9 (1.4) | 59.6 (1.0) | 54.6 (1.7) | 56.2 (1.8) | 67.8 (1.5) | 60.3 (1.0) | 53.9 (2.56) | |

^aiPTH, intact parathyroid hormone; Ca × P, calcium-phosphorus ion product.

Dialysate calcium concentration also could be adjusted at the discretion of the investigator.

Laboratory Determinations

Laboratory assessments of plasma iPTH, serum calcium, and serum phosphorus were performed at a central laboratory (Covance Central Laboratory Services, Indianapolis, IN). Blood collections were performed before the dose of study medication on study visit days, approximately 24 h after the previous dose. Plasma iPTH levels were determined using a double-antibody immunoradiometric assay (Nichols Institute Diagnostics, San Clemente, CA) (23).

End Points

Analyses included the proportion of patients with a mean iPTH level ≤ 250 pg/ml as the primary end point and the proportion of patients with a reduction in iPTH of at least 30% from baseline as a secondary end point. Mean percentage changes from baseline for iPTH, serum calcium, phosphorus, and Ca × P were determined in each group and were secondary end points. In addition, the proportion of patients with a mean iPTH level ≤ 300 pg/ml or reductions in iPTH of at least 20, 40, or 50% from baseline; the proportion of patients with Ca × P < 55 mg²/dl²; and the proportion of patients with a mean reduction in Ca × P of at least 5 or 10 mg²/dl² were determined.

Statistical Analyses

Baseline levels of iPTH, calcium, phosphorus, and Ca × P were computed for each patient by averaging the values from the two blood samples taken during the screening phase. During the efficacy assessment phase, the mean value for each laboratory measure was calculated for each patient, based on all available results. For patients who withdrew before the efficacy assessment phase, the mean of the last two on-study, postbaseline values was carried forward. Efficacy analyses were performed for all patients in each treatment group and were repeated in cinacalcet-treated patients according to randomization stratum. Safety was analyzed for all patients who received at least one dose of study medication. The generalized Cochran-Mantel-Haenszel test (24) was used for statistical comparisons. Statistical calculations were performed using SAS (Version 8.2; SAS Institute, Cary, NC).

Estimation of sample size was based on a χ^2 test of equal proportions

of patients with a mean iPTH value ≤ 250 pg/ml during the efficacy assessment phase, with a statistical significance level of 0.05 (two-sided). The placebo response was predicted on the basis of previous cinacalcet phase 2 studies to be $\leq 13\%$. With a cinacalcet response rate of 30% assumed for the purpose of sample size considerations, a sample size of 380 patients (285 cinacalcet, 95 placebo) yielded 91% power.

Results

Study Participants

Similar proportions of patients in the cinacalcet and control groups completed the dose-titration (81 versus 83%, respectively) and efficacy assessment phases (74 versus 76%, respectively). Reasons for early withdrawal included adverse events (13% cinacalcet, 8% control), withdrawal of consent (4% cinacalcet, 1% control), kidney transplantation (3% cinacalcet, 6% control), parathyroidectomy (0% cinacalcet, 2% control), and death (1% cinacalcet, 2% control; Figure 1).

Baseline demographics were comparable between treatment groups and across the randomization strata among cinacalcet-treated patients. At baseline, mean iPTH and serum calcium levels were similar between control and cinacalcet-treated patients overall but were higher in cinacalcet-treated patients who received PD than in cinacalcet-treated patients who received HD (Table 1).

Attainment of iPTH Targets

During the efficacy assessment phase, mean predose iPTH was significantly lower in the cinacalcet group (525.5 ± 30.1 pg/ml) than in the control group (852.0 ± 55.1 pg/ml; $P < 0.001$; Table 2). Mean iPTH decreased by 40% from baseline in the cinacalcet group and increased by 4% in the control group (Table 2). Cinacalcet-treated patients were significantly more likely than control patients to achieve each of the therapeutic targets for iPTH reduction: 39 versus 7% achieved an iPTH level ≤ 250 pg/ml ($P < 0.001$), 46 versus 9% achieved an iPTH level ≤ 300 pg/ml ($P < 0.001$); 65 versus 13% had a 30% or greater

Table 2. Reduction of iPTH during efficacy assessment phase

| | Control (n = 101) | Cinacalcet (n = 294) | Cinacalcet Randomization Strata | | | | Peritoneal Dialysis (n = 34) |
|---|----------------------|----------------------------|---|---------------------|-------------------|------------------|------------------------------------|
| | | | Hemodialysis/Baseline iPTH Strata (pg/ml) | | | | |
| | | | 300–500 (n = 74) | 501–800 (n = 84) | >800 (n = 102) | All (n = 260) | |
| Mean iPTH level (pg/ml) ^a | | | | | | | |
| n | 100 | 288 | 70 | 83 | 101 | 254 | 34 |
| mean (SE) | 852.0 (55.1) | 525.5 (30.1) ^c | 223.1 (17.4) | 362.1 (26.5) | 857.2 (55.2) | 520.6 (29.7) | 561.9 (126.8) |
| Percentage change in mean iPTH ^{a,b} | 100 | 288 | 70 | 83 | 101 | 254 | 34 |
| mean (SE) | 4.1 (3.4) | –40.3 (2.1) ^c | –46.7 (3.9) | –44.0 (3.8) | –33.3 (3.6) | –40.5 (2.2) | –38.8 (5.7) |
| No. (%) achieving target mean level ≤250 pg/ml ^a | 7/100 (7%) | 111/288 (39%) ^c | 54/70 (77%) | 34/83 (41%) | 10/101 (10%) | 98/254 (39%) | 13/34 (38%) |
| mean level ≤300 pg/ml ^a | 9/100 (9%) | 132/288 (46%) ^c | 57/70 (81%) | 41/83 (49%) | 17/101 (17%) | 115/254 (45%) | 17/34 (50%) |
| reduction ≥20% ^{a,b} | 21/100 (21%) | 213/288 (74%) ^c | 58/70 (83%) | 64/83 (77%) | 66/101 (65%) | 188/254 (74%) | 25/34 (74%) |
| reduction ≥30% ^{a,b} | 13/100 (13%) | 187/288 (65%) ^c | 55/70 (79%) | 57/83 (69%) | 53/101 (52%) | 165/254 (65%) | 22/34 (65%) |
| reduction ≥40% ^{a,b} | 10/100 (10%) | 172/288 (60%) ^c | 49/70 (70%) | 55/83 (66%) | 48/101 (48%) | 152/254 (60%) | 20/34 (59%) |
| reduction ≥50% ^{a,b} | 6/100 (6%) | 139/288 (48%) ^c | 45/70 (64%) | 42/83 (51%) | 38/101 (38%) | 125/254 (49%) | 14/34 (41%) |

^aMean value in efficacy assessment phase was based on an average of biweekly measurements during weeks 18 to 26 of study treatment (up to five values for each patient). For patients with no values during weeks 18 to 26, the mean of the last two on-study postbaseline values was used as the week 18 to 26 average.

^bPercentage change/reduction from baseline in each subject was calculated from mean values in the efficacy-assessment phase and the average of two values during the 30-day baseline period before study treatment.

^c*P* < 0.001 versus control group.

reduction in mean iPTH from baseline (*P* < 0.001); and 48 versus 6% achieved a 50% or greater reduction in iPTH from baseline (*P* < 0.001; Table 2).

Regardless of severity of HPT at baseline, patients experienced significant reductions in mean iPTH level during cinacalcet treatment. Among the HD-treated patients who received cinacalcet, the percentage reduction in mean iPTH from baseline was 47% in patients with mild secondary HPT, 44% in patients with moderate secondary HPT, and 33% in patients with severe secondary HPT (Table 2).

Among patients who received PD and cinacalcet, the magnitude of reduction in iPTH and achievement of target iPTH levels were similar to HD patients (Figure 2). Mean iPTH decreased by approximately 39% from baseline (Table 2). Fifty percent of these patients achieved an iPTH level ≤300 pg/ml; 65% had at least a 30% reduction in mean iPTH from baseline; and 41% achieved at least a 50% reduction in iPTH from baseline (Table 2).

The median doses of cinacalcet used by patients who achieved the PTH end points were determined. For patients who achieved a mean iPTH ≤300 pg/ml, the median dose of cinacalcet was 60 mg overall, using the last on-study dose.

Attainment of Calcium and Phosphorus Targets

Mean serum calcium and phosphorus concentrations both decreased by approximately 7% from baseline in the cinacalcet group, compared with essentially no change in serum calcium (+1%) or phosphorus (–2%) in the control group (*P* < 0.001 and *P* = 0.039 for cinacalcet compared with control for calcium

and phosphorus, respectively; Table 3). Consequently, mean Ca × P decreased by 13% from baseline with cinacalcet therapy and remained relatively unchanged (decrease of 1%) with control treatment (*P* < 0.001; Table 3). Nearly two thirds of patients who received cinacalcet (65%), compared with fewer than one

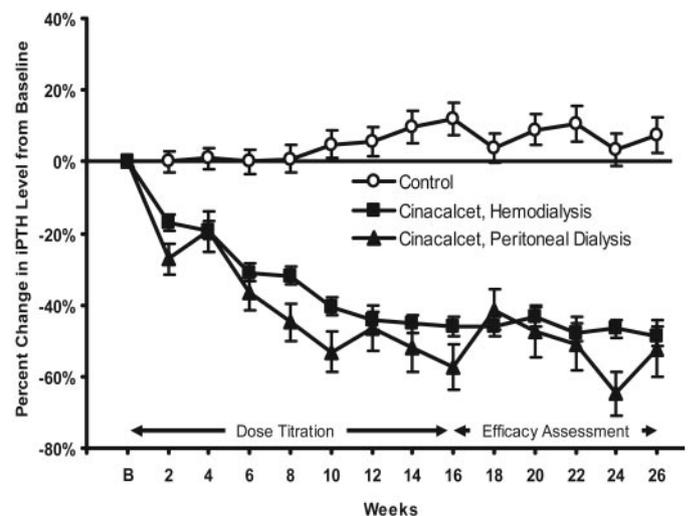


Figure 2. Mean percentage change in intact parathyroid hormone (iPTH) at each study visit, according to dialysis modality. B, baseline. At baseline: n = 101 control; n = 258 cinacalcet, hemodialysis (HD); and n = 34 cinacalcet, peritoneal dialysis (PD). At week 26: n = 77 control; n = 194 cinacalcet, HD; and n = 22 cinacalcet, PD.

Table 3. Calcium and phosphorus levels during efficacy assessment phase

| | Control (n = 101) | Cinacalcet (n = 294) | Cinacalcet Randomization Strata | | | | Peritoneal Dialysis (n = 34) |
|--|----------------------|----------------------------|---|---------------------|-------------------|------------------|------------------------------------|
| | | | Hemodialysis/Baseline iPTH Strata (pg/ml) | | | | |
| | | | 300–500 (n = 74) | 501–800 (n = 84) | >800 (n = 102) | All (n = 260) | |
| Serum calcium (mg/dl) ^a | | | | | | | |
| n | 100 | 288 | 70 | 83 | 101 | 254 | 34 |
| mean (SE) | 10.1 (0.1) | 9.1 (0.1) ^c | 9.1 (0.1) | 9.1 (0.1) | 9.1 (0.1) | 9.1 (0.1) | 9.4 (0.1) |
| Percent change in calcium ^{a,b} | | | | | | | |
| n | 100 | 288 | 70 | 83 | 101 | 254 | 34 |
| mean (SE) | 0.9 (0.5) | −6.5 (0.6) ^c | −5.5 (1.0) | −5.8 (1.1) | −7.4 (1.0) | −6.3 (0.6) | −7.4 (1.4) |
| Serum phosphorus (mg/dl) ^a | | | | | | | |
| n | 100 | 289 | 71 | 83 | 101 | 255 | 34 |
| mean (SE) | 5.8 (0.1) | 5.5 (0.1) | 5.1 (0.2) | 5.3 (0.2) | 6.0 (0.2) | 5.5 (0.1) | 5.0 (0.2) |
| Percent change in phosphorus ^{a,b} | | | | | | | |
| n | 100 | 289 | 71 | 83 | 101 | 255 | 34 |
| mean (SE) | −2.2 (2.5) | −7.2 (1.6) ^d | −8.6 (2.7) | −2.9 (3.6) | −11.7 (2.3) | −8.0 (1.7) | −1.5 (4.0) |
| Ca × P (mg ² /dl ²) ^a | | | | | | | |
| n | 100 | 288 | 70 | 83 | 101 | 254 | 34 |
| mean (SE) | 58.1 (1.3) | 50.0 (0.9) ^c | 46.9 (1.8) | 48.5 (1.7) | 54.1 (1.5) | 50.3 (1.0) | 47.4 (2.2) |
| Percent change in Ca × P ^{a,b} | | | | | | | |
| n | 100 | 287 | 69 | 83 | 101 | 253 | 34 |
| mean (SE) | −1.4 (2.4) | −12.8 (1.7) ^c | −12.0 (3.4) | −9.1 (3.5) | −18.0 (2.5) | −13.4 (1.8) | −8.5 (4.1) |
| No. (%) achieving Ca × P target | | | | | | | |
| mean Ca × P <55 mg ² /dl ^{2a} | 45/100 (45%) | 186/288 (65%) ^c | 51/70 (73%) | 58/83 (70%) | 51/101 (50%) | 160/254 (63%) | 26/34 (76%) |
| Ca × P reduction ≤5 mg ² /dl ^{2a,b} | 39/100 (39%) | 175/287 (61%) ^c | 41/69 (59%) | 48/83 (58%) | 67/101 (66%) | 156/253 (62%) | 19/34 (56%) |
| Ca × P reduction ≤10 mg ² /dl ^{2a,b} | 24/100 (24%) | 135/287 (47%) ^c | 29/69 (42%) | 32/83 (39%) | 59/101 (58%) | 120/253 (47%) | 15/34 (44%) |

^aMean value in efficacy assessment phase was based on an average of biweekly measurements during weeks 18 to 26 of study treatment (up to five values for each patient). For patients with no values during weeks 18 to 26, the mean of the last two on-study post-baseline values was used as the week 18 to 26 average.

^bPercentage change/reduction from baseline in each patient was calculated from mean values in the efficacy assessment phase and the average of two values during the 30-day baseline period before study treatment.

^c $P < 0.001$ versus control group.

^d $P < 0.05$ versus control group.

half of control patients (45%), had a mean Ca × P level <55 mg²/dl² during the efficacy assessment phase ($P < 0.001$; Table 3). Patients who received cinacalcet also were significantly more likely than control patients to achieve the therapeutic targets of at least 5 or 10 mg²/dl² reductions in mean Ca × P from baseline ($P < 0.001$; Table 3).

Within each randomization stratum, cinacalcet treatment was associated with a significant reduction in mean serum Ca × P from baseline. Compared with the HD-treated patients with mild-to-moderate secondary HPT at baseline, HD-treated patients with severe secondary HPT were less likely to achieve a mean Ca × P <55 mg²/dl² (Table 3). However, HD-treated patients with severe secondary HPT were more likely than those with mild to moderate secondary HPT to have reductions in Ca × P of at least 5 or 10 mg²/dl² from baseline (Table 3), possibly because patients with severe secondary HPT had higher phosphorus and Ca × P levels at baseline (Table 1). The magnitude of reductions in calcium, phosphorus, and Ca × P in PD patients was similar to those in HD patients (Figure 3).

Concomitant Medications

The proportion of patients who received vitamin D sterols or phosphate binders remained relatively constant throughout the

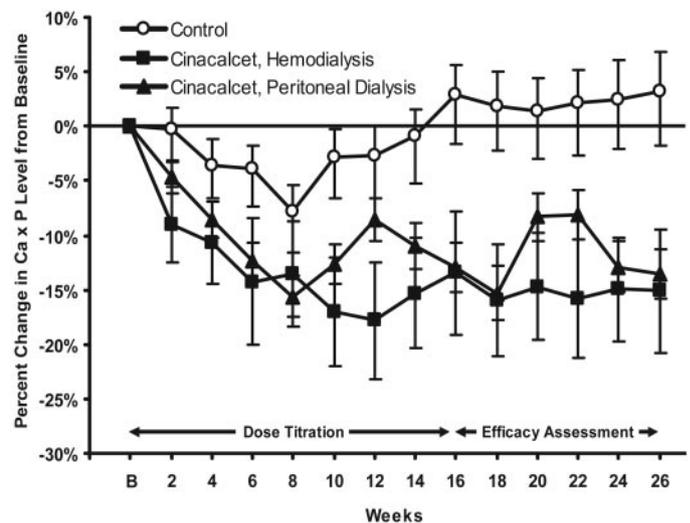


Figure 3. Mean percentage change in Ca × P at each study visit, according to dialysis modality. At baseline: n = 101 control; n = 257 cinacalcet, HD; and n = 34 cinacalcet, PD. At week 26: n = 77 control; n = 193 cinacalcet, HD; and n = 22 cinacalcet, PD.

study, regardless of treatment group. Sixty-five percent of cinacalcet patients and 69% of control patients received vitamin D sterols at baseline. At the end of the study, 64 and 67% of patients, respectively, were receiving vitamin D sterols. In cinacalcet-treated patients who were receiving PD, doxercalciferol and oral calcitriol were the predominant vitamin D sterols used. Reasons for vitamin D sterol or phosphate binder dose changes and the patient incidence of changes for these reasons were generally comparable between treatment groups. However, low serum calcium resulted in dose changes more commonly in the cinacalcet group than in the control group, and hypercalcemia or hyperphosphatemia led to dose changes more commonly in the control group than in the cinacalcet group. Mean doses of vitamin D sterols and phosphate binders remained fairly stable throughout the study in both treatment groups.

Treatment Safety/Tolerability

Adverse events were reported by 91% of cinacalcet-treated patients and 93% of control patients, as expected for a patient population with significant comorbidity. Nausea (30 *versus* 22%), vomiting (23 *versus* 12%), diarrhea (24 *versus* 19%), upper respiratory tract infection (18 *versus* 13%), headache (17 *versus* 12%), and asthenia (8 *versus* 2%) occurred more often in those who were given cinacalcet, whereas abdominal pain (12 *versus* 18%) and hypotension (7 *versus* 12%) occurred more often in control patients. Twenty-seven percent of cinacalcet-treated patients and 26% of control patients experienced a serious adverse event; however, investigators considered these events related to study medication in only 2% of patients in each group. Five patients (three cinacalcet-treated and two control) died during the study; none of the deaths was considered treatment related.

Gastrointestinal complaints in patients who were treated with cinacalcet were generally mild to moderate in severity and of limited duration. Nine percent of cinacalcet-treated patients and 3% of control patients were withdrawn from the study because of nausea, vomiting, or other gastrointestinal events.

Five percent of serum calcium measurements in cinacalcet-treated patients and <1% of serum calcium measurements in control patients were <7.5 mg/dl. The decreases in serum calcium were transient and returned to normal range upon adjustment to dialysate calcium concentration, calcium-containing phosphate binders, vitamin D sterols, or cinacalcet. Low serum calcium was rarely associated with symptoms, and no patient was withdrawn from study because of hypocalcemia. No difference was observed between HD and PD patients in the incidence or type of adverse events.

Discussion

The results of this study demonstrate that once-daily oral cinacalcet is effective and safe for the management of secondary HPT in patients who are receiving HD or PD. Cinacalcet was superior to control treatment for all targets of iPTH reduction in this study, including mean percentage reduction in iPTH from baseline; the proportion of patients whose mean predose iPTH was ≤ 250 pg/ml or ≤ 300 pg/ml; and the proportion of patients

with at least a 20, 30, 40, or 50% reduction in mean iPTH from baseline.

More than 35% of patients who were enrolled in this study had baseline iPTH levels >800 pg/ml, compared with 20% of patients in a previously reported phase 3 study with cinacalcet (22). Consequently, baseline iPTH levels were approximately 200 pg/ml higher in these patients. Despite the high prevalence of patients with severe disease at baseline, 46% of cinacalcet-treated patients in this study achieved a mean iPTH level ≤ 300 pg/ml, the upper limit of the PTH target range recently set by the NKF-K/DOQI guidelines (12), and 65% of cinacalcet-treated patients achieved a $\geq 30\%$ reduction in iPTH, whereas 13% of control patients achieved this target, comparable to the proportion who achieved this target in the previous study (22).

This study further demonstrates that cinacalcet is effective regardless of the modality of dialysis. A similar response was observed in patients who were treated with PD and HD; 65% of patients in both groups experienced $\geq 30\%$ reductions in iPTH levels with cinacalcet therapy. Furthermore, patients on who were on PD or HD and were treated with cinacalcet experienced significant reductions in both serum calcium and phosphorus, leading to a greater proportion of patients' attaining the Ca \times P study targets as compared with those in the control group.

Traditional therapies for secondary HPT are limited by side effects that may place patients at higher risk for vascular calcification. Vitamin D increases calcium and phosphorus absorption from the intestine. Consequently, up to 44% of patients experience hypercalcemia and up to 65% of patients experience hyperphosphatemia during vitamin D therapy (5). Hypercalcemia and hyperphosphatemia frequently necessitate treatment interruptions and may result in inadequate control of PTH and disease progression (25,26). Poor control of mineral metabolism is also associated with a higher risk for death, calcification of the coronary arteries and aorta, increased arterial stiffness, and cardiac valve calcification (8–11,27). A recent report from a large international dialysis database demonstrated that among HD patients in five European countries, hospitalization rates for cardiovascular-related causes were as high as 26% (28). Because cinacalcet is not associated with elevations in calcium and phosphorus, treatment strategies that include cinacalcet may allow better achievement of the K/DOQI targets and possibly reduce complications associated with secondary HPT. In addition, lowering calcium and phosphorus levels with cinacalcet may allow the use of physiologic doses of vitamin D sterols with a reduced risk for occurrence of hypercalcemia and hyperphosphatemia. Further studies to evaluate vascular calcification and cardiovascular outcomes will be needed to determine whether reductions in these parameters are associated with improved cardiovascular health.

Treatment with cinacalcet was generally well tolerated in this study. Episodes of nausea and vomiting occurred more frequently in patients who were treated with cinacalcet but were mild to moderate in severity and transient in duration. Serum calcium values below the normal range were infrequently symptomatic and readily managed by modest adjustments to

the dialysate calcium concentration or doses of calcium-containing phosphate binders, vitamin D sterols, or study drug.

In summary, these findings demonstrate that cinacalcet is a safe and effective treatment for secondary HPT in PD and HD patients. Once-daily oral treatment with cinacalcet at doses up to 180 mg effectively reduced iPTH levels, regardless of dialysis modality or disease severity. Furthermore, cinacalcet significantly improved serum calcium and phosphorus levels, leading to reductions in $\text{Ca} \times \text{P}$ values. The calcimimetic cinacalcet is an important new therapeutic option for controlling secondary HPT and associated disturbances in mineral metabolism in patients who receive PD or HD.

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