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Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism

JOHN CUNNINGHAM, MARK DANESE, KURT OLSON, PRESTON KLASSEN, and GLENN M. CHERTOW

University College London, The Middlesex Hospital, London, UK; Outcomes Insights, Inc., Newbury Park, California; Amgen, Inc., Thousand Oaks, California; and Department of Medicine, University of California, San Francisco, California

Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism.

Background. Secondary hyperparathyroidism (HPT) and abnormal mineral metabolism are thought to play an important role in bone and cardiovascular disease in patients with chronic kidney disease. Cinacalcet, a calcimimetic that modulates the calcium-sensing receptor, reduces parathyroid hormone (PTH) secretion and lowers serum calcium and phosphorus concentrations in patients with end-stage renal disease (ESRD) and secondary HPT.

Methods. We undertook a combined analysis of safety data (parathyroidectomy, fracture, hospitalizations, and mortality) from 4 similarly designed randomized, double-blind, placebo-controlled clinical trials enrolling 1184 subjects (697 cinacalcet, 487 control) with ESRD and uncontrolled secondary HPT (intact PTH ≥300 pg/mL). Cinacalcet or placebo was administered to subjects receiving standard care for hyperphosphatemia and secondary HPT (phosphate binders and vitamin D). Relative risks (RR) and 95% CI were calculated using proportional hazards regression with follow-up times from 6 to 12 months. Health-related quality-of-life (HRQOL) data were obtained from the Medical Outcomes Study Short Form-36 (SF-36), and the Cognitive Functioning scale from the Kidney Disease Quality of Life instrument (KDQOL-CF).

Results. Randomization to cinacalcet resulted in significant reductions in the risk of parathyroidectomy (RR 0.07, 95% CI 0.01–0.55), fracture (RR 0.46, 95% CI 0.22–0.95), and cardiovascular hospitalization (RR 0.61, 95% CI 0.43–0.86) compared with placebo. Changes in HRQOL favored cinacalcet, with significant changes observed for the SF-36 Physical Component Summary score and the specific domains of Bodily Pain and General Health Perception.

Conclusion. Combining results from 4 clinical trials, randomization to cinacalcet led to significant reductions in the risk of parathyroidectomy, fracture, and cardiovascular hospitalization, along with improvements in self-reported physical function and diminished pain. These data suggest that, in addition to its effects on PTH and mineral metabolism, cinacalcet had favorable effects on important clinical outcomes.

Key words: calcimimetics, cinacalcet, outcomes, PTH, secondary hyperparathyroidism.

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Secondary hyperparathyroidism (HPT) is a frequent component of the natural progression of chronic kidney disease (CKD), typically developing when the glomerular filtration rate (GFR) drops below approximately 80 mL/min/1.73m^2 for ≥3 months [1]. Secondary HPT is an adaptive response to CKD and arises from disruptions in the homeostatic control of serum calcium, serum phosphorus, and vitamin D, which are associated with CKD. Characteristic skeletal features of secondary HPT include increased bone turnover with abnormally high rates of bone resorption, often accompanied by bone pain and fractures [2–6]. Extraskeletal manifestations of secondary HPT include vascular calcification, hypertension, anemia with erythropoietin resistance, pruritus, and sexual dysfunction [7–14]. Conventional therapy for secondary HPT can contribute to hypercalcemia and hyperphosphatemia [15–17], laboratory abnormalities associated with mortality in end-stage renal disease (ESRD) [18–21]. We have recently demonstrated higher risks of cardiovascular disease and fracture associated with hyperphosphatemia and secondary HPT [19].

Vitamin D sterols are frequently used to control secondary HPT and have been shown to be effective in suppressing parathyroid hormone (PTH) [22–24] and improving bone histology [22, 25]. Despite the use of vitamin D, a large fraction of ESRD patients have refractory HPT [21]. Moreover, vitamin D enhances intestinal absorption of calcium and phosphorus, complicating the management of mineral metabolism [26]. Cinacalcet HCl is a calcimimetic agent that binds the calcium-sensing receptor (CaR) of the parathyroid gland, resulting in diminished PTH secretion [27]. Cinacalcet acts by allosterically modulating the CaR, enhancing the sensitivity of the CaR to extracellular calcium and, thus, exerting a suppressive

effect on PTH secretion [27]. Several published studies have demonstrated the efficacy of cinacalcet compared with placebo in lowering PTH concentrations in ESRD patients with secondary HPT [28–31]. In contrast with vitamin D, when using cinacalcet the reduction in PTH secretion has been accompanied by simultaneous reduction of the calcium × phosphorus product (Ca × P), serum calcium, and phosphorus [28–30].

The phase 2 and phase 3 studies comparing cinacalcet with placebo administered to subjects receiving standard care for hyperphosphatemia and secondary HPT were designed with sufficient power to answer questions related to biochemical end points (e.g., proportion of subjects with end-of-study PTH concentrations below 250 pg/mL or with a reduction of 30% or more from baseline). However, these individual studies were not designed to evaluate the effects of cinacalcet on morbidity (including hospitalization and fracture), mortality, or other outcomes believed to be related to the severity of secondary HPT, such as physical function and health-related quality of life (HRQOL). Data for these clinical end points were obtained for safety evaluation in selected phase 2 and all phase 3 clinical trials, all of which shared similar subject inclusion and exclusion criteria and virtually all basic design elements. Herein we present combined results from these clinical trials.

METHODS

Study selection

We analyzed data pooled from all clinical trials investigating the approved dose range of cinacalcet (30 to 180 mg) with at least 6 months of follow-up. One 12-month phase 2 trial and 3 6-month phase 3 trials were included. A 6-month extension trial of participants in 2 of the phase 3 studies was also included. The study design, including study drug dosing, was similar across all studies included in this analysis and is described below. The phase 2 trial was performed in the United States and Europe and treated 48 subjects at 17 sites. The 3 phase 3 trials were performed in North America (63 sites with 410 subjects), Europe, and Australia (62 sites with 331 subjects), and North America and Australia (60 sites with 395 subjects). The extension trial included subjects from the first 2 phase 3 trials who completed study between June 20, 2002 and December 27, 2002. All subjects completing the initial phase 3 study during this 12-month period were asked to continue their randomized treatment for an additional 6-month period. Of the 504 subjects who completed the 2 initial phase 3 trials, 266 subjects agreed to continue in the extension study (128 in the cinacalcet group and 138 in the control group).

Study subjects

The randomized clinical trials included in this analysis had similar inclusion and exclusion criteria. Each required that eligible subjects were ≥18 years old, exhibited an intact PTH level ≥300 pg/mL and an albumin-corrected serum calcium ≥8.4 mg/dL, and had received hemodialysis 3 times per week for a minimum of 1 to 3 months or peritoneal dialysis for ≥1 month. In 2 of the phase 3 trials, intact PTH >800 pg/mL and Ca × P >70 mg^2/dL^2 were stratification variables. In these 2 studies, the number of subjects with intact PTH >800 pg/mL was limited to no more than 20% (similar to the percentage observed in the general dialysis population), although this limitation was not a requirement in the other trials.

Exclusion criteria included parathyroidectomy or myocardial infarction within 3 to 6 months of the start of treatment and change of vitamin D therapy within 30 days of the start of treatment. Additional exclusion criteria included the use of flecainide, lithium, thioridazine, haloperidol, or tricyclic antidepressant (except for amitriptyline) therapy within 21 days of the start of the trial, gastrointestinal disturbances that could impair the absorption of the study drug, the existence of an unstable medical condition, and pregnancy or nursing.

The studies were approved by the Independent Ethics Committee or the Institutional Review Board, as appropriate, at each study center, and were conducted in accordance with the principles of the Declaration of Helsinki. All subjects provided written informed consent.

Study design

All trials were randomized, double-blind, and placebo-controlled. Subjects were randomized by a computer-generated randomization system. For the 2 phase 3 studies in hemodialysis subjects, 1:1 randomization was stratified by baseline PTH and Ca × P. For the phase 3 study enrolling hemodialysis and peritoneal dialysis subjects, a 3:1 ratio (cinacalcet:placebo) was used for randomization, which was stratified by dialysis modality, and within the hemodialysis subjects by baseline PTH. The phase 2 study utilized no stratification for the randomization. Matching placebos were used, and the blinds were maintained through the use of numbered study drug bottles. The phase 2 study had a 24-week titration phase and a 28-week assessment phase. The first 2 phase 3 studies used 12-week titration phases, while the third used a 16-week titration. All 3 phase 3 studies were 26 weeks in duration, with assessment phases ranging from 10 to 14 weeks. Subjects who entered the extension portion of the phase 3 trials received blinded treatment for an additional 26 weeks.

Subjects received cinacalcet at doses from 30 to 180 mg/day (30, 50, 70, 90, 120, 180 mg in the phase 2 trial and 30, 60, 90, 120, 180 mg in the phase 3 and extension

trials). These doses were titrated every 3 to 4 weeks. Subjects receiving vitamin D sterols at baseline continued at the same dose throughout the trial. Reductions in vitamin D doses were permitted for albumin-adjusted serum calcium ≥11 mg/dL, serum phosphorus ≥6.5 mg/dL or Ca × P ≥70 mg^2/dL^2. Vitamin D doses could be increased for serum calcium <8.4 mg/dL. Phosphate binders were permitted, with dose changes allowed at the discretion of the investigator. Detailed reports on the biochemical effects and general safety of cinacalcet have been previously published [28–31].

Clinical end points

Outcomes were identified prospectively based on reasons for discontinuation and adverse-event data [defined using World Health Organization Adverse Reaction Terminology [WHO-ART)] collected in all studies. Hospitalizations were captured from the adverse event form, with a primary preferred term (i.e., reason for hospitalization) provided for each event. Vital status and hospitalization were assessed for an additional 30 days and 7 days, respectively, beyond the official study completion. Follow-up time was adjusted accordingly for the analyses shown here.

Outcomes examined include parathyroidectomy (considered a failure of therapy for secondary HPT and a reason for study discontinuation), fracture, cardiovascular hospitalization (e.g., myocardial infarction, unstable angina, exacerbation of heart failure), as well as all-cause and noncardiovascular hospitalization. Reported events were confirmed using source document verification, and the medical records of all subjects were monitored during the study to facilitate complete event capture.

Subject-reported outcomes

Subject-reported outcomes used in these analyses were obtained in the phase 3 studies using touch-screen computer technology (Assist Technologies, Scottsdale, AZ, USA). Instruments used in all studies included the Medical Outcomes Study Short Form-36 (SF-36) and the Cognitive Functioning scale from the Kidney Disease Quality of Life (KDQOL) instrument (KDQOL-CF). Translated and culturally adapted versions of these instruments were used where appropriate. Data were collected before the first dose of study drug (baseline), at the end of the titration period, once during the middle of the efficacy assessment phase, and at the end of the efficacy assessment phase (i.e., the end of the study) for the phase 3 studies. Change from baseline was calculated as the difference between the baseline value and the mean of the 2 efficacy assessment phase values. Subjects with missing baseline data were excluded from the analyses ($N = 22$), as were subjects with no values during the efficacy assessment phase ($N = 238$). Data from the phase 2 study were not included because subject-reported outcomes were not assessed during the efficacy assessment phase of the study.

Norm-based scoring was used for the SF-36, meaning that for all scales a score of 50 represents the U.S. general population mean, with a standard deviation of 10 points. The KDQOL-CF was scored from 0 to 100, with a higher score indicating better function.

Statistical analysis

Analyses were based on all randomized subjects using an intent-to-treat approach. Cox proportional hazards models, stratified by study, were used to make statistical comparisons for the outcomes of parathyroidectomy, fracture, and death. The primary analyses for hospitalizations used the Andersen-Gill model to permit multiple events [32]. As the Andersen-Gill model essentially treats the second event as independent of the first, a conditional model (where the risk for a second event depends on having experienced a first event) was also used to confirm the results. Relative risk (RR) estimates and 95% CIs were calculated from model parameter coefficients and their standard errors. Survival curves were plotted using the time-to-event Kaplan-Meier product limit estimate. The estimated least squares means of each of the SF-36 scale scores, as well as the KDQOL-CF score, adjusted for study, were compared between treatment groups using *t* tests. Subjects with no values either at baseline or during the efficacy assessment phase ($N = 71$, 6.0%) were not included in the analysis of the subject-reported outcomes data. Two-tailed P values < 0.05 were considered statistically significant. All analyses were conducted using SAS 8.2 (Cary, NC, USA).

RESULTS

A total of 1184 subjects (697 cinacalcet, 487 control) enrolled in the studies. Table 1 shows baseline characteristics of subjects enrolled in the clinical trials. Overall, the mean ± SD age was 53.7 ± 14.4 years; 38% were women and 49% non-white. As expected, the median PTH was higher in the studies with no limit on inclusion of subjects with PTH ≥800 pg/mL. Generally, clinical characteristics were similar across studies, and no differences in baseline characteristics were noted among subjects enrolled in the phase 3, 6-month extension trial and the larger population of the 2 parent studies.

Clinical end points

Parathyroidectomy

In the cinacalcet group, there was 1 parathyroidectomy in 374.2 subject-years of follow-up (0.3 parathryoidectomies per 100 subject-years). In the control group,

Table 1. Baseline demographics and biochemical parameters

	Cinacalcet ($N = 697$) N (%)	Control ($N = 487$) N (%)	Total ($N = 1184$) N (%)	P value
Age				
<65 years	538 (77)	348 (71)	886 (75)	0.025
≥65 years	159 (23)	139 (29)	298 (25)	
Age at randomization *years*, mean ± SD	53.0 ± 14.2	54.7 ± 14.6	53.7 ± 14.4	0.037
Sex				
Female	272 (39)	181 (37)	453 (38)	0.52
Male	425 (61)	306 (63)	731 (62)	
Ethnicity				
White	332 (48)	270 (55)	602 (51)	0.018
Black	265 (38)	166 (34)	431 (36)	
Other	100 (14)	51 (10)	151 (13)	
Dialysis modality				
Hemodialysis	663 (95)	475 (98)	1138 (96)	0.034
Peritoneal dialysis	34 (5)	12 (2)	46 (4)	
Vintage *months*, mean ± SD	65.8 ± 59.9	70.1 ± 67.1	67.6 ± 63.0	0.25
Diabetes				
No	480 (69)	333 (68)	813 (69)	0.86
Yes	217 (31)	154 (32)	371 (31)	
Phosphate binder use				
No	49 (7)	36 (7)	85 (7)	0.81
Yes	648 (93)	451 (93)	1099 (93)	
Calcium-containing only	258 (37)	200 (41)	458 (39)	
Sevelamer only	211 (30)	128 (26)	339 (29)	
Calcium-containing plus sevelamer	86 (12)	49 (10)	135 (11)	
Other	93 (13)	74 (15)	167 (14)	
Vitamin D sterol use				
No	244 (35)	160 (33)	404 (34)	0.44
Naïve	70 (10)	41 (8)	111 (9)	
Withheld for elevated Ca, P, or Ca × P	132 (19)	86 (18)	218 (18)	
Other	8 (1)	3 (1)	11 (1)	
Not prescribed	30 (4)	29 (6)	59 (5)	
Not indicated	4 (1)	1 (0)	5 (0)	
Yes	453 (65)	327 (67)	780 (66)	
Oral	180 (26)	126 (26)	306 (26)	
Intravenous	234 (34)	179 (37)	413 (35)	
Oral plus intravenous	4 (1)	2 (0)	6 (1)	
Not indicated	35 (5)	20 (4)	55 (5)	
Plasma PTH *pg/mL*, mean ± SD	731 ± 531	682 ± 399	711 ± 481	0.074
Serum Ca × P mg^2/dL^2, mean ± SD	60.9 ± 16.0	61.1 ± 15.1	61.0 ± 15.6	0.84
Serum calcium *mg/dL*, mean ± SD	9.9 ± 0.8	9.9 ± 0.8	9.9 ± 0.8	0.26
Serum phosphorus *mg/dL*, mean ± SD	6.2 ± 1.7	6.2 ± 1.5	6.2 ± 1.6	0.85

there were 12 parathyroidectomies in 294.5 subject-years of follow-up (4.1 parathyroidectomies per 100 subject-years) (Table 2). The RR of parathyroidectomy was much lower (93% reduction) for the cinacalcet group (RR 0.07, 95% CI 0.01–0.55) (Fig. 1A). The median PTH at the time of parathyroidectomy was 1056 (interquartile range 523–1502).

Fractures

Fracture rates were lower in the cinacalcet group compared with the control group (3.2 vs. 6.9 per 100 subject-years) (Table 2). The RR of fractures was significantly reduced in the cinacalcet group (RR 0.46, 95% CI 0.22–0.95) (Table 2, Fig. 1B). In the control group, there were 7 fractures of the lower extremities (hip, femur, tibia, etc.), and 13 other fractures (ribs and upper extremities). Corresponding data for the cinacalcet group were 11 fractures of the lower extremities, and 1 other fracture, this being equivalent to approximately half the rate observed with placebo due to the larger number of subjects randomized to receive cinacalcet.

Cardiovascular hospitalization

The rate of cardiovascular hospitalizations was lower in the cinacalcet group compared with the control group (15.0 vs. 19.7 hospitalizations per 100 subject-years) (Table 2). Using the Andersen-Gill method, the RR of cardiovascular hospitalization was significantly reduced among subjects receiving cinacalcet (RR 0.61, 95% CI 0.43–0.86) (Table 2, Fig. 1C). Results were virtually identical using the conditional model (RR 0.63, 95% CI 0.44–0.90). In the control group, cardiovascular

Table 2. Event rates by treatment group

Clinical outcome	Events per 100 subject-years		Hazard ratio[a] (95% CI)	*P* value for hazard ratio
	Cinacalcet	Control		
Parathyroidectomy	0.3	4.1	0.07 (0.01–0.55)	0.009
Fracture	3.2	6.9	0.46 (0.22–0.95)	0.04
Cardiovascular hospitalization	15.0	19.7	0.61 (0.43–0.86)	0.005
All-cause hospitalization	67.0	71.0	1.03 (0.87–1.22)	0.74
Mortality	5.2	7.4	0.81 (0.45–1.45)	0.47

[a]Placebo was used as the reference group.

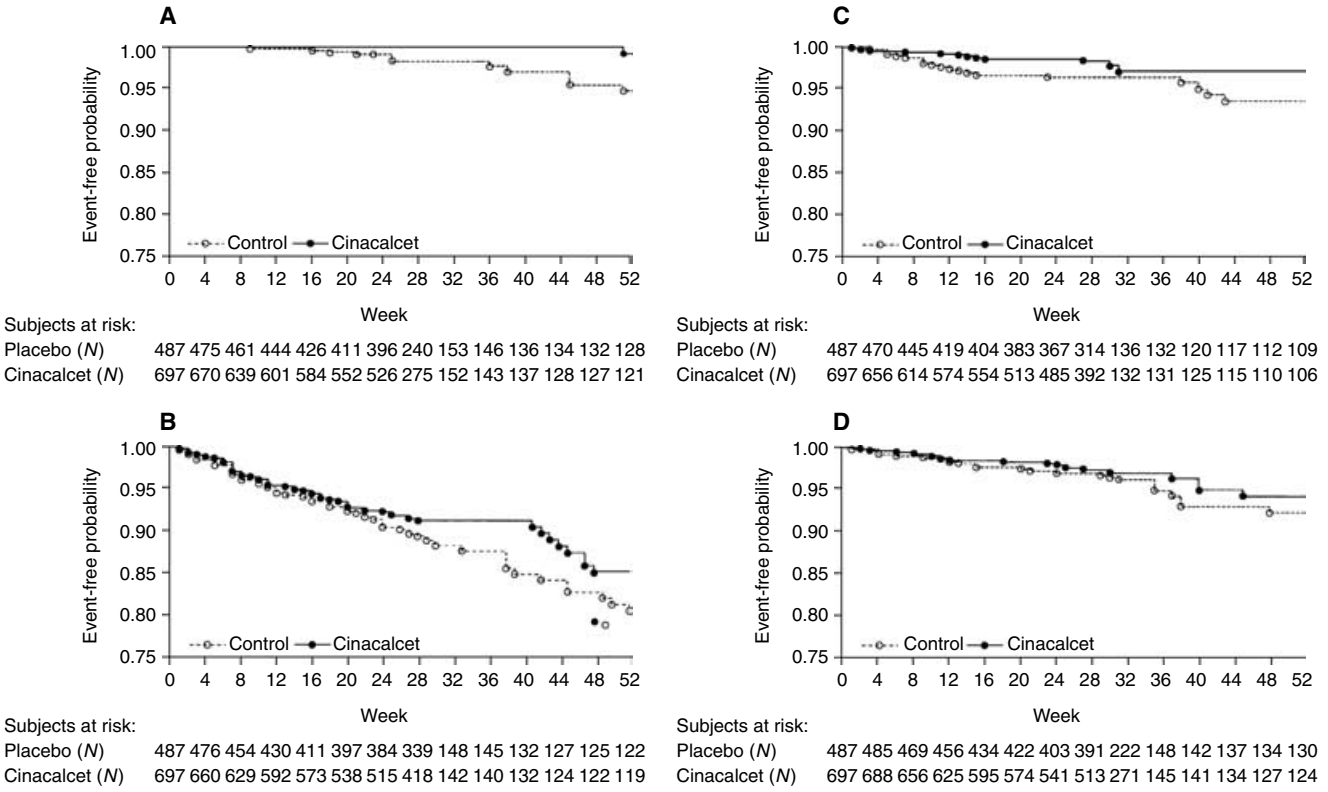

Fig. 1. Kaplan-Meier time-to-event plots for (*A*) parathyroidectomy, (*C*) bone fractures, (*B*) cardiovascular hospitalization, and (*D*) mortality in subjects on cinacalcet versus control.

hospitalizations included 29 hospitalizations for ischemic heart disease (including myocardial infarction and angina pectoris), 19 for heart failure, 18 for arrhythmia, 7 for peripheral vascular disease, and 4 for stroke. Corresponding data for the cinacalcet group were 22 hospitalizations for ischemic heart disease, 26 for heart failure, 17 for arrhythmia, 2 for peripheral vascular disease, and 5 for stroke.

All-cause hospitalization

There was no significant difference in all-cause hospitalizations between treatment groups (RR 1.03, 95% CI 0.87–1.22) using the Andersen-Gill method (Table 2). These results were confirmed with the conditional model (RR 1.02, 95% CI 0.86–1.21). No significant differences were observed between the treatment groups for non-cardiovascular hospitalizations (Andersen-Gill RR 1.16, 95% CI 0.96–1.39) or for hospitalizations unrelated to cardiovascular disease, fracture, or parathyroidectomy (Andersen-Gill RR 1.18, 95% CI 0.98–1.42).

Mortality

The rate of mortality in the study population was 5.2 and 7.4 per 100 subject-years in the cinacalcet and control groups, respectively. This difference was not statistically significant (RR 0.81, 95% CI 0.45–1.45) (Table 2, Fig. 1D).

Table 3. Mean baseline scores on the eight domains of the SF-36 and on the KDQOL-CF at baseline (combined phase 3 studies)

HRQOL scales	Cinacalcet ($N = 665$)		Control ($N = 471$)	
	N	Mean (SE)	*N*	Mean (SE)
SF-36				
Physical Component Summary	640	39.8 (0.39)	459	40.6 (0.47)
Mental Component Summary	640	49.4 (0.43)	459	49.3 (0.51)
Physical functioning	649	38.9 (0.46)	464	39.2 (0.55)
Role Limitations—Physical	645	41.7 (0.46)	463	42.5 (0.54)
Bodily Pain	649	46.3 (0.45)	463	47.2 (0.55)
General Health Perception	647	39.0 (0.37)	462	39.9 (0.46)
Social Functioning	649	45.1 (0.43)	463	45.6 (0.51)
Vitality	648	47.9 (0.38)	464	47.9 (0.47)
Role Limitations—Emotional	647	44.6 (0.50)	462	44.1 (0.60)
Emotional Well Being	648	48.8 (0.43)	464	49.5 (0.51)
KDQOL				
Cognitive functioning	647	79.7 (0.71)	464	79.4 (0.86)

Note: Higher values indicate better health status for all scales.

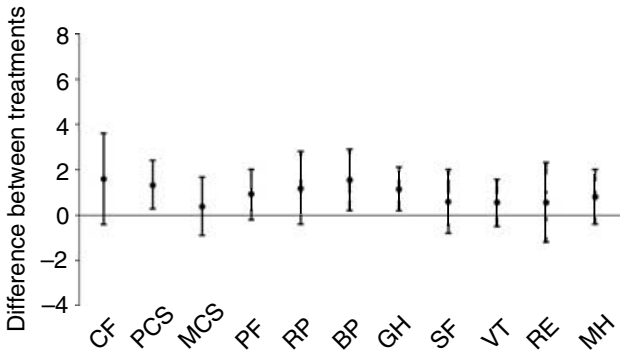

Fig. 2. Differences in score changes (cinacalcet-treated minus control subject scores) of combined phase 3 data on KDQOL-CF (CF) and SF-36 (PCS, Physical Component Summary; MCS, Mental Component Summary; SF-36 domains: PF, Physical Functioning; RP, Role Limitations-Physical; BP, Bodily Pain; GH, General Health Perception; SF, Social Functioning; VT, Vitality; RE, Role Limitations-Emotional; MH, Mental Health). A positive score represents a greater improvement with cinacalcet treatment compared to control treatment. Bars represent 95% CI.

HRQOL and self-reported cognitive function

Mean baseline scores on the 8 domains of the SF-36 were approximately one half to one standard deviation below the population mean and were similar between the randomized groups (Table 3). Changes in HRQOL (baseline to end-of-study) were consistently in favor of cinacalcet (Fig. 2). There were statistically significant differences between treatment groups for the SF-36 Physical Component Summary (PCS) score (0.5-unit improvement in the cinacalcet group compared with 0.8-unit decrease in the control group, $P = 0.01$), as well as the Bodily Pain scale (0.6-unit improvement in the cinacalcet group compared with 1.0-unit decrease in the control group, $P = 0.03$) and the General Health Perception scale (0.2-unit improvement in the cinacalcet group compared with 1.0-unit decrease in the control group, $P = 0.02$). A similar proportion of subjects in both groups experienced a large decline in self-reported physical function (decrease in PCS >5) points (21% vs. 23%, for cinacalcet and control groups, respectively, $P = 0.52$). However, significantly more subjects in the cinacalcet group experienced a large improvement in self-reported physical function (increase in PCS >5) points (26% vs. 20%, $P = 0.03$).

Baseline values on the KDQOL-CF were 79.7 and 79.4 in the cinacalcet and control groups, respectively. There were no significant differences in the mean change in KDQOL-CF score by treatment group (+0.2 vs. −0.8 in cinacalcet and control groups, respectively, $P = 0.12$).

DISCUSSION

Analyses of combined data from randomized, blinded, placebo-controlled, 6- to 12-month studies of cinacalcet versus standard care for secondary HPT showed statistically significant and clinically meaningful reductions in the risks of parathyroidectomy, fracture, and cardiovascular hospitalization. Although the individual clinical studies were designed to assess changes in biochemical parameters and not a priori clinical end points, the prospective and interventional nature of the combined data lends credibility to the clinical relevance of biochemical control in secondary HPT and suggests that therapy with cinacalcet may lead to beneficial effects on clinical outcomes.

Several mechanisms of action have been proposed that support the findings observed in these trials. Reduction in parathyroidectomy may be mediated through improved control of PTH and reductions in parathyroid cell proliferation and gland hyperplasia, which have been demonstrated using cinacalcet in an animal model of secondary HPT [33]. The reduction in fractures observed in this study is consistent with preclinical evidence demonstrating that calcimimetics ameliorated high bone turnover

and increased femoral cortical bone mineral density and cortical bone strength [34, 35]. In multiple phase 2 and phase 3 clinical trials, treatment with cinacalcet was associated with favorable changes in the biochemical markers of bone formation (bone-specific alkaline phosphatase) and resorption (serum N-telopeptide), as well as improvement in bone turnover parameters [28, 36]. In addition, although the increased cardiovascular risk evident in subjects with end-stage renal disease is multifactoral, this risk has been related to abnormalities of vascular biology, including calcification and arterial stiffness [37–40]. Elevations in serum calcium, phosphorus, and Ca × P are known to be independent risk factors for vascular calcification and mortality in hemodialysis subjects [11, 19, 41]. In vitro data suggest that elevated calcium and phosphorus concentrations play a role in the calcification of human vascular smooth muscle cells [42]. Preliminary evidence also demonstrates that calcimimetics do not increase the arterial content of calcium and phosphorus in vitro and may mitigate vascular calcification in uremic rats treated with calcitriol [43, 44].

In addition to the effects on fracture and cardiovascular hospitalization, the current analysis also demonstrated improvements in HRQOL with statistically significant improvements in the PCS scale and Pain and General Health Perception scales, and positive trends in other physical health domains. Several large cohort studies and clinical trials have linked higher scores on the PCS with reduced mortality and morbidity [45–48].

The results of these analyses highlight the importance of examining clinical outcomes in a disease dominated by reliance on biochemical parameters for diagnosis and therapeutic management. These data represent the first examination of clinical outcomes collected from prospective, randomized, and placebo-controlled studies of any therapy used for secondary HPT. Despite the introduction of newer vitamin D analogs and increased overall utilization of vitamin D sterols during the past decade, no outcomes data are available from prospective clinical trials. Over the same time period, the increasing trend in parathyroidectomy and fracture rates and unchanged rates of mortality and cardiovascular morbidity emphasize the need to examine clinical outcomes in an unbiased manner when evaluating therapeutic interventions [49, 50].

The analyses presented here have several strengths. The clinical trials were randomized and blinded, and clinical characteristics were well balanced by randomization. Although the clinical end points for this analysis were obtained from the safety records of each clinical trial and were not independently adjudicated, each event was verified by review of medical records. However, this analysis has several important limitations. The studies were not designed to evaluate differences in event rates. Follow-up times were relatively short; longer-term follow-up would have increased the likelihood of demonstrating significant treatment effects. Ascertainment of less severe events (e.g., fracture not requiring hospitalization) was likely limited, and also reduced the power to detect treatment effects.

CONCLUSION

Despite the limitations in study design, combined data demonstrate that cinacalcet treatment of subjects on dialysis with secondary HPT resulted in improvement in clinical outcomes, especially parathyroidectomy, fracture, cardiovascular hospitalization, and specific components of health-related quality of life. Future trials are required to confirm and expand on these results.

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Reprint requests to Glenn M. Chertow, M.D., MPH, Department of Medicine Research UCSF, University of California San Francisco, Laurel Heights, Suite 430, 3333 California Street, San Francisco, CA 94118-1211. E-mail: chertowg@medicine.ucsf.edu

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