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A Randomized Study Evaluating Cinacalcet to Treat Hypercalcemia in Renal Transplant Recipients With Persistent Hyperparathyroidism

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Persistent hyperparathyroidism (HPT) after kidney transplantation (KTx) is associated with hypercalcemia, hypophosphatemia and abnormally high levels of parathyroid hormone (PTH). In this randomized trial, cinacalcet was compared to placebo for the treatment of hypercalcemia in adult patients with persistent HPT after KTx. Subjects were randomized 1:1 to cinacalcet or placebo with randomization stratified by baseline corrected total serum calcium levels ($\leq$11.2 mg/dL [2.80 mmol/L] or $>$11.2 mg/dL [2.80 mmol/L]). The primary end point was achievement of a mean corrected total serum calcium value $<$10.2 mg/dL (2.55 mmol/L) during the efficacy period. The two key secondary end points were percent change in bone mineral density (BMD) at the femoral neck and absolute change in phosphorus; 78.9% cinacalcet- versus 3.5% placebo-treated subjects achieved the primary end point with a difference of 75.4% (95% confidence interval [CI]: 63.8, 87.1), $p < 0.001$. There was no statistical difference in the percent change in BMD at the femoral neck between cinacalcet and placebo groups, $p = 0.266$. The difference in the change in phosphorus between the two arms was 0.45 mg/dL (95% CI: 0.26, 0.64), $p < 0.001$ (nominal). No new safety signals were detected. In conclusion, hypercalcemia and hypophosphatemia were effectively corrected after treatment with cinacalcet in patients with persistent HPT after KTx.

Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; BMD, bone mineral density; CaSR, calcium-sensing receptor; CKD, chronic kidney disease; EAP, efficacy assessment phase; eGFR, estimated GFR; FGF-23, fibroblast growth factor-23; HPT, hyperparathyroidism; iPTH, intact parathyroid hormone; KTx, kidney transplantation; PTH, parathyroid hormone; RANKL, receptor activator of nuclear factor kappa-B ligand

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Introduction

Kidney transplantation (KTx) continues to be a desirable goal of renal replacement therapy. The development of novel immunosuppressive therapies has led to a tremendous increase in the 1-year survival rates of renal allografts (1). Accordingly, improving the long-term survival and quality of life for renal transplant recipients has become a major focus of posttransplant patient care and includes prevention of cardiovascular complications (2,3), diabetes mellitus and fractures secondary to bone disease (4,5).

Secondary hyperparathyroidism (HPT) is a common consequence of end-stage renal disease and often does not resolve completely after successful KTx. In progressive renal failure, the ongoing functional demand for parathyroid hormone (PTH) induces morphological transformations of parathyroid tissue, including gland hyperplasia and adenoma formation. These morphological transformations are associated with down-regulation of the vitamin D receptor and calcium-sensing receptor (CaSR), which result in parathyroid gland resistance to inhibitory feedback mechanisms (6). Successful renal transplantation corrects the physiologic and metabolic abnormalities responsible for the

pathogenesis of secondary HPT (7–9). However, while end-organ resistance to the action of PTH rapidly wanes parallel to the recovery of renal function, regression of parathyroid gland hyperplasia is uncommon. Inappropriately high PTH levels contribute to common complications such as hypercalcemia and hypophosphatemia in a substantial proportion of incident renal transplant recipients (10)—otherwise referred to as tertiary or persistent HPT.

Hypercalcemia occurs in up to 66% of incident renal transplant recipients and is most prevalent 3–6 months after transplantation (10,11). Persistent increases in PTH secretion after renal transplantation, can also result in decreased renal phosphate reabsorption. Consequently, hypophosphatemia is observed in up to 90% of incident renal transplant recipients in the early posttransplant period (5,12). Persistent increases in fibroblast growth factor-23 (FGF-23), a phosphaturic hormone, are also thought to contribute to the development of hypophosphatemia after renal transplantation (13,14). Although the prevalence of abnormal levels of PTH, calcium and phosphorus tend to diminish over time, disordered mineral metabolism may persist in some patients for many years after successful renal transplantation. Persistent HPT may complicate posttransplant care by increasing the risk of fractures (5), vascular calcification (3,15) and renal allograft nephropathy (16,17). These complications have been associated with significant cardiovascular morbidity and mortality (18).

Given the body of evidence that associates persistent HPT with complications, clinical management is thought to be important to optimize clinical outcomes after KTx. Treatment with loop diuretics and antiresorptive agents to correct hypercalcemia, or phosphate supplements to correct hypophosphatemia, may lead to transient improvement, yet have poor efficacy and may even prove harmful in the long term. Parathyroidectomy is an option, but limitations include need for general anesthesia and difficulties associated with dosing (the amount of parathyroid gland tissue to be excised) with inherent risks of either unresolved persistent HPT or frank hypoparathyroidism (19,20).

Studies suggest that calcimimetics might be an effective alternative to existing therapies. Cinacalcet (Sensipar®/Mimpara®; Amgen Inc., Thousand Oaks, CA), an allosteric modulator of the CaSR, has demonstrated efficacy in decreasing calcium and PTH in patients with secondary HPT on dialysis (21); and in a number of small, open-label, single arm, single-center and retrospective studies, cinacalcet decreased serum calcium and PTH and increased serum phosphorus levels in renal transplant recipients with persistent HPT (22–28). In these studies, cinacalcet was well tolerated with no evidence of adverse effects on immunosuppressive therapy or allograft function. Because some single arm studies have suggested that cinacalcet may have an adverse effect on renal function (29), the current randomized study is important in evaluating the safety of cinacalcet in kidney transplant recipients.

To our knowledge, the current study is the first randomized placebo-controlled trial to evaluate the efficacy and safety of cinacalcet to lower calcium in renal transplant recipients with hypercalcemia and persistent HPT. The effects of cinacalcet on PTH and phosphorus levels were also assessed. Furthermore, this controlled trial allows for evaluation of the potential impact of cinacalcet on graft function and bone mineral density (BMD) during the treatment of persistent HPT in postkidney transplant patients.

Materials and Methods

This was a randomized, double-blind, placebo-controlled, multicenter, global, phase 3 study (Amgen protocol 20062007) to assess the effects of cinacalcet on hypercalcemia in patients who received a kidney transplant. Key inclusion criteria include the following at time of screening: a first or repeat kidney transplant $\geq$9 weeks and $\leq$24 months before first dose of study drug; a functional, stable kidney transplant defined as an estimated GFR (eGFR) $\geq$30 mL/min/1.73 m^2 (chronic kidney disease [CKD] stage 3 or better); corrected total serum calcium >10.5 mg/dL (2.63 mmol/L), defined as the mean of two values during screening; and intact PTH (iPTH) >100 pg/mL (10.6 pmol/L). Subjects were required to have a 4-week washout if they received cinacalcet for more than 14 days cumulatively posttransplant. Ongoing use of bisphosphonates, vitamin D analogs, calcium supplements, phosphate binders or thiazide diuretics were not allowed during the study.

After informed consent (approved by the center's Internal Review Board), eligible subjects ($\geq$18 years of age) were randomized 1:1 to cinacalcet or placebo. Randomization was stratified by baseline corrected total serum calcium levels ($\leq$11.2 mg/dL [2.80 mmol/L] or >11.2 mg/dL [2.80 mmol/L]). At least 30% of subjects were randomized into the high calcium stratum (>11.2 mg/dL [2.80 mmol/L]) to capture the spectrum of subjects with mild-to-moderate (calcium <11.2 mg/dL) and moderate-to-severe (calcium >11.2 mg/dL [2.80 mmol/L]) disease.

Administration of cinacalcet doses occurred within the range of the current label with a starting dose of 30 mg/day (orally) for either cinacalcet or placebo. Cinacalcet or placebo (study drugs) were titrated every 4 weeks during the dose-titration and maintenance phases (maximum dose of 180 mg/day) based on iPTH level, corrected total serum calcium value and safety evaluations. Investigators were instructed to decrease the dose of study drug if there were two consecutive corrected total serum calcium values <8.4 mg/dL (2.1 mmol/L) or three consecutive values of iPTH <35 pg/mL (3.7 pmol/L) or if the subject experienced an adverse event (AE) that required a decrease in dose. With the exception of medications previously noted, concomitant medications were permitted to resolve any signs or symptoms of AEs and manage persistent HPT at the discretion of the investigator in accordance with local practice guidelines.

Samples were collected at protocol specified intervals during the dose-titration phase (day 1, weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20), efficacy assessment phase (EAP; weeks 22, 24 and 26), maintenance phase (weeks 34, 42 and 52) and posttreatment follow-up phase (week 56). Blood samples were taken for measurement of: creatinine, iPTH, FGF-23 (Immunotopics, Inc., San Clemente, CA), total serum calcium and albumin (for corrected calcium), serum phosphorus and 25(OH)D_3. Measures of BMD at the femoral neck by dual X-ray absorptiometry (Synarc Imaging, Newark, CA) were collected at baseline and week 52. Synarc provided oversight for reading the imaging scans and standardizing machines across all sites.

Statistical analysis

A sample size of 100 subjects (50 per arm) was estimated to provide 91% power to achieve a statistical significance of 0.05 (two-sided) using the chi-square test. This assumed a response rate for the correction in total serum calcium of 35% in the placebo group and 70% in the cinacalcet group, and 13% subjects being excluded in the analyses due to loss of kidney transplant function.

Statistical considerations were based on the hypothesis that 6 months of treatment with cinacalcet would enable a greater proportion of subjects to achieve a mean corrected total serum calcium concentration <10.2 mg/dL (2.55 mmol/L) during the EAP, compared with those who received placebo. The primary end point is the achievement of a mean corrected total serum calcium value <10.2 mg/dL (2.55 mmol/L) during the EAP. Hierarchical testing procedure (30) was used to test the primary and the two secondary end points. First, the primary end point was tested at a significance level of 0.05. If the primary end point achieved a significant result, the two key secondary end points were tested using the same hierarchical testing procedure. Among the two key secondary end points, the percent change in BMD was tested first; if the result achieved statistical significance, the change in serum phosphorus would be tested. Comparisons of the proportion of subjects, between the two treatment groups, achieving the primary end point was performed using a Cochran–Mantel–Haenszel test stratified by baseline corrected total serum calcium level (≤11.2 mg/dL [2.80 mmol/L] and >11.2 mg/dL [2.80 mmol/L]). Percent change or change from baseline in BMD parameters, mean total serum calcium, iPTH, phosphorus and kidney transplant function (eGFR) during the EAP or week 52 was compared between the two treatment groups using an analysis of covariance (ANCOVA). Baseline corrected total serum calcium was used as a covariate. The eGFR was calculated by the MDRD formula. The frequency of safety end points was tabulated by treatment group.

Results

Subject disposition and baseline demographics

A total of 114 subjects were randomized to receive cinacalcet (N = 57) or placebo (N = 57), while 104 (91.2%) subjects completed the study and 10 (8.8%) discontinued study, of which five were in the cinacalcet group.

Of the total number of subjects enrolled, mean (SD) age was 52.3 (10.3) years with 55.3% subjects male and 81.6% white or Caucasian. Mean (SD) dialysis vintage was 62.4 (40.1) months and age of most recent kidney transplant was 7.2 (4.5) months. These characteristics were similar between groups. Details of subject demographics are summarized in Table 1. Table 2 summarizes the number of subjects within each dose category at the end of each study phase for the cinacalcet-treated subjects. For cinacalcet and placebo, the mean (SD) average daily dose for investigational product was 61.6 (31.2) mg and 129.5 (29.1) mg, respectively.

Mean (SD) baseline iPTH was 327.7 (262.6) pg/mL for the cinacalcet group versus 307.5 (180.5) pg/mL for the placebo group. Mean (SD) baseline corrected total serum calcium was 11.28 (0.41) mg/dL for the cinacalcet group versus 11.31 (0.50) mg/dL for the placebo group. Mean (SD) baseline serum phosphorus was 2.66 (0.54) mg/dL for the cinacalcet group versus 2.48 (0.52) mg/dL for the placebo group. Baseline mean (SD) eGFR values were 57.00 (17.31) and 54.68 (14.79) mL/min/1.73 m^2 for the cinacalcet and placebo groups, respectively. Laboratory values are presented in Table 3.

Primary end point

Overall, the proportion of subjects achieving the primary end point (i.e. the achievement of a mean corrected total serum calcium value <10.2 mg/dL [2.55 mmol/L]) was 78.9% and 3.5% for the cinacalcet and placebo groups, respectively. The difference (cinacalcet − placebo) in proportions was 75.4% (95% confidence interval [CI]: 63.8, 87.1), which was statistically significant ($p < 0.001$). The odds ratio (cinacalcet/placebo) was 91.41 (95% CI: 18.76, 445.41). In the corrected total serum calcium ≤11.2 mg/dL stratum there were 20/23 (87.0%) and 2/22 (9.1%) subjects who achieved the primary end point in the cinacalcet and placebo arms, respectively; whereas in the corrected total serum calcium >11.2 mg/dL stratum there were 25/34 (73.5%) and 0/35 (0%) who achieved the primary end point in the respective groups.

Table 1: Subject demographics and characteristics

	Cinacalcet /(N = 57)	Placebo (N = 57)	Total (N = 114)
Age, mean (SD)	53.0 (10.7)	51.7 (9.9)	52.3 (10.3)
Sex, n (%)			
Male	31 (54.4)	32 (56.1)	63 (55.3)
Female	26 (45.6)	25 (43.9)	51 (44.7)
Race, n (%)			
White	47 (82.5)	46 (80.7)	93 (81.6)
Black	5 (8.8)	4 (7.0)	9 (7.9)
Other	5 (8.7)	7 (12.3)	12 (10.5)
Blood pressure, mean (SD)			
Systolic (mmHg)	133.9 (18.4)	129.9 (14.0)	131.9 (16.4)
Diastolic (mmHg)	77.4 (10.4)	77.7 (9.3)	77.5 (9.8)
Dialysis vintage, mean (SD), months	62.0 (44.2)	62.7 (35.8)	62.4 (40.1)
Age of most recent kidney transplant, mean (SD), months	7.8 (5.6)	6.5 (3.0)	7.2 (4.5)
Number of subjects exposed to cinacalcet, n (%)	36 (63.2)	35 (61.4)	71 (62.3)

Table 2: Summary of cinacalcet dose level (mg/day) by study phase

	Cinacalcet (N = 57)			
Dose level (mg/day)	End of titration (N1 = 57) n (%)	End of EAP (N1 = 52) n (%)	End of maintenance (N1 = 53) n (%)	End of study (N1 = 57) n (%)
30	17 (29.8)	15 (28.8)	17 (32.1)	19 (33.3)
60	21 (36.8)	19 (36.5)	17 (32.1)	18 (31.6)
90	11 (19.3)	10 (19.2)	11 (20.8)	12 (21.1)
120	5 (8.8)	3 (5.8)	3 (5.7)	3 (5.3)
180	3 (5.3)	5 (9.6)	5 (9.4)	5 (8.8)

EAP, efficacy assessment phase; %, n/N1.

BMD and bone turnover markers

Mean (SE) percent changes in BMD are presented in Table 4 and mean (SE) Z scores are presented in Table S1. Mean (SE) percent change in BMD at the femoral neck (first secondary end point) measured from baseline to week 52 by treatment group was 2.16% (1.07%) in the cinacalcet group compared to 0.73% (0.63%) in the placebo group. Least square mean estimate for the difference in the percent change in BMD between the two treatment groups (cinacalcet − placebo) is 1.41% with a 95% CI of (−1.10, 3.93). Test of treatment effect adjusting for baseline corrected total calcium level yields a p-value of 0.266. Markers of bone turnover are presented in Table 5. For blood alkaline phosphatase, osteocalcin and urine N-telopeptide, the mean values decreased over time from baseline to week 52 with some fluctuation in between in the cinacalcet arm while the mean values decreased over time from baseline to week 52 in the placebo arm. For 25 $(OH)D_3$, the mean increased over time from baseline to week 52 for both cinacalcet and placebo arm.

Serum calcium and phosphorus

Corrected total serum calcium decreased from baseline to EAP such that the mean (SE) change was −1.53 (0.10) mg/dL for the cinacalcet group and −0.14 (0.07) mg/dL for the placebo group (Figure 1). Results from the ANCOVA analysis yielded a nominal p-value of <0.001 for a difference of −1.39 mg/dL (95% CI: −1.62, −1.16) between the two groups. The mean (SE) change in serum phosphorus from baseline to EAP was 0.52 (0.07) mg/dL for the cinacalcet group and 0.07 (0.06) mg/dL for the placebo group (Figure 2). The least square mean estimate for the difference in the absolute change in mean serum phosphorus from baseline to EAP between the two treatment groups (cinacalcet − placebo) was 0.45 mg/dL (95% CI: 0.26, 0.64), $p < 0.001$. Because the first secondary end point (BMD) was not statistically significant, the second secondary end point of phosphorus was not statistically tested. Subsequently, the p-value was considered nominal.

Table 3: Mean (SD) laboratory values at baseline, week 26, week 52 and posttreatment washout

	Cinacalcet				Placebo			
	Baseline	Week 26	Week 52	Week 56[1]	Baseline	Week 26	Week 52	Week 56[1]
Mean (SD)								
Albumin (mg/dL)	4.02 (0.29)	3.97 (0.39)	4.01 (0.31)	3.97 (0.31)	4.08 (0.28)	4.01 (0.35)	4.05 (0.26)	4.00 (0.36)
Corrected total calcium (mg/dL)	11.28 (0.41)	9.79 (0.76)	9.57 (0.71)	11.04 (0.69)	11.31 (0.50)	11.19 (0.55)	11.09 (0.53)	11.01 (0.63)
iPTH (pg/mL)	327.7 (262.6)	189.3 (86.0)	169.0 (83.5)	234.2 (119.0)	307.5 (180.5)	292.0 (214.1)	304.8 (368.8)	276.7 (243.9)
Phosphorus (mg/dL)	2.66 (0.54)	3.20 (0.57)	3.29 (0.53)	2.87 (0.54)	2.48 (0.52)	2.60 (0.46)	2.66 (0.44)	2.71 (0.47)
FGF-23 (pg/mL)	26.243 (23.981)	21.248 (13.695)	17.059 (10.490)	–	23.907 (14.078)	22.357 (14.955)	20.216 (22.346)	–
25$(OH)D_3$ (ng/mL)	18.49 (8.92)	23.34 (8.97)	22.96 (9.59)	–	20.48 (10.54)	21.60 (9.87)	22.67 (8.95)	–
eGFR (mL/min/1.73 m^2)	57.00 (17.31)	55.87 (17.05)	55.80 (17.94)	–	54.68 (14.79)	53.89 (15.18)	54.17 (15.24)	–

eGFR, estimated GFR; FGF-23, fibroblast growth factor-23; iPTH, intact parathyroid hormone.
[1]Posttreatment follow-up phase; subjects did not receive study drug from weeks 53 to 56.

Table 4: Mean (SE) bone mineral density (BMD) at baseline and week 52 with percent change in BMD at the femoral neck, lumbar spine and distal 1/3 radius

	BMD at femoral neck (g/cm^2)			
	n	Cinacalcet	n	Placebo
Baseline	56	0.737 (0.023)	57	0.732 (0.022)
Week 52	52	0.751 (0.024)	49	0.728 (0.024)
% Change	52	2.16 (1.07)	49	0.73 (0.63)
	BMD at lumbar spine (g/cm^2)			
	n	Cinacalcet	n	Placebo
Baseline	56	0.985 (0.021)	55	0.966 (0.29)
Week 52	52	0.991 (0.021)	48	0.963 (0.031)
% Change	52	0.598 (0.827)	48	1.172 (0.766)
	BMD at distal 1/3 radius (g/cm^2)			
	n	Cinacalcet	n	Placebo
Baseline	53	0.653 (0.010)	56	0.622 (0.016)
Week 52	48	0.641 (0.012)	46	0.602 (0.018)
% Change	47	−2.714 (0.781)	46	−1.992 (0.591)

Plasma PTH and FGF-23

iPTH decreased from baseline to EAP such that the mean (SE) change was −127.9 (33.7) pg/mL in the cinacalcet group and −10.6 (14.1) pg/mL in the placebo group (Figure 3). The ANCOVA analysis yielded a nominal p-value of 0.002 for a difference of −117.2 pg/mL (95% CI: −189.9, −44.6) between the two groups. Mean (SE) change of FGF-23 from baseline to week 26 was −3.54 (2.19) pg/mL and 0.20 (2.48) pg/mL for the cinacalcet and placebo groups, respectively based on subjects with both baseline and week 26 measurements. Mean (SE) change from baseline to week 52 was −7.06 (2.06) pg/mL and −1.18 (4.25) pg/mL for the cinacalcet and placebo groups, respectively.

eGFR and urinary calcium

Data for eGFR indicated that renal function remained stable over time with no difference between the groups (Figure 4). The ANCOVA analysis on change from baseline to week 52 yielded a nominal p-value of 0.842 for a difference of −0.40 mL/min/1.73 m^2 (95% CI: −4.37, 3.57) from baseline to week 52 between the two groups. Urinary calcium (UCa) to urinary creatinine (UCr) ratio was calculated. The mean (SE) UCa/UCr ratio is 0.17 (0.02) mg/mg for cinacalcet arm and 0.13 (0.01) mg/mg for placebo arm at baseline. The mean (SE) change from baseline was −0.03 (0.02) mg/mg for the cinacalcet arm and 0.01 (0.02) mg/mg for the placebo arm at week 52.

Safety

Two (3.5%) subjects in the cinacalcet group and three (5.3%) subjects in the placebo group discontinued the study drug due to an AE. The most frequently reported treatment-emergent AE in the cinacalcet group was diarrhea: cinacalcet (n = 9, 15.8%) versus placebo (n = 3, 5.3%) groups. One subject randomized to the cinacalcet group had a fatal AE and died of metastatic adenocarcinoma of the lung. Due to the subject's history, the investigator reported that there was no reasonable association between the event and the study drug. Furthermore, one subject from the cinacalcet group experienced a foot fracture, while two subjects from the placebo group developed a femoral neck and a vertebral fracture. No new safety risks were identified.

Discussion

This randomized, double-blind, placebo-controlled study demonstrated that cinacalcet is a highly effective treatment option for correcting serum calcium and phosphorous levels in renal transplant recipients with persistent HPT. Almost 80% of patients with hypercalcemia and persistent HPT treated with cinacalcet versus 4% treated with placebo achieved a corrected total serum calcium value <10.2 mg/dL. Achievement of target calcium levels was accompanied by an increase in phosphorus and a decrease in PTH levels without requiring maximal escalation of cinacalcet dose over time. There was no statistically significant difference between treatment groups for the secondary end point of percent change in BMD, nor were there remarkable differences in bone turnover markers. It is worth noting that renal transplant function was not affected

Table 5: Markers of bone turnover, mean (SD)

	Cinacalcet (N = 57)				Placebo (N = 57)			
	Baseline	Week 12	Week 26	Week 52	Baseline	Week 12	Week 26	Week 52
BALP (ng/mL)	30.93 (14.99)	35.58 (21.52)	33.82 (22.43)	26.30 (13.68)	34.73 (25.46)	33.08 (28.49)	27.14 (16.97)	23.85 (13.47)
Urine NTx (nmol/L)	104.77 (60.69)	125.08 (83.43)	118.93 (90.48)	82.42 (50.21)	116.78 (92.85)	94.42 (70.35)	93.31 (72.91)	80.57 (54.86)
Osteocalcin (ng/mL)	74.37 (39.27)	77.37 (41.89)	76.72 (42.21)	69.43 (37.22)	79.39 (59.37)	76.89 (56.08)	68.17 (43.13)	62.85 (36.31)
25(OH)D_3 (ng/mL)	18.49 (8.92)	21.33 (9.22)	23.34 (8.97)	22.96 (9.59)	20.48 (10.54)	20.83 (9.50)	21.60 (9.87)	22.67 (8.95)

BALP, bone-specific alkaline phosphatase (ng/mL); urine NTx, urine N-telopeptide.

Normal ranges for each analyte: BALP male 8.8–30 ng/mL, female 5.7–22 ng/mL; urine NTx male 11–103 nmol/mmol, female 10–110 nmol/mmol; osteocalcin 7.3–38.5 ng/mL; 25(OH)D_3 9.2–37.6 ng/mL.

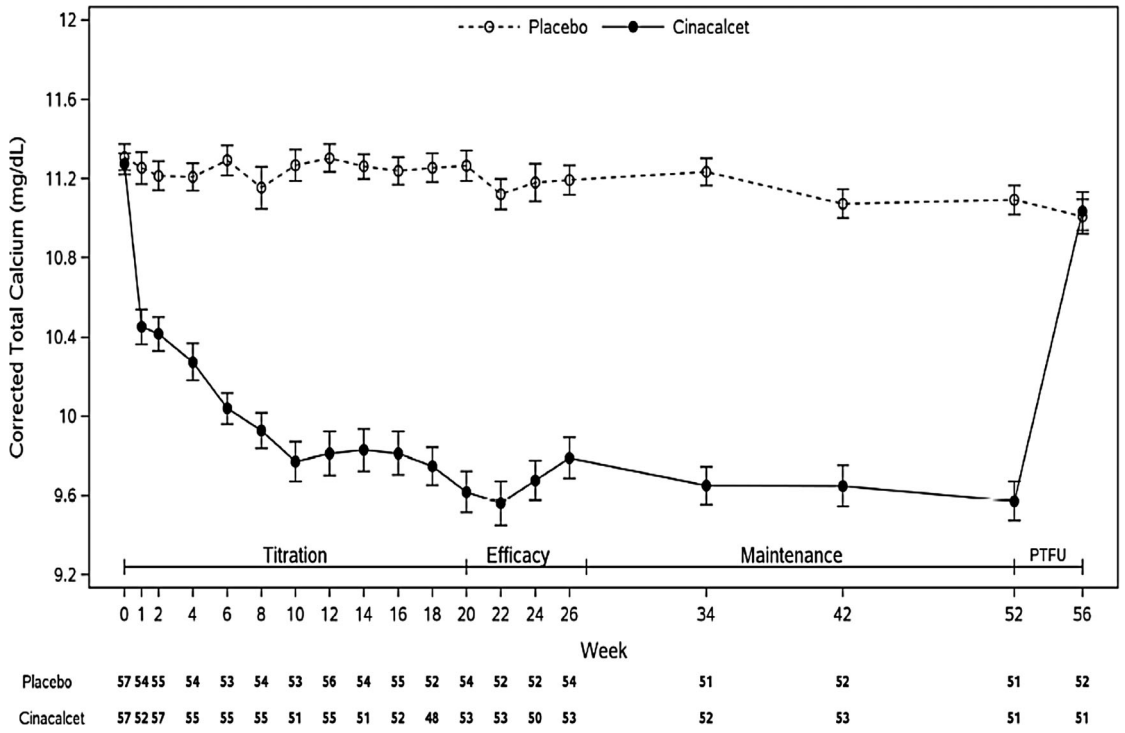

Figure 1: Mean (SE) corrected total serum calcium (mg/dL) over time. PTFU, posttreatment follow-up.

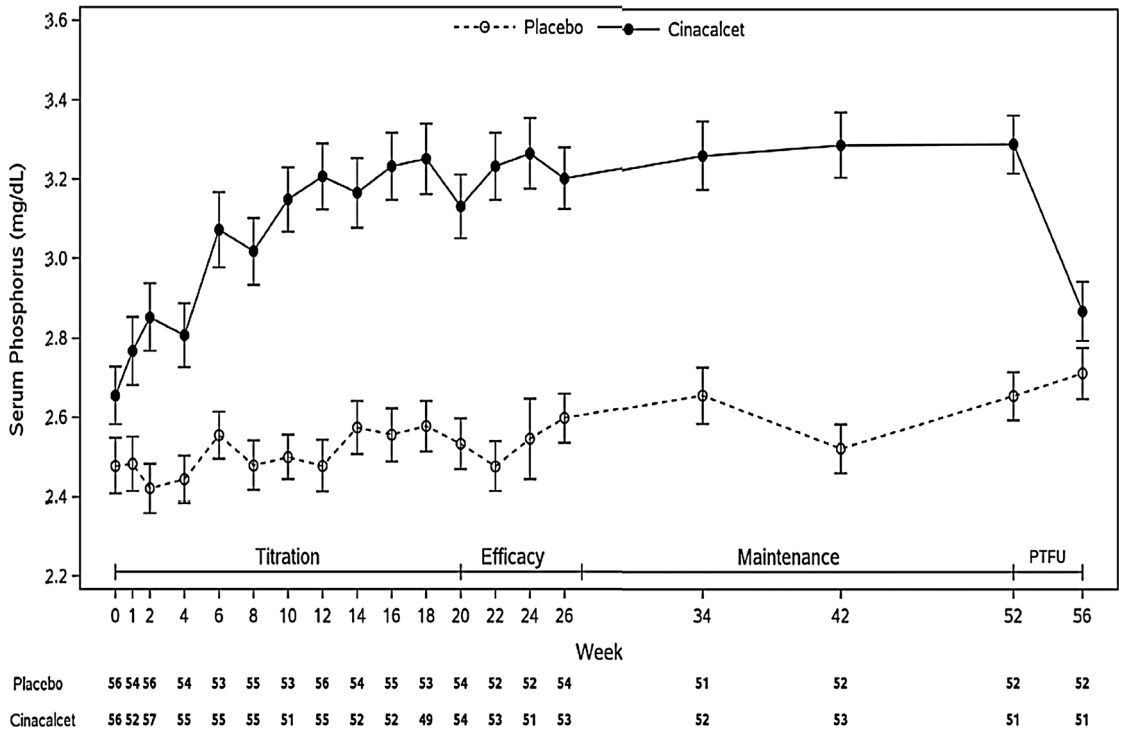

Figure 2: Mean (SE) phosphorus (mg/dL) over time. PTFU, posttreatment follow-up.

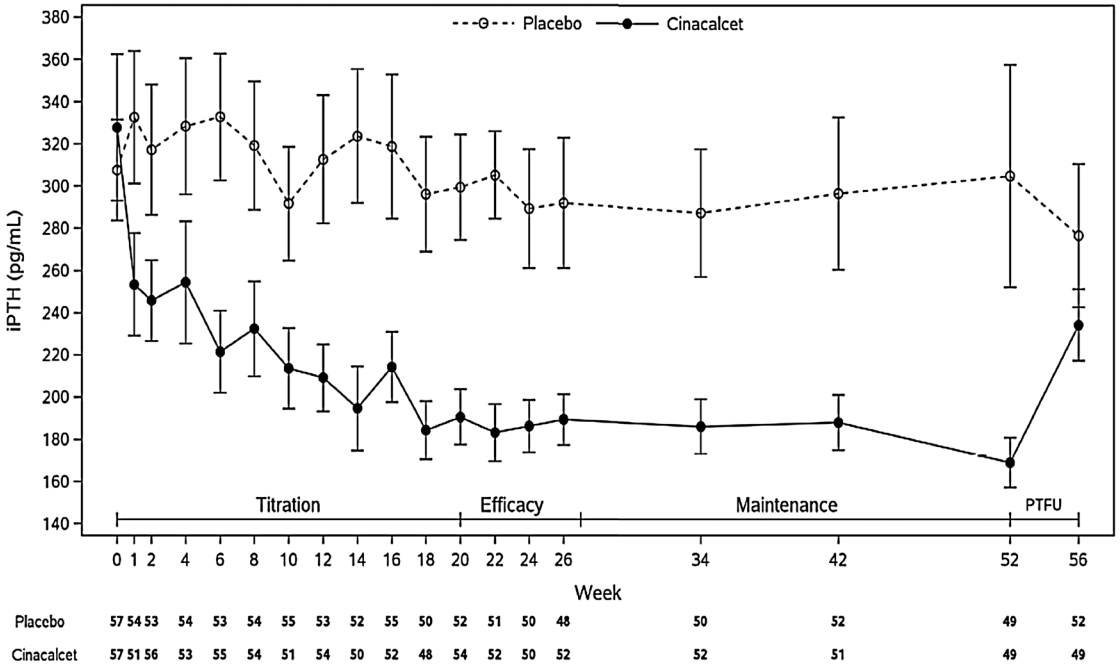

Figure 3: Mean (SE) intact PTH (iPTH) (pg/mL) at scheduled visits (baseline, weeks 26 and 52). PTFU, posttreatment follow-up.

by treatment with cinacalcet. Furthermore, no apparent interaction with standard immunosuppressive therapies and cinacalcet was observed (data not shown). In addition, no new AEs were identified. As such, this study confirms and extends data from previous small and/or uncontrolled intervention studies regarding the efficacy and safety of cinacalcet when used to treat hypercalcemia and persistent HPT in renal transplant recipients (22,25,27,28,31–33).

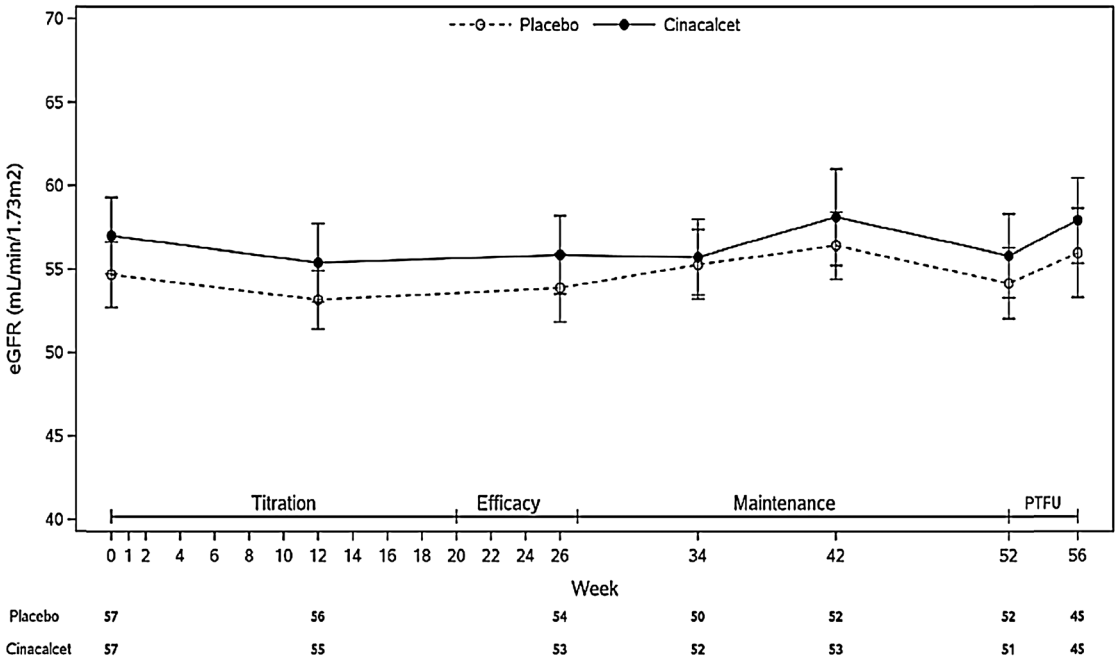

Figure 4: Mean (SE) estimated GFR (eGFR) (mL/min/1.73 m^2) over time. PTFU, posttreatment follow-up.

HPT does not completely resolve in a substantial proportion of kidney transplant recipients (34). Risk factors for persistent HPT after renal transplantation include increased dialysis vintage and more severe secondary HPT prior to transplantation (10,35). Despite successful KTx, persistent HPT has been observed in 17% of patients to as high as 50% up to 2 years after transplantation. In addition, hypercalcemia is seen in up to 66% of patients within 3 months of surgery and decreases to 10–40% 2 years posttransplantation; whereas, hypophosphatemia occurs in up to 68% of patients 3 months posttransplantation and decreases to 16% after 2 years (10). Quantifying the proportion of patients with underlying persistent HPT has been difficult due to the absence of clearly defined guidelines for the disease. Adding to this difficulty is the inability to discern the relative contributions from parathyroid hyperplasia in persistent HPT in optimally functioning allografts versus recurrent secondary HPT in marginally functioning allografts. The trends in calcium, phosphorus and PTH in placebo-treated subjects confirm that spontaneous correction of hypercalcemic HPT is uncommon at least within the first 2 years of renal transplantation. The increases in calcium and PTH and the decrease in phosphorus levels after withdrawal of cinacalcet to comparable values in the placebo arm support the chronic nature of posttransplant HPT (36) wherein cinacalcet may not alter the natural history. Subsequently, long-term medical treatment may be required. To date, parathyroidectomy is the only available, approved therapeutic option. When surgical treatment is indicated for those with severe HPT, refractory hypercalcemia or evident clinical sequelae (37), parathyroidectomy has not clearly demonstrated tangible health outcomes (38) though it has proven efficacy (39). Thus, under similar indications and unclear outcomes, a medical treatment may provide an alternative to surgery. It should, however, be emphasized that at present cinacalcet is not approved for use in postrenal transplant patients.

Although the main alteration in bone remodeling is a decrease in bone formation against persistent bone resorption (36), there remains the hypothesis that treating persistent HPT with hypercalcemia may curb morbidity risks such as fractures, which occurs in approximately 10–25% of all renal transplant recipients over their lifetime (40–45). In fact, fracture risk is substantially higher in renal transplant recipients than in recipients of other solid organs. Recent clinical evidence suggests that risk factors specific to the renal transplant setting, such as persistent HPT, may be involved (4,5,46–49). As PTH is a master regulator of bone remodeling, it activates osteoblasts both directly and indirectly via decreased expression of the osteocyte-derived Wnt antagonist sclerostin. The activation of osteoclasts by PTH involves the RANKL (receptor activator of nuclear factor kappa-B ligand) signaling pathway. In addition, hypophosphatemia may blunt PTH-mediated osteoblastogenesis and, thus, contribute to the uncoupling of bone resorption and formation (36). Thus, modulating PTH may affect the underlying cellular bone physiology that contributes to fracture in a particularly vulnerable population. Furthermore, correction of hypercalcemia may allow for the use of vitamin D supplementation. This may prove beneficial as renal transplant recipients are often nutritional vitamin D deficient (31).

Of note, FGF-23 levels were not elevated in this study, and no significant changes were observed during the 1-year period or between treatment groups. These data, support recent experimental evidence pointing to interactions between calcium and phosphorus in the regulation of FGF-23 production (50,51). Because increases of FGF-23 in renal transplant patients have been correlated with both poor graft function and patient survival (52), it is reassuring that levels remained low.

The present study confirms that cinacalcet is well tolerated in postrenal transplant recipients. In addition, it supports studies that have shown that cinacalcet has no clinically relevant interaction with standard immunosuppressive drugs (53). The most frequently reported treatment-emergent AE in the cinacalcet group was diarrhea, similar to what has been reported in other CKD cohorts (7,9,21,54). Previously, concerns have been raised about decreases in renal function following cinacalcet therapy for the treatment of persistent HPT including limited, but significant drops in eGFR (29). However, renal function in these studies returned to baseline after cessation of cinacalcet, suggesting a hemodynamic rather than a structural mechanism. A similar acute decline of renal function has been observed following parathyroidectomy (19); however, long-term graft outcome was not affected by this procedure (55). It is encouraging that in the current trial, cinacalcet treatment had no negative impact on renal function and eGFR levels remained relatively unchanged in both treatment arms. Although this trial confirms the efficacy and safety of cinacalcet with regard to improvement in both hypercalcemia and elevated PTH randomized trials designed to evaluate the impact of treatment on clinical outcomes in this patient population have not been conducted. The choice to treat hypercalcemia, including cost considerations, risk of prolonged drug exposure and perceived benefit, remains a decision by the physician and patient.

Limitations of study

The present study did not aim to investigate the impact of cinacalcet on the incidence of fractures in renal transplant recipients, yet the effect of cinacalcet on BMD was studied as a secondary end point. The hip was selected as the evaluation site as it includes cortical bone and may have the greatest impact on morbidity or mortality when it undergoes fracture. Albeit no intergroup differences in change of BMD could be demonstrated, this may be due to insufficient power to determine a statistical difference as well as the short observation period. Data on bone histomorphometry are unfortunately lacking in the present

study. Studies evaluating bone histomorphometry in renal transplant recipients are limited and yielded heterogeneous or even contradictory data. This heterogeneity is likely due to indication bias and variable time interval since transplantation (36). It should be acknowledged that in a recent bone biopsy study in 10 renal transplant recipients with hypercalcemic HPT a high proportion of low bone disease was observed (56). Additional bone biopsy studies are required to evaluate the impact of cinacalcet on bone histomorphometry. This was a placebo-controlled, blinded study; however, PTH and calcium levels were not blinded to investigators as dosing decisions required assessment of both. This may have compromised the blinding of treatment assignment.

Conclusion

These findings demonstrate the effectiveness and safety of cinacalcet to correct hypercalcemia in renal transplant recipients. An increase in phosphorus and decrease in PTH was observed in the cinacalcet-treated group, consistent with the known mechanism of action of cinacalcet and its effect on parathyroid function. Cinacalcet can be considered a therapeutic option for the treatment of hypercalcemia and persistent HPT. Providing a medical alternative to parathyroidectomy for renal transplant patients allows for the individualization of therapy and choice for patients and physicians. These data support further investigation of cinacalcet in the renal transplant population, focusing not only on biochemical and hormonal parameters, but also on clinical outcomes.

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Disclosure

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1: Mean (SE) BMD Z scores.