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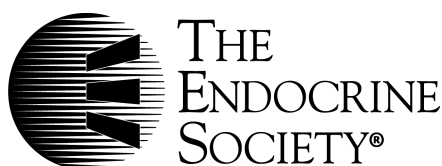
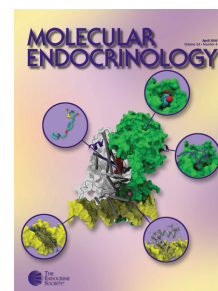
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Cinacalcet Treatment of Primary Hyperparathyroidism: Biochemical and Bone Densitometric Outcomes in a Five-Year Study

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Context: Primary hyperparathyroidism (PHPT) is characterized by chronically elevated serum calcium and inappropriately normal or increased PTH.

Objective: Our objective was to evaluate long-term tolerability, safety, and efficacy of cinacalcet in PHPT patients.

Design and Setting: A 4.5-yr open-label extension study was conducted at 14 study centers in the United States.

Patients or Other Participants: Forty-five subjects with PHPT from a double-blind, placebo-controlled, 1-yr trial were continued into this study.

Interventions: After the parent study, all subjects were treated with 30 mg cinacalcet twice daily, increasing to 50 mg twice daily during the 12-wk titration if serum calcium levels were 10.3 mg/dl or higher and then maintained on cinacalcet for up to 4.5 yr.

Main Outcome Measures: Assessments included serum calcium, PTH, phosphate and alkaline phosphatase, and areal bone mineral density (aBMD). Vital signs, safety chemistries and hematology, and adverse events were monitored throughout.

Results: Compared with baseline, cinacalcet treatment improved biochemical measures of PHPT including reducing serum calcium and PTH and increasing serum phosphate with slight increases in alkaline phosphatase. No changes in z-scores of aBMD at spine, hip, or wrist were seen with annual percent changes, consistent with reports for untreated postmenopausal women or PHPT patients. Safety biochemistries remained normal, and adverse events (most commonly arthralgia, myalgia, diarrhea, respiratory infection, and nausea) were mild to moderate in severity.

Conclusions: Treatment of PHPT patients with cinacalcet for up to 5.5 yr maintained normocalcemia, reduced plasma PTH, increased serum phosphate and alkaline phosphatase with no significant effects on aBMD, and was well tolerated. (*J Clin Endocrinol Metab* 94: 4860–4867, 2009)

Primary hyperparathyroidism (PHPT) is an endocrinopathy diagnosed by chronically elevated serum calcium and inappropriately normal or increased PTH. Disease complications vary extensively among patients,

with renal stones, fractures, loss of bone mass, and hypercalcemic and neurocognitive symptoms most commonly found. Most patients, however, are asymptomatic. Parathyroidectomy usually cures the disease, but few

treatment alternatives exist for patients who fail surgery, have contraindications or refuse surgery, or do not meet current operative guidelines (1). Thus, medical therapies capable of reducing serum Ca and PTH concentrations and increasing bone mass in PHPT patients are needed.

Calcium-sensing receptors (CaSR) are strongly expressed on parathyroid cells and widely viewed as the principal regulator of PTH secretion (2). Calcimimetics quickly and directly reduce PTH levels by binding to CaSR and increasing sensitivity to extracellular Ca (3). The calcimimetic cinacalcet is currently indicated for treatment of secondary HPT in patients with chronic kidney disease on dialysis and treatment of hypercalcemia in patients with parathyroid carcinoma. In Europe, cinacalcet is approved for reduction of hypercalcemia in patients with PHPT for whom parathyroidectomy is indicated on the basis of calcium levels but in whom surgery is clinically inappropriate or is contraindicated.

We initially demonstrated that short-term (15 d) cinacalcet treatment reduced serum Ca and PTH in patients with PHPT (4). In a subsequent randomized, double-blind, placebo-controlled, 52-wk trial in patients with mild to moderate PHPT (5), cinacalcet normalized serum Ca and reduced, but did not normalize, plasma PTH levels. Cinacalcet increased biochemical bone turnover markers, within the normal range, with areal bone mineral density (aBMD) at the spine, hip, and wrist remaining stable throughout the study.

This study assessed long-term tolerability, safety, and efficacy (effects on serum Ca, plasma PTH, and aBMD) of treatment of patients with mild to moderate PHPT with cinacalcet. Patients with PHPT who participated in the 1-yr, placebo-controlled trial of cinacalcet were continued into an open-label extension lasting an additional 4.5 yr.

Subjects and Methods

Subjects

Forty-five subjects [21 of the 40 subjects who received cinacalcet in the parent study (prior cinacalcet) and 24 of the 38 subjects who received placebo in the parent study (prior placebo)] completing a randomized, placebo-controlled study of cinacalcet treatment of PHPT (5) were enrolled into this 4.5-yr, open-label extension study conducted at 14 centers in the United States (Fig 1 and Table 1). All subjects in the parent study were offered the opportunity to volunteer for the extension study. There was no difference in the subjects who did or did not enroll in the extension study. Inclusion criteria for the 52-wk parent study included serum Ca higher than 10.3 mg/dl (2.57 mmol/liter) and lower than 12.5 mg/dl (3.12 mmol/liter) and plasma PTH higher than 45 pg/ml (4.73 pmol/liter). Exclusion criteria included creatinine clearance lower than 50 ml/min (0.83 ml/sec), treatment with bisphosphonates or fluoride in the 90 d before baseline, familial hypocalciuric hypercalcemia, and fasting urine Ca/creatinine, in milligrams (molar), ratio lower than

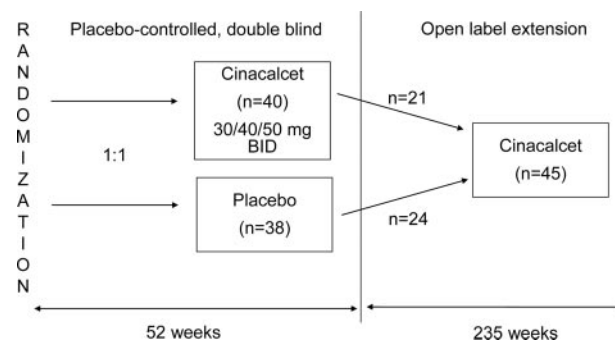


FIG. 1. Study design showing the parent, 52-wk, double-blind, randomized, placebo-controlled trial in which subjects were allocated 1:1 to placebo ($n = 38$) or cinacalcet ($n = 40$) in doses of 30 mg twice daily. Doses were titrated to 40 or 50 mg according to the serum Ca concentration that remained above reference normal (10.3 mg/dl). After completing the parent trial, an open-label extension study enrolled 45 subjects who then received cinacalcet twice daily and were followed for 234 wk.

0.05 (0.14). Subjects requiring drugs metabolized by cytochrome P450 2D6 and with narrow therapeutic indices (e.g. flecainide, thioridazine, and many tricyclic antidepressants) were excluded because of cytochrome P450 2D6 inhibition by cinacalcet (6). Women on stable doses of selective estrogen receptor modulators or estrogen replacement therapy were eligible. This study was conducted in accordance with the Declaration of Helsinki and in compliance with the Food and Drug Administration and the International Conference on Harmonisation Good Clinical Practice regulations/guidelines. The Institutional Review Board at each center approved the study. Written informed consent was obtained from all subjects.

Study design

Immediately upon parent study completion, all subjects continuing into the open-label extension received cinacalcet 30 mg twice daily. During the initial 12-wk dose-titration phase, one possible cinacalcet dose increase from 30 mg twice daily to 50 mg twice daily (maximum allowed by protocol) could occur at wk 6 if subjects remained hypercalcemic (serum Ca ≥ 10.3 mg/dl) at the wk-3 and -4 visits. In the maintenance phase, visits were approximately every 4 wk for 12 wk and then approximately every 14 wk thereafter, during which doses could be adjusted (increased if subject not already on highest dose and Ca ≥ 10.3 mg/dl from two consecutive measurements). As specified by the protocol, if a patient developed hypocalcemia (serum Ca < 8.0 mg/dl), cinacalcet treatment was withheld for approximately 1 wk until the next serum Ca measurement was at least 8.4 mg/dl. Medication could be resumed at a lower dose (30 mg twice daily if previously 50 mg twice daily; 30 mg daily if previously 30 mg twice daily) and the subject maintained in the study. If the previous dose was 30 mg daily, the subject was withdrawn. After July 2004, because of a change in dose strengths, subjects receiving 50 mg twice daily were switched to 60 mg twice daily. Blood was drawn after an overnight fast before the morning dose of cinacalcet and adverse events (AE) recorded. aBMD was measured at the end of the parent study (yr 1) and yearly in the open-label study. Patients were not given any instructions about calcium and vitamin D intake during the study.

TABLE 1. Demographics, biochemistries, and BMD of subjects enrolled in the 4.5-yr, open-label extension study at baseline upon entry into the parent study

	Prior placebo (n = 24)	Prior cinacalcet (n = 21)
Age (yr), mean \pm SD (Min, Max) years	60.3 \pm 12.0 (41.0, 81.0)	64.7 \pm 11.6 (28.0, 80.0)
Sex		
Men, n (%)	6 (25)	8 (38)
Women, n (%)	18 (75)	13 (62)
Failed parathyroidectomy, n (%)	6 (25)	6 (29)
Biochemical values, mean \pm SD (Min, Max)		
Serum Ca (mg/dl)	10.7 \pm 0.4 (10.2, 11.9)	10.9 \pm 0.5 (10.4, 12.5)
Serum P (mg/dl)	2.7 \pm 0.5 (2.0, 3.4)	2.6 \pm 0.4 (2.0, 3.5)
Plasma intact PTH (pg/ml)	115 \pm 55 (46.0, 320.0)	104 \pm 32 (54.5, 198.5)
Total AP (U/liter)	84 \pm 40 (29, 212)	91 \pm 25 (40, 134)
BMD z-score, mean \pm SD (Min, Max)		
Lumbar spine	0.3 \pm 1.6 (–3.0, 2.9)	0 \pm 1.4 (–2.0, 2.7)
Femoral neck	–0.4 \pm 1.1 (–2.1, 1.5)	–0.7 \pm 0.7 (–1.6, 0.8)
Total hip	–0.4 \pm 1.0 (–1.22, 0.77)	–0.5 \pm 1.0 (–1.06, 0.53)
Distal one third radius	0.7 \pm 0.2 (–4.5, 1.7)	0.7 \pm 0.2 (–3.8, 0.7)

Measurements

Biochemistries

Blood samples for measurement of serum Ca, P, alkaline phosphatase (AP), PTH, and safety biochemistries were collected at each study visit after an overnight fast before morning drug administration. Serum Ca, P, creatinine, and AP were measured by standard methods (Covance Central Laboratories, Indianapolis, IN). Intact PTH was measured using a double-antibody immunoradiometric assay (Allegro PTH; Nichols Institute Diagnostics, San Juan Capistrano, CA). Estimated glomerular filtration rate (eGFR) was calculated using the six-variable modification of diet in renal disease (MDRD) equation: $\text{GFR} = 170 \times (\text{serum creatinine})^{-0.999} \times (\text{age in years})^{-0.176} \times 0.762$ (if female) $\times 1.18$ (if Black) $\times (\text{blood urea nitrogen})^{-0.17} \times (\text{albumin})^{+0.318}$.

aBMD

aBMD of the lumbar spine, total femur, femoral neck, and one third distal radius was measured by dual-energy x-ray absorptiometry using a Hologic densitometer (Hologic, Waltham, MA) (n = 25) or a Lunar densitometer (Lunar Inc., Madison, WI) (n = 20). For each patient, aBMD was measured on the same densitometer throughout the study. aBMD measurements from Hologic and Lunar densitometers were analyzed separately. To allow for a combined analysis in both men and women spanning a wide age range, aBMD values made on both instruments were expressed as Z-scores. A central laboratory (Synarc, Inc., San Francisco, California) conducted all dual-energy x-ray absorptiometry analyses after cross-calibration of all instruments at each study site.

Safety and tolerability

All AE were tabulated by body system affected, preferred term within body system (according to a modified World Health Organization Adverse Reaction Terminology dictionary), seriousness (on a scale of 1–5 representing mild, moderate, severe, life-threatening, or fatal), and relationship to study drug (determined by prior placebo-controlled trials and on investigator judgment). The most frequent AE during the double-blind study phase and extension phase were presented.

Analysis

Efficacy measurements included the values from the parent study (wk 0–52) and the open-label extension (wk 53–287) giving a maximum cumulative exposure of up to 5.5 yr. Baseline values were defined as the baseline measurements of the parent study. Efficacy variables were reported by treatment group in the parent study and as a combined group after roll-over to the open-label extension. Values presented for the parent study were calculated for only the subset of each treatment group continued into the open-label extension and not the full subject population previously reported (5). Efficacy analyses were performed based on the group of subjects receiving at least one dose of cinacalcet and with data available for the analysis time point. At each study visit, mean values of serum Ca, PTH, P, and AP were presented over time, percent changes in Ca and PTH from parent study baseline for each individual were calculated and summarized as mean percent change over time, and number and percentage of subjects achieving a reduction in serum Ca to below the upper limit of the normal range (≤ 10.3 mg/dl) were determined. Longitudinal changes in aBMD were examined by calculating changes in Z-score for each individual and combining summarized Z-scores from both densitometers for presentation as mean changes from baseline over time. Because BMD values continue to change over time, data are presented by prior treatment group to avoid confounding by lag time in the prior placebo group. *Post hoc* analysis of aBMD was conducted in the subgroup of postmenopausal women (either age > 55 yr or reported postmenopausal medical history or concomitant hormone replacement therapy or selective estrogen receptor modulator use).

Statistics

Descriptive statistics used to summarize safety and efficacy data included number of subjects (n), mean, SD, SE, median, quartiles (Q1, Q3), and range (Min, Max) for continuous variables and count and frequency for discrete variables. Statistical analyses were performed using SAS version 9. Significance was determined using the Wilcoxon signed rank test or paired *t* test as indicated.

Results

Baseline demographics, biochemistries, and aBMD

Prior treatment groups (prior cinacalcet and prior placebo) were balanced in baseline subject demography, including age and sex (Table 1). Serum Ca, PTH, P, and AP and aBMD of the spine, hip, and forearm were also balanced between treatment groups (Table 1). Mean serum Ca and PTH were above the normal range, mean serum P was in the low normal range, and mean total AP was in the normal range. Mean Z-scores at spine, forearm, femoral neck, and total femur were normal (between +1 and –1). Twelve subjects (six prior cinacalcet and six prior placebo) had failed parathyroidectomy (Table 1).

Biochemical and densitometric responses

During the parent study for subjects subsequently enrolled into the open-label extension, mean predose serum Ca in the cinacalcet group decreased into the normal range (8.4–10.3 mg/dl) within a month of starting cinacalcet ($n = 21$; $P < 0.0001$, Wilcoxon signed rank test), whereas serum Ca in the placebo arm remained elevated at 1 yr (Fig. 2A), similar to results reported for the full subject population (5). Upon continuation into the open-label extension,

a similar response in serum Ca to that of the cinacalcet group in the parent study occurred in the prior placebo group ($n = 23$; $P < 0.0001$, Wilcoxon signed rank test). Thereafter, mean serum Ca for all subjects remained within the normal range throughout the open-label extension (Fig. 2A). The proportion of subjects with serum Ca of 10.3 mg/dl or lower remained stable throughout the study from yr 2–5 (ranging from 74–92%).

During the parent study, for subjects subsequently enrolled into the open-label extension, predose plasma PTH (mean \pm SE) in the prior cinacalcet group decreased gradually from baseline of 104.4 ± 7.1 pg/ml to 95.4 ± 6.8 pg/ml, but never into the normal range (Fig. 2B; $n = 21$; nonsignificant), similar to results reported for the full subject population (5). Plasma PTH for all subjects at 2 yr (104.0 ± 7.7 pg/ml; $n = 40$; nonsignificant, paired t test), 3 yr (103.4 ± 9.2 pg/ml; $n = 36$; nonsignificant, paired t test), 4 yr (88.6 ± 7.4 pg/ml; $n = 32$; $P = 0.01$, paired t test), and 5 yr (87.7 ± 7.3 pg/ml; $n = 30$; $P = 0.03$, paired t test) was lower than baseline (109.8 ± 6.8 pg/ml) but never reached normal levels (10–65 pg/ml). In all subjects, the reduction in PTH from baseline remained constant, ranging from a mean of 1–21% across the study.

Although remaining within normal range (2.6–4.1 mg/dl) throughout the study (Fig. 3A), mean serum P increased over the initial 12 wk of cinacalcet exposure after which levels remained constant. In the prior cinacalcet group, this increase occurred during the parent lead-in study (Fig. 3A). In the prior placebo group, it remained in the low-normal range for the length of the parent study, increased to levels comparable to the prior cinacalcet group over the first 12 wk of the open-label extension and remained stable for the rest of the trial (Fig. 3A).

Throughout the study, mean serum total AP remained within the normal range (35–115 U/liter) but increased after cinacalcet (Fig. 3B) during the parent study in the prior cinacalcet group and during the open-label extension in the prior placebo group. After the initial increase, serum total AP remained at the higher level within the normal range for the remainder of the study (Fig. 3B).

Mean aBMD remained in the normal range (Z-scores of –1 to +1) for the length of the study with no improvements in aBMD observed when expressed as mean \pm SE change from parent study baseline at the spine, wrist, femoral neck, and total femur (Fig. 4). There was a nonsignificant trend to increased Z-scores expressed as mean \pm SE change from baseline (original placebo; original cinacalcet) at the lumbar spine, for all subjects during the open-label extension at yr 2 (0.03 ± 0.08 ; 0.20 ± 0.09), yr 3 (0.07 ± 0.10 ; 0.28 ± 0.09), yr 4 (0.14 ± 0.12 ; 0.33 ± 0.10), and yr 5 (0.30 ± 0.14 ; 0.22 ± 0.19) (Fig. 4B). A *post hoc* analysis of the postmenopausal women subgroup ($n = 23$) showed

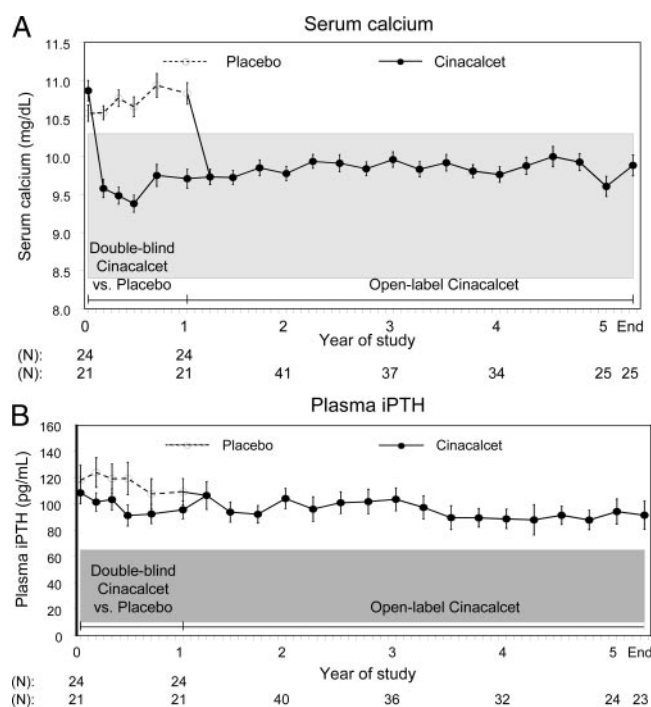


FIG. 2. Predose serum Ca and plasma intact PTH levels over time during the parent, randomized, placebo-controlled trial in those subjects that entered the 4.5-yr extension. Fasting samples were taken about 12 h after the prior evening dose of placebo or cinacalcet. A, Serum Ca levels (mean \pm SE). The shaded region represents the normal serum Ca (8.4–10.3 mg/dl). B, Plasma intact PTH levels (mean \pm SE). The shaded region represents the normal plasma intact PTH (10–65 pg/ml). The numbers of subjects (N) followed during each year of the study are shown in each panel for the placebo (upper row of numbers) and cinacalcet-treated groups (lower row of numbers).

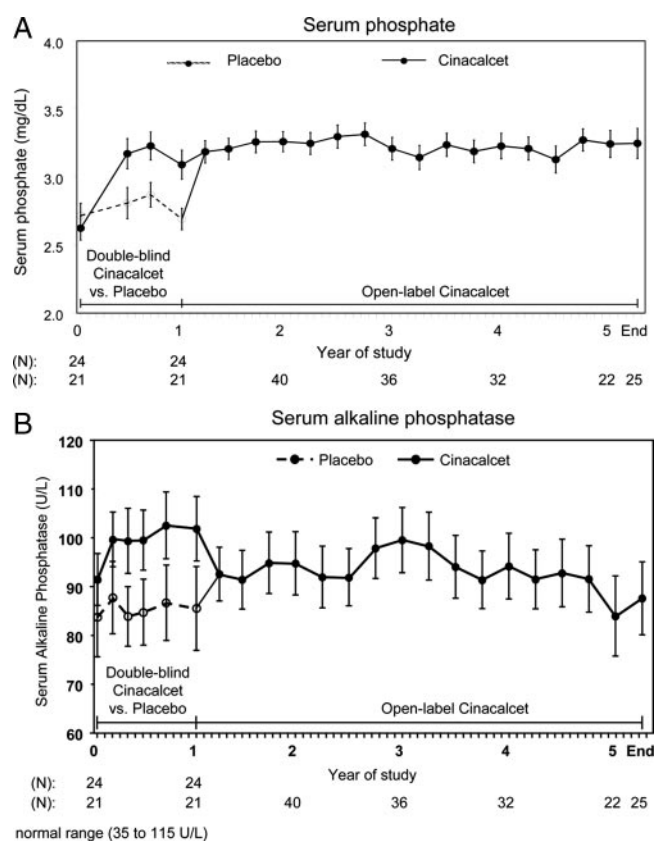


FIG. 3. Predose serum P and serum AP levels over time during the parent, randomized, placebo-controlled trial in those subjects that entered the 4.5-yr extension. Fasting samples were taken in the fasting state about 12 h after the prior evening dose of placebo or cinacalcet. A, Serum P levels (mean \pm SE). The normal range for serum P levels is 2.6–4.1 mg/dl. B, Serum AP levels (mean \pm SE). The normal range for serum AP levels is 35–115 U/liter. The numbers of subjects (N) followed during each year of the study are shown in each panel for the placebo (upper row of numbers) and cinacalcet-treated groups (lower row of numbers).

that their baseline mean aBMD T-scores were in the osteopenic (spine, femoral neck, and total femur; T-score between -1 and -2.5) and osteoporotic (one third distal radius; T-score < -2.5) ranges. This is comparable to the reported greater effects of PHPT on BMD at sites rich in cortical bone (7). There were no significant changes in T-scores during the 5-yr of the study. Analysis of Z-scores showed no improvements in aBMD at the spine, wrist, femoral neck, and total femur and a nonsignificant trend to increased Z-scores at the lumbar spine (supplemental Table 1, published as supplemental data on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>).

Adverse events

All 45 subjects received at least one dose of cinacalcet during the 6–235 wk of the open-label extension, with a mean \pm SE of 183 ± 10.8 wk of treatment. The prior cinacalcet group received an additional 52 wk treatment

during the parent study, producing a maximum cumulative exposure of 5.5 yr. Forty-two subjects (93%) completed the titration phase (wk 1–12) and entered the maintenance phase (wk 13–287) with two subjects withdrawing consent and one lost to follow-up. Thirty-one subjects completed between 5 and 5.5 yr of the study with 33 subjects completing at least 4 yr, 37 subjects completing at least 3 yr, and 41 subjects completing at least 2 yr of the study. During the maintenance phase before the fifth-year assessment, a total of 11 subjects withdrew from the study. Two subjects died while on study, due to AE (metastatic colon cancer and cerebral ischemia) unrelated to treatment. Two subjects withdrew due to AE (worsening nodular goiter and malignant neoplasm, rectal carcinoma, and sepsis) unrelated to treatment. The other subjects withdrew due to withdrawal of consent ($n = 5$), protocol-specified criteria ($n = 1$), and no information available on withdrawal reason ($n = 1$).

Over 98% of patients experienced at least one mild to moderate AE with similar incidences in both prior treatment groups. AE most commonly reported during the open-label extension were arthralgia (38%), myalgia (27%), diarrhea (22%), upper respiratory infection (20%), and nausea (20%), with only nausea showing a significant increase over placebo in the parent study (Table 2). Treatment-related AE occurred in the open-label extension in 13 subjects [29%; eight (33%) prior placebo and five (24%) prior cinacalcet] with the most frequent AE being myalgia (four subjects, 9%), hypocalcemia, nausea, paresthesia, and renal stones (two subjects, 4%, for each event). None of these treatment-related AE were serious, life-threatening, or fatal, and most (nine of 13) were of less than 1 month duration. Five subjects experienced a single serum Ca value of less than 8.0 mg/dl during the entire 5-yr study. Four of the five subjects were able to resume cinacalcet at reduced doses. Paresthesia was reported in only two of these subjects when serum Ca was lower than 8.0 mg/dl. Safety biochemistries including serum creatinine, liver function tests, and complete blood counts remained normal throughout the study. During the parent 1-yr study for those subjects who subsequently enrolled into the open-label extension, both groups experienced similar eGFR declines (mean \pm SE) of $-4.7 \pm 2.5\%$ (prior placebo) and $-5.6 \pm 3.8\%$ (prior cinacalcet) over 1 yr. Year over year changes in eGFR (mean \pm SE) were $-1.9 \pm 2.4\%$ at 2 yr ($n = 40$), $+1.7 \pm 2.5\%$ at 3 yr ($n = 36$), $+4.8 \pm 3.9\%$ at 4 yr ($n = 34$), and $-2.9 \pm 2.8\%$ at 5 yr ($n = 29$) (supplemental Fig. 1; all were nonsignificant; one-sample t test). The slope of the reciprocal of serum creatinine over time was not significantly different before and after cinacalcet administration in the subjects who were on placebo in the parent study (supplemental Fig. 1).

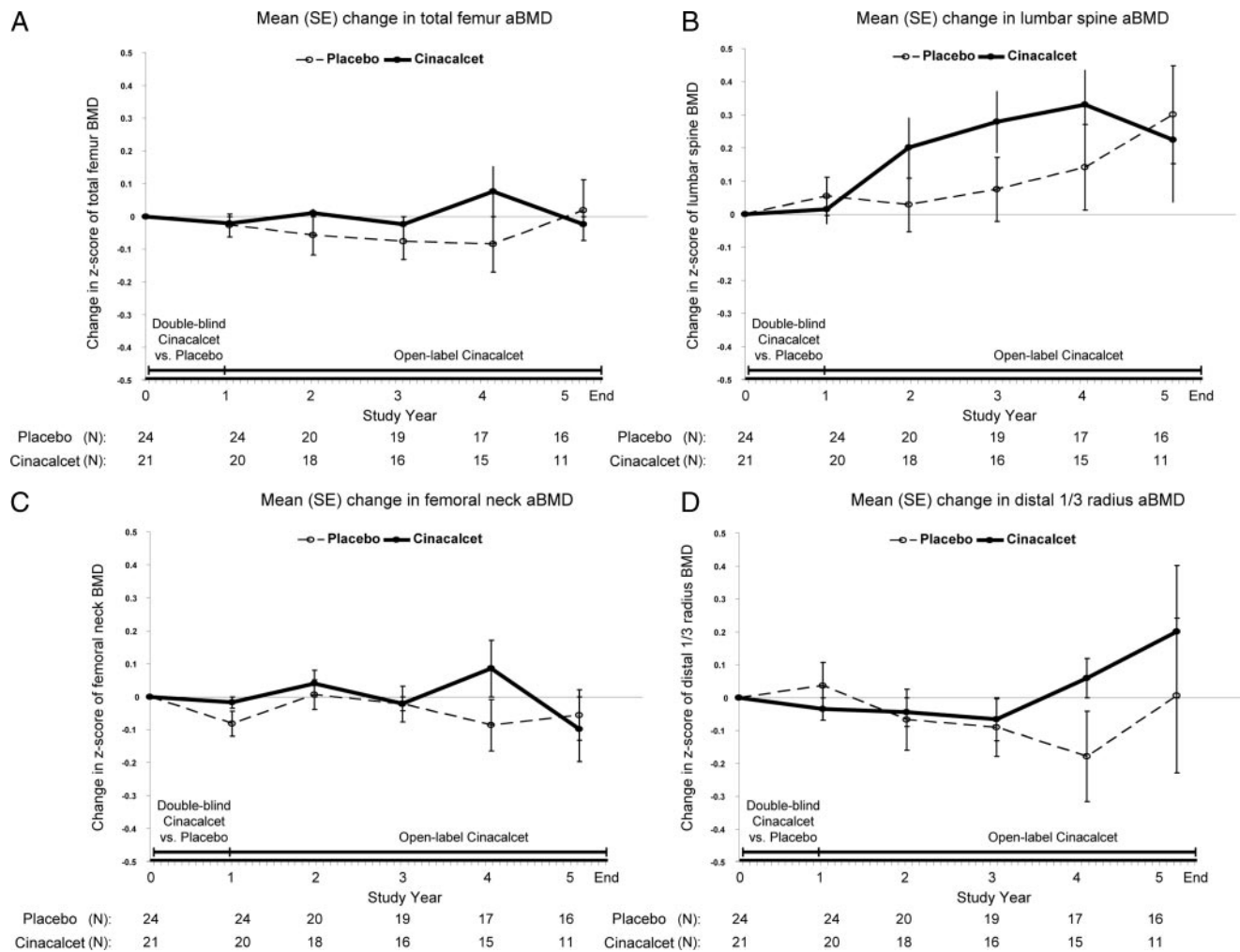


FIG. 4. Change in aBMD over time in patients during the first 52 wk of the parent, randomized, placebo-controlled trial followed by the 4.5-yr, open-label extension (placebo represents the original placebo group; cinacalcet represents the original cinacalcet group). Data are shown as the absolute change in z-score (mean \pm SE) for the total femur (A), lumbar spine (B), femoral neck (C), and distal one third radius (D).

Discussion

This 4.5-yr, open-label extension study of cinacalcet in subjects with mild to moderate PHPT substantially extends the findings of the original 1-yr, placebo-controlled trial (5). Cinacalcet rapidly (within a few weeks) normalized the elevated serum Ca levels in PHPT patients and, thereafter, maintained normocalcemia for a total of up to 5.5 yr of follow-up. After maintenance doses were established, serum Ca levels remained remarkably stable. Only five of 41 subjects required further dose adjustments over the next 4 yr. This was necessary because of mild hypocalcemia, which was symptomatic in two patients. In this group, four of the five were able to continue the study on lower doses of cinacalcet. It is likely that the intermittent mild hypercalcemia experienced by a few patients during the maintenance phase would have normalized with an increase in dose of cinacalcet above the 50 mg twice daily allowed by protocol. The studies in intractable PHPT (8) and parathyroid cancer (9) also indicate that higher baseline concentrations of serum calcium require

higher doses of cinacalcet to achieve normocalcemia. In this study in mild hyperparathyroidism, the same general trend was present but not of sufficient consistency to avoid a dose titration phase. Once the dose of cinacalcet to achieve normocalcemia was established, the subject continued to respond at this dose level.

Plasma PTH levels decreased substantially with cinacalcet therapy, especially by yr 4 and 5, but never normalized at the predose morning time point (12 h after prior drug administration). Compared with serum Ca responses, changes in plasma PTH were slower. Once cinacalcet maintenance doses, based on the serum Ca responses, were achieved, plasma PTH remained relatively stable. Previous pharmacokinetic studies demonstrated that predose plasma PTH levels do not accurately reflect the total changes in plasma PTH. Levels fall by 50–60% within 2–4 h of cinacalcet administration, returning to predose baseline by 8–12 h (4, 5). Despite these dynamic changes in PTH, cinacalcet doses that maintained normal serum Ca levels in PHPT patients did so

TABLE 2. AE rate over the course of the parent trial and the open-label extension (no significant differences)

	Placebo (n = 24)	Cinacalcet
AE during initial 52-wk placebo-controlled trial (%)		
Headache	38	10
Arthralgia	25	14
Myalgia	25	24
Nausea	17	29
AE during the 4.5-yr, open-label extension study (%)		
Arthralgia		38
Myalgia		27
Diarrhea		22
Upper respiratory infection		20
Nausea		20

For the cinacalcet values, n = 21 for the initial trial and 45 for the extension study.

at PTH concentrations above normal. As previously suggested (5), this may be due to cinacalcet's actions on CaSR in tissues other than the parathyroid glands (*e.g.* kidney, bone). Another consistent effect of cinacalcet was to increase serum P, probably through increased tubular reabsorption of P (5), reflecting reduced PTH secretion. The effects of cinacalcet reflect both direct activation of CaSR in the parathyroids and other tissues and indirect effects of reduced PTH receptor activation in kidney and bone, due to the resetting of baseline PTH levels and changes in plasma PTH dynamics throughout a 24-h day.

The relatively stable doses of cinacalcet that maintained normocalcemia over 5 yr suggest that the abnormal parathyroid glands in these patients with relatively mild PHPT did not expand their cell mass or secretory capacity sufficiently to require increasing calcimimetic doses to control PTH production. Even though parathyroid cells divide slowly, the length of this study should have been sufficient to detect emerging resistance to treatment due to cell mass or function. This suggests possible restraint on cell proliferation by cinacalcet, as demonstrated with other CaSR agonists in animal models of uremic parathyroid hyperplasia (10). We have no data on parathyroid gland size, volume, or histology in our patients to directly address this possibility.

During the 5 yr of cinacalcet treatment in PHPT patients, there were no effects on aBMD at spine, hip, or wrist sites, with mean aBMD and annual percent changes in BMD consistent with those expected for patients with PHPT or untreated postmenopausal women. This contrasts with the ability of parathyroidectomy to increase aBMD in PHPT patients. Removal of abnormal parathyroid glands leads to rapid increases in skeletal calcium retention (11) and long-term increases in bone mass (12–16). Increases in aBMD after parathyroidectomy are greatest in subjects with the highest baseline levels of bone

turnover (17). However, the majority of our subjects had mild disease with normal bone turnover markers at baseline. This may explain, in part, the lack of a significant increase in aBMD with lowering of serum Ca and PTH in our patients. Cinacalcet increased total AP levels, albeit within the normal range, suggesting a mild stimulation rather than suppression of bone turnover. This may reflect the induction of twice-daily fluctuations in plasma PTH (4, 5), which may stimulate bone turnover, as observed with daily PTH injections (18). It is also possible that chronic treatment with cinacalcet activates bone CaSR to stimulate bone turnover and promote bone loss. In a transgenic mouse model of constitutive CaSR activation targeted to mature osteoblasts, osteopenia developed progressively over time and was accompanied by increased bone turnover (19). Thus, it is possible that the response in BMD to cinacalcet is a composite result of an effect on bone CaSR to promote BMD loss and on the degree of PTH suppression of baseline bone turnover levels to promote BMD gain.

AE in the open-label study were mild to moderate in severity and similar to those in the 1-yr, placebo-controlled trial. Incidence of myalgia and arthralgia increased in the open-label trial. Nausea decreased, perhaps indicating that nausea usually occurs early in cinacalcet treatment and is self-limiting. Two patients had episodes of renal stones, not unexpected because serum 1,25-dihydroxyvitamin D and 24-h urine Ca were unchanged and no different from placebo in the placebo-controlled trial (5), suggesting that these stone formation risk factors are unaffected by cinacalcet. The decline in eGFR, greater than normal age-related declines, suggests that our patients had underlying renal disease (20, 21). The unchanged slope before and after cinacalcet exposure suggests that cinacalcet did not affect anticipated eGFR declines. However, AE are partly dependent on cinacalcet dose. In studies of intractable PHPT (8) and parathyroid cancer (9) in which doses higher than 50 mg twice daily were required, AE tended to be more common and more severe with the higher doses. Treatment-related AE occurred somewhat more often in subjects initially treated with placebo, suggesting that the AE do not increase with time on cinacalcet. The strengths of the study are its long duration, careful follow-up, and excellent subject retention on study: at least 80% at yr 3 and at least 60% at yr 4. Biochemical assessments made in the placebo-controlled trial were not extended into the extension study, limiting identification of mechanisms underlying the long-term cinacalcet action on Ca homeostasis in PHPT. Effects of serum 25-hydroxyvitamin D, at baseline and during the study, on responsiveness to calcimimetic therapy were not evaluated. Cinacalcet's effects on serum 1,25-dihy-

droxyvitamin D, bone turnover markers, and urinary Ca and P excretion were not extended beyond the first year.

This 4.5-yr open-label extension study describes a favorable safety and efficacy profile of cinacalcet therapy in patients with mild to moderate PHPT. Data from this long-term experience are consistent with findings of the initial 1-yr, placebo-controlled trial in patients with mild to moderate PHPT. Cinacalcet normalized serum Ca, reduced plasma PTH, did not affect aBMD, and was well tolerated with AE that were mild to moderate in severity. Cinacalcet is useful in the management of PHPT in patients in whom parathyroidectomy is contraindicated or who have failed surgical correction of their PHPT.

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