ORIGINAL ARTICLE

Cinacalcet for Secondary Hyperparathyroidism in Patients Receiving Hemodialysis

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ABSTRACT

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BACKGROUND

Treatment of secondary hyperparathyroidism with vitamin D and calcium in patients receiving dialysis is often complicated by hypercalcemia and hyperphosphatemia, which may contribute to cardiovascular disease and adverse clinical outcomes. Calcimimetics target the calcium-sensing receptor and lower parathyroid hormone levels without increasing calcium and phosphorus levels. We report the results of two identical randomized, double-blind, placebo-controlled trials evaluating the safety and effectiveness of the calcimimetic agent cinacalcet hydrochloride.

METHODS

Patients who were receiving hemodialysis and who had inadequately controlled secondary hyperparathyroidism despite standard treatment were randomly assigned to receive cinacalcet (371 patients) or placebo (370 patients) for 26 weeks. Once-daily doses were increased from 30 mg to 180 mg to achieve intact parathyroid hormone levels of 250 pg per milliliter or less. The primary end point was the percentage of patients with values in this range during a 14-week efficacy-assessment phase.

RESULTS

Forty-three percent of the cinacalcet group reached the primary end point, as compared with 5 percent of the placebo group (P<0.001). Overall, mean parathyroid hormone values decreased 43 percent in those receiving cinacalcet but increased 9 percent in the placebo group (P<0.001). The serum calcium–phosphorus product declined by 15 percent in the cinacalcet group and remained unchanged in the placebo group (P<0.001). Cinacalcet effectively reduced parathyroid hormone levels independently of disease severity or changes in vitamin D sterol dose.

CONCLUSIONS

Cinacalcet lowers parathyroid hormone levels and improves calcium–phosphorus homeostasis in patients receiving hemodialysis who have uncontrolled secondary hyperparathyroidism.

SECONDARY HYPERPARATHYROIDISM IS common in patients with chronic kidney disease, affecting most of those who are receiving hemodialysis.[1,2] The disorder is characterized by persistently elevated levels of parathyroid hormone and complicated by important disturbances in mineral metabolism.[3]

Bone disease is the most widely recognized consequence of secondary hyperparathyroidism.[4] Several reports indicate, however, that alterations in calcium and phosphorus metabolism, as a result of either secondary hyperparathyroidism or the therapeutic measures used to manage it, contribute to soft-tissue and vascular calcification, cardiovascular disease, and the risk of death.[5-10] Episodes of hypercalcemia and hyperphosphatemia are often aggravated by the use of large doses of calcium as a phosphate-binding agent, particularly in combination with vitamin D sterols, which increase the absorption of calcium and phosphorus.[10-13] There is thus considerable interest in identifying therapeutic alternatives that control secondary hyperparathyroidism while limiting these side effects.

The calcium-sensing receptor regulates the secretion of parathyroid hormone.[14] Calcimimetic agents increase the sensitivity of the calcium-sensing receptor to extracellular calcium ions,[15,16] inhibit the release of parathyroid hormone, and lower parathyroid hormone levels within a few hours after administration.[17-19] This mechanism of action differs fundamentally from that of vitamin D sterols, which diminish the transcription of the parathyroid hormone gene and hormone synthesis over a period of many hours or several days.[20] Results of previous small clinical trials indicate that the calcimimetic agent cinacalcet hydrochloride not only reduces parathyroid hormone levels but also lowers serum calcium and phosphorus levels in patients with secondary hyperparathyroidism.[21-23] We report the combined results of two large phase 3 clinical trials of identical design to determine the safety and effectiveness of cinacalcet for treating secondary hyperparathyroidism in patients undergoing hemodialysis.

METHODS

STUDY PARTICIPANTS

Study candidates were patients in medically stable condition with secondary hyperparathyroidism who were 18 years of age or older and who had been treated with thrice-weekly hemodialysis for at least three months. The primary eligibility criterion was a mean plasma parathyroid hormone level of at least 300 pg per milliliter (31.8 pmol per liter), established by three measurements obtained within a 30-day screening period. Dialysate calcium levels remained unchanged throughout the study.

Exclusion criteria included evidence of cancer, active infection, diseases known to cause hypercalcemia, or a serum calcium level below 8.4 mg per deciliter (2.1 mmol per liter), corrected for albumin.[24] Because cinacalcet can inhibit cytochrome P-450 2D6, patients were excluded if they were receiving drugs such as flecainide, thioridazine, and most tricyclic antidepressants, which have a narrow therapeutic index and are metabolized by this enzyme.

The study protocols were reviewed and approved by the institutional review board at each study site, and written informed consent was obtained from each patient before enrollment. The study was designed by Amgen in collaboration with the authors. The complete data set was held at the central data-processing facility at Amgen. Statistical analyses and data interpretation were conducted by Amgen in collaboration primarily with Drs. Block and Goodman. The investigators had unrestricted access to the primary data and were not limited by the sponsor with regard to statements made in the final article. The lead investigators were responsible for writing the article, with editorial assistance from Amgen.

STUDY DESIGN

Two identical randomized, double-blind, placebo-controlled clinical trials were conducted at 63 sites in North America and 62 sites in Europe and Australia between December 20, 2001, and January 16, 2003. A total of 1270 patients were screened for entry. Of these, 741 satisfied eligibility criteria (410 in North America and 331 in Europe and Australia) and were randomly assigned to receive cinacalcet (371 patients) or placebo (370 patients). Randomization was stratified according to disease severity and base-line values for the calcium–phosphorus product. No more than 20 percent of the study population could have parathyroid hormone levels exceeding 800 pg per milliliter (84.8 pmol per liter).

The treatment phase of both studies lasted 26 weeks and consisted of a 12-week dose-titration phase followed by a 14-week efficacy-assessment phase. The initial dose of cinacalcet (or placebo) was 30 mg given orally once daily. The doses were

increased sequentially every three weeks during the dose-titration phase to 60, 90, 120, or 180 mg once daily. Increases in the dose were permitted if parathyroid hormone levels remained above 200 pg per milliliter (21.2 pmol per liter) and serum calcium levels were at least 7.8 mg per deciliter (1.95 mmol per liter). The dose was not increased if symptoms of hypocalcemia developed, if serum calcium levels were less than 7.8 mg per deciliter, or if patients had an adverse event that precluded an increase in the dose. The dose was reduced if parathyroid hormone levels were less than 100 pg per milliliter (10.6 pmol per liter) on three consecutive study visits or if patients reported an adverse event requiring a reduction in the dose. Dose adjustments were permitted at four-week intervals during the efficacy-assessment phase.

Mineral metabolism was managed according to current standards of care with the use of phosphate-binding medications, vitamin D sterols, or both. No restrictions were imposed on the dose or type of phosphate binder. Increases in the dose of vitamin D sterols were permitted if parathyroid hormone levels rose by 50 percent or more from base line, if serum calcium levels were below 8.4 mg per deciliter (2.1 mmol per liter), or if patients had symptoms of hypocalcemia. Doses of vitamin D sterols were reduced if calcium levels were 11.0 mg per deciliter (2.75 mmol per liter) or higher, phosphorus levels were 6.5 mg per deciliter (2.1 mmol per liter) or higher, calcium–phosphorus product values were 70 mg² per square deciliter (5.6 mmol² per square liter) or greater, or parathyroid hormone levels were less than 100 pg per milliliter on three consecutive study visits for patients receiving the lowest daily dose of cinacalcet.

BIOCHEMICAL DETERMINATIONS

Plasma parathyroid hormone levels and serum calcium and phosphorus levels were measured at each study visit before hemodialysis, approximately 24 hours after the preceding dose but before the next daily dose of study medication. Serum levels of bone-specific alkaline phosphatase were measured at base line and at 26 weeks.

Biochemical measurements were made at three regional reference laboratories (Covance Laboratory Services, Indianapolis; Covance Central Laboratory Services, Geneva; and Sonic Clinical Trials, Sydney, Australia). Parathyroid hormone levels were determined in all patients with the use of a conventional immunometric assay (Allegro PTH, Nichols Institute Diagnostics).[25] For patients in the North American trial, measurements were also made with the use of an immunometric assay that detects only the full-length hormone (Bio-Intact PTH, Nichols Institute Diagnostics). Bone-specific alkaline phosphatase levels were determined with the use of the Tandem-R Ostase two-site immunoradiometric assay (Beckman-Coulter).

STUDY END POINTS

The primary study end point was the proportion of randomized patients who had a mean parathyroid hormone level of 250 pg per milliliter (26.5 pmol per liter) or less during the efficacy-assessment phase. Secondary end points included the proportion of patients with a reduction from base line of at least 30 percent in mean parathyroid hormone levels and the percent change in the values for parathyroid hormone, calcium, phosphorus, and the calcium–phosphorus product.

STATISTICAL ANALYSIS

Data from the two identical studies were combined for this analysis. Logistic regression confirmed that the country of enrollment had no effect on the likelihood of achieving the primary end point (P=0.82). Base-line laboratory measurements were obtained and patients' characteristics were noted during the screening period. Mean values for parathyroid hormone, calcium, phosphorus, and the calcium–phosphorus product during the efficacy-assessment phase were calculated with the use of all available results from each patient (up to seven values per patient). A single measurement of bone-specific alkaline phosphatase at week 26 was used to assess changes from base line.

Patients who withdrew from the study during the dose-titration phase were considered not to have met either the primary end point or the secondary end point of a reduction in parathyroid hormone levels of at least 30 percent. For patients who did not have any values for the efficacy-assessment phase, the mean of the last two values obtained during the study was used as the average for weeks 13 through 26 for parathyroid hormone, calcium, phosphorus, and the calcium–phosphorus product. The safety analysis included all patients who received at least one dose of study medication.

Results for all laboratory variables except bone-specific alkaline phosphatase are expressed as means ±SD or means ±SE, as indicated. Because bone-specific alkaline phosphatase values were not normally distributed, the results are expressed as medians and interquartile ranges. For categorical

variables, the Cochran–Mantel–Haenszel test,[26] stratified according to base-line parathyroid hormone levels and calcium–phosphorus product values, was used to examine differences between treatment groups during the efficacy-assessment phase. The generalized Cochran–Mantel–Haenszel test[26] was used for continuous variables. No interim analyses were performed.

Cochran–Mantel–Haenszel tests were used to estimate the relative risk of the primary end point in the cinacalcet group, as compared with the placebo group, according to age, sex, race, duration of dialysis, base-line biochemical variables, presence or absence of diabetes, and use (or nonuse) of vitamin D sterols. Logistic regression was used to identify factors that predicted a reduction in parathyroid hormone levels of at least 30 percent. All P values were two-sided, and those less than 0.05 were considered to indicate statistical significance. Statistical calculations were performed with SAS software (version 8.2, SAS Institute).

RESULTS

The base-line demographic characteristics and biochemical results did not differ significantly between groups (Tables 1 and 2). Nearly all patients were receiving phosphate-binding agents, and there were no significant differences between groups in the type of agents used. Two thirds of patients were receiving vitamin D sterols at enrollment. Although 9 percent of patients (63 of 741) had never been treated with vitamin D sterols, 20 percent (149 of 741) were not being treated because hypercalcemia, hyperphosphatemia, or both precluded their use.

Eighty-two percent of patients who were randomly assigned to cinacalcet (306 of 371) and 88 percent of patients who were randomly assigned to placebo (325 of 370) completed the dose-titration phase; 68 percent and 78 percent, respectively, completed 26 weeks of treatment. Reasons for early discontinuation included adverse events (15 percent of patients receiving cinacalcet and 7 percent of those receiving placebo), withdrawal of consent (4 percent and 3 percent, respectively), kidney transplantation (4 percent in each group), and death (2 percent in each group). None of the deaths were considered to be related to treatment.

Forty-three percent of patients receiving cinacalcet (160 of 371) reached the primary end point — a mean parathyroid hormone level of 250 pg per milliliter or less during the efficacy-assessment phase — as compared with 5 percent of those re-

Table 1. Base-Line Demographic Characteristics.*		
Characteristic	Cinacalcet (N=371)	Placebo (N=370)
Age (yr)	54±14	55±15
Sex (%)		
Male	61	62
Female	39	38
Race (%)		
White	56	61
Black	35	32
Other	9	7
Duration of dialysis (mo)	72±63	72±68
Concomitant diabetes (%)	30	29
Use of vitamin D sterols (%)	66	67
Calcitriol	8	10
Paricalcitol	14	15
Oral calcitriol	24	25
Combined vitamin D therapy	<1	<1
Other	19	16
Use of phosphate binders (%)	92	93
Calcium-containing only	40	44
Sevelamer only	25	24
Combination of calcium-containing and sevelamer	13	11
Other binders	14	14

* Plus–minus values are means ±SD. There were no significant differences between the groups.

ceiving placebo (19 of 370, P<0.001) (Fig. 1A). The proportion of patients who reached the primary end point rose throughout the study in the cinacalcet group but remained unchanged in the placebo group (Fig. 1B). Mean parathyroid hormone levels decreased by 30 percent or more in 64 percent of patients given cinacalcet (239 of 371), as compared with 11 percent of those given placebo (42 of 370, P<0.001) (Fig. 1A). The proportions of patients whose parathyroid hormone levels decreased by at least 30 percent during treatment with cinacalcet did not differ significantly according to base-line values (Fig. 1C).

Parathyroid hormone levels were significantly lower in patients given cinacalcet than in those receiving placebo (P<0.001) (Fig. 2A). During the efficacy-assessment phase, mean parathyroid hormone levels were 43 percent lower than base line in patients receiving cinacalcet but 9 percent higher in those receiving placebo (P<0.001) (Fig. 2B and Table 2). Among the 410 patients who had parathyroid hormone levels measured by two different methods (Table 2), results were highly correlated both before (r=0.923) and during treatment (r=0.962 in the cinacalcet group and r=0.949 in the placebo group). Mean levels of full-length parathyroid hormone were reduced by 38 percent in cina-

Table 2. Biochemical Determinations.*

Variable	Cinacalcet (N=371)	Placebo (N=370)	P Value†
Plasma parathyroid hormone			
Base line (pg/ml)‡	643±18	642±19	0.88
Wk 13–26 (pg/ml)§	374±19¶	693±23	<0.001
Percent change‖	−43±2	9±2	<0.001
Plasma full-length parathyroid hormone**			
Base line (pg/ml)‡	326±14	337±16	0.60
Wk 13–26 (pg/ml)§	200±15¶	396±18††	<0.001
Percent change‖	−38±3	23±4	<0.001
Serum calcium			
Base line (mg/dl)‡	9.9±0.0	9.9±0.0	0.68
Wk 13–26 (mg/dl)§	9.2±0.0¶	9.9±0.0	<0.001
Percent change‖	−6.8±0.4	0.4±0.3	<0.001
Serum phosphorus			
Base line (mg/dl)‡	6.2±0.1	6.2±0.1	0.76
Wk 13–26 (mg/dl)§	5.6±0.1¶	6.0±0.1	<0.001
Percent change‖	−8.4±1.3	0.2±1.3	<0.001
Calcium–phosphorus product			
Base line (mg²/dl²)‡	62±0.8	61±0.8	0.49
Wk 13–26 (mg²/dl²)§	51±0.8¶	60±0.8	<0.001
Percent change‖	−14.6±1.3	0.5±1.3	<0.001
Bone-specific alkaline phosphatase			
Base line (ng/ml)			
Median	23.3	24.2	0.94
Interquartile range	16.5 to 35.3	16.5 to 36.8	
Week 26 (ng/ml)			
Median	15.6	22.6	<0.001
Interquartile range	9.8 to 23.6‡‡	14.3 to 36.4	
Percent change			
Median	−35.1	−4.0	<0.001
Interquartile range	−58.6 to −1.7	−32.1 to 29.6	

* Plus–minus values are means ±SE. To convert values for parathyroid hormone to picomoles per liter, multiply by 0.106. To convert values for calcium to millimoles per liter, multiply by 0.25. To convert values for phosphorus to millimoles per liter, multiply by 0.3229. To convert values for the calcium–phosphorus product to square millimoles per square liter, multiply by 0.0807.

† Comparisons between groups were made with the use of a generalized Cochran–Mantel–Haenszel test, stratified according to base-line values for parathyroid hormone and calcium–phosphorus product.

‡ Base-line values were calculated as the mean of three measurements during the screening period.

§ For each patient, mean values during the efficacy-assessment phase were calculated as the mean of all available values from weeks 13 through 26, with 1 to 7 values per patient (median, 7). For patients who did not have any values for the efficacy-assessment phase, the mean of the last two values obtained during the study was used as the average for weeks 13 through 26.

¶ P<0.001 for the comparison with the base-line value with the use of a one-sample t-test.

‖ For each patient, the percent change from the base-line value was determined with the use of his or her mean value for the efficacy-assessment phase and base-line value.

** Full-length parathyroid hormone values were determined for patients in the North American study only (205 in the cinacalcet group and 205 in the placebo group).

†† P=0.01 for the comparison with the base-line value with the use of a one-sample t-test.

‡‡ P<0.001 for the comparison with the base-line value with the use of a signed-rank test.

calcet-treated patients but increased by 23 percent in those receiving placebo (P<0.001) (Table 2 and Fig. 2C). Median serum values for bone-specific alkaline phosphatase decreased 35 percent in patients given cinacalcet and 4 percent in those given placebo (P<0.001) (Table 2).

In stratified analyses, the likelihood of achieving the primary end point was greater among patients given cinacalcet than among those given placebo and was not influenced by sex, race, age, duration of dialysis, base-line biochemical variables, the presence of diabetes, or the use of vitamin D sterols (Fig. 3). Multivariate logistic-regression analysis showed that the odds of achieving at least a 30 percent reduction in parathyroid hormone were 15 times as great among patients who received cinacalcet as among patients who received placebo (odds ratio, 15.38; 95 percent confidence interval, 10.31 to 22.95) and nearly 1.7 times as great among whites as among blacks (odds ratio, 1.68; 95 percent confidence interval, 1.12 to 2.54). Blacks were 4.1 times (95 percent confidence interval, 2.6 to 6.6) as likely to have a reduction of at least 30 percent in parathyroid hormone levels during cinacalcet therapy as during placebo administration.

Treatment with cinacalcet was associated with moderate reductions in serum calcium and phosphorus levels, averaging 6.8 percent and 8.4 percent, respectively (P<0.001), whereas values were not significantly changed in the placebo group (Table 2). Values for the calcium–phosphorus product decreased by 14.6 percent in the cinacalcet group (P<0.001) but did not change significantly in the placebo group (Fig. 4 and Table 2). Eighty-nine percent of cinacalcet-treated patients who reached the primary end point (143 of 160) had a concurrent reduction in the calcium–phosphorus product.

The average doses of phosphate-binding agents and vitamin D sterols did not differ significantly between groups. The proportion of patients who received vitamin D during the study was 82 percent in the cinacalcet group and 78 percent in the placebo group. Cinacalcet reduced parathyroid hormone levels regardless of whether the vitamin D doses were increased, were decreased, or remained unchanged (reductions of 52 percent, 43 percent, and 44 percent, respectively). The percent reductions in the calcium–phosphorus product were greater in the cinacalcet group than in the placebo group, regardless of whether the vitamin D dose was increased, was decreased, or remained unchanged
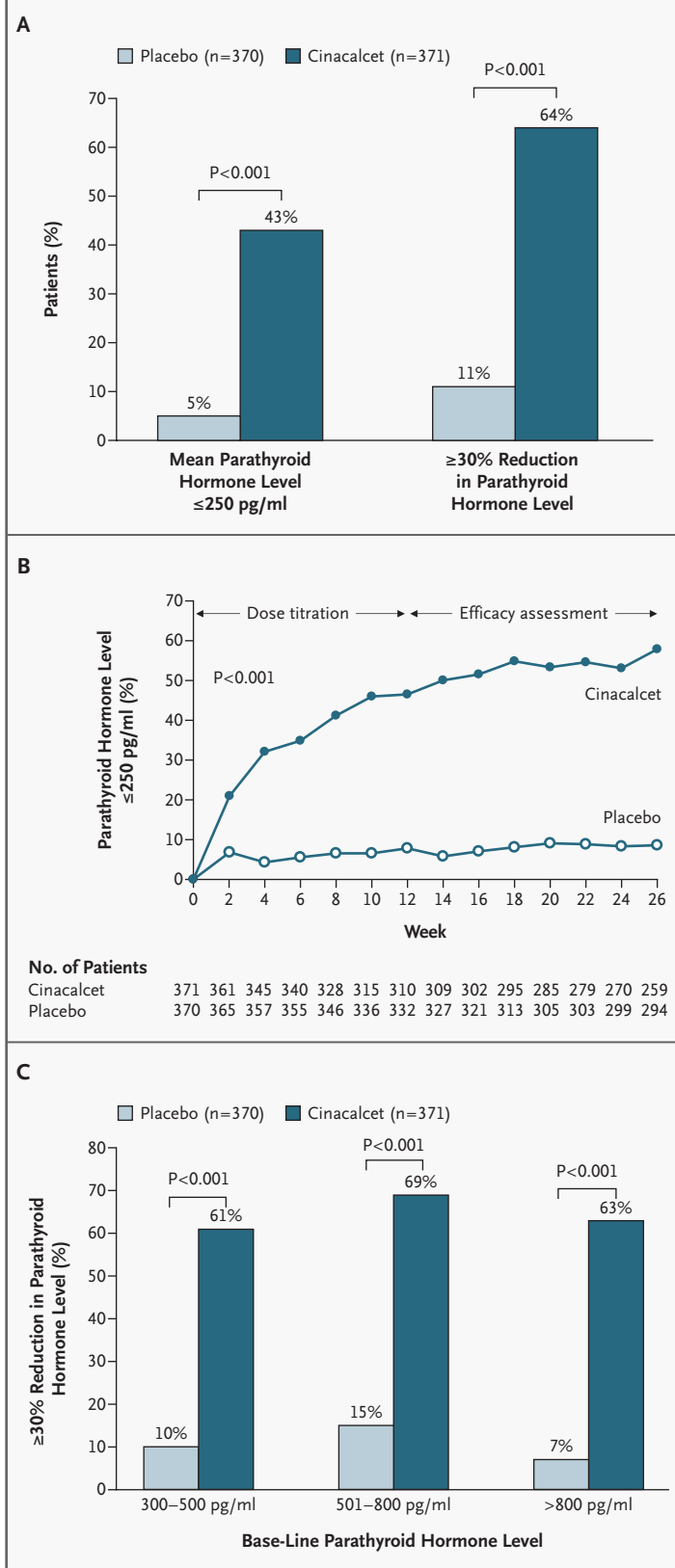
Figure 1. Percentage of Randomized Patients Who Had a Parathyroid Hormone Level of 250 pg per Milliliter or Less or a Reduction in the Parathyroid Hormone Level of 30 Percent or More (Panel A), Percentage of Randomized Patients with a Parathyroid Hormone Level of 250 pg per Milliliter or Less at Each Time Point (Panel B), and Percentage of Patients with a Reduction from Base Line in the Parathyroid Hormone Level of at Least 30 Percent during the Efficacy-Assessment Phase, Stratified According to the Severity of Secondary Hyperparathyroidism (Panel C).
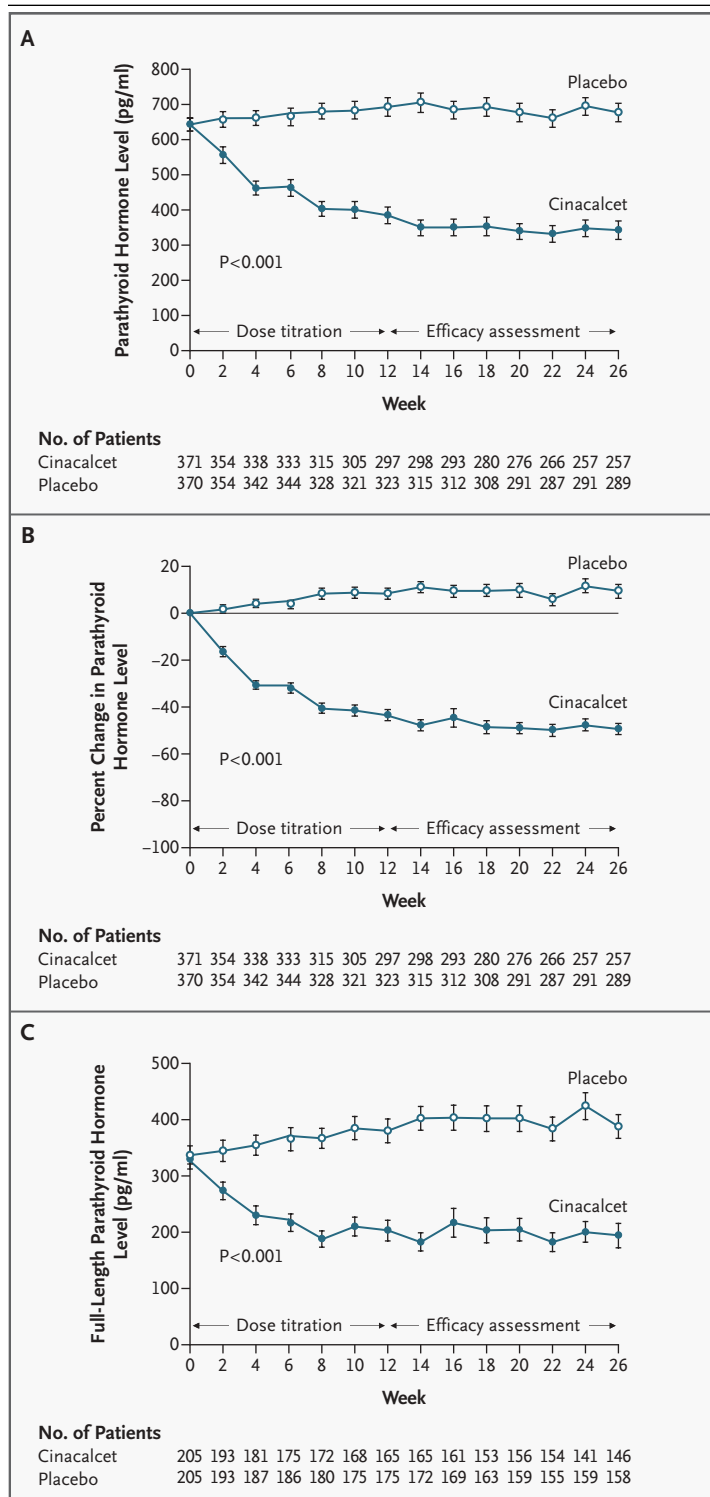
P values were determined by means of the Cochran–Mantel–Haenszel test. Week 0 represents base line. To convert values for parathyroid hormone to picomoles per liter, multiply by 0.106. In panel C, 162 patients in the placebo group had base-line levels of 300 to 500 pg per milliliter, 136 had levels of 501 to 800 pg per milliliter, and 72 had levels greater than 800 pg per milliliter; in the cinacalcet group, the respective numbers were 161, 137, and 73.

(reductions of 13 percent, 19 percent, and 17 percent, respectively).

At least one adverse event was reported by 91 percent of patients in the cinacalcet group (333 of 365) and 94 percent of patients in the placebo group (346 of 369, P=0.21). Nausea occurred more often in those given cinacalcet than in those given placebo (32 percent vs. 19 percent, P<0.001), as did vomiting (30 percent vs. 16 percent, P<0.001), whereas upper respiratory tract infection occurred more often in those given placebo than in those who received cinacalcet (13 percent vs. 7 percent, P=0.007), as did hypotension (12 percent vs. 6 percent, P=0.014). The frequency of nausea was unrelated to the dose of cinacalcet, whereas vomiting occurred more frequently at higher doses. Gastrointestinal effects among patients treated with cinacalcet were generally mild to moderate in severity and of limited duration. Fewer than 5 percent of patients in the cinacalcet group and less than 1 percent of patients in the placebo group were withdrawn from the study because of either nausea or vomiting.

Serum calcium levels were below 7.5 mg per deciliter (1.9 mmol per liter) on at least two consecutive measurements in 5 percent of patients given cinacalcet and in less than 1 percent of patients given placebo (P<0.001). Episodes were transient, rarely associated with symptoms, and managed by modifying doses of calcium-containing phosphate-binding agents, vitamin D sterols, or both. Overall, the extent of the decreases in the serum calcium level did not differ significantly between patients

A

No. of Patients

Cinacalcet	371	354	338	333	315	305	297	298	293	280	276	266	257	257
Placebo	370	354	342	344	328	321	323	315	312	308	291	287	291	289

B

No. of Patients

Cinacalcet	371	354	338	333	315	305	297	298	293	280	276	266	257	257
Placebo	370	354	342	344	328	321	323	315	312	308	291	287	291	289

C

No. of Patients

Cinacalcet	205	193	181	175	172	168	165	165	161	153	156	154	141	146
Placebo	205	193	187	186	180	175	175	172	169	163	159	155	159	158

Figure 2. Mean (±SE) Plasma Parathyroid Hormone Level (Panel A), Percent Change in the Level from Base Line at Each Time Point (Panel B), and Mean (±SE) Plasma Full-Length Parathyroid Hormone Level (Panel C).

P values are for the comparison of mean values in the two groups during the efficacy-assessment phase and were determined by means of the generalized Cochran–Mantel–Haenszel test. Full-length parathyroid hormone levels were measured only in patients in the North American trial. Week 0 represents base line. To convert values for parathyroid hormone to picomoles per liter, multiply by 0.106.
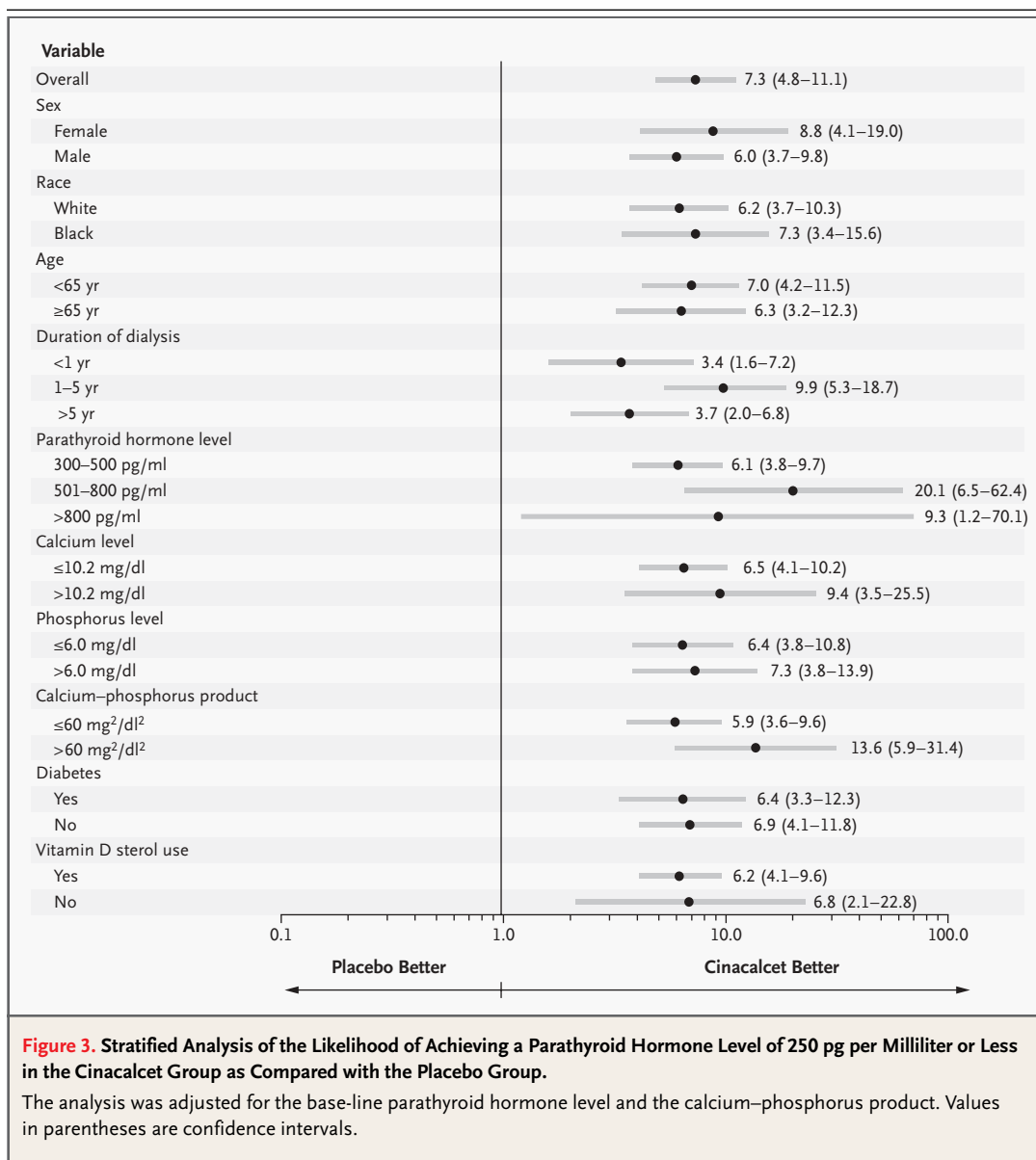
DISCUSSION

Our results indicate that cinacalcet effectively reduces parathyroid hormone levels in patients with secondary hyperparathyroidism who are receiving hemodialysis and ameliorates disturbances in serum calcium and phosphorus that have been associated with adverse clinical outcomes. Our patients had been treated with dialysis for an average of six years and had persistently elevated parathyroid hormone levels despite the use of vitamin D sterols and phosphate binders. Nevertheless, parathyroid hormone levels declined rapidly during treatment with cinacalcet, and this response was sustained for the duration of the study. Forty-three percent of cinacalcet-treated patients had a mean parathyroid hormone level of 250 pg per milliliter or less, a value generally considered to reflect adequate control of secondary hyperparathyroidism.[27] Over 60 percent of those receiving cinacalcet had a decrease of at least 30 percent in plasma parathyroid hormone levels. The reductions in parathyroid hormone in those given cinacalcet were accompanied by decreases in serum calcium, phosphorus, and bone-specific alkaline phosphatase levels and the calcium–phosphorus product.

In previous studies, parathyroid hormone levels decreased rapidly after the administration of cinacalcet, with maximal responses at two to four hours.[21,22] In our study, parathyroid hormone was measured 24 hours after dosing and thus represents a conservative estimate of efficacy.

The use of vitamin D sterols to lower parathyroid hormone levels, particularly in combination with calcium-containing phosphate binders, can cause hypercalcemia and hyperphosphatemia by promoting intestinal absorption of calcium and phosphorus.[12,13,28,29] These disturbances often interrupt treatment, leading to inadequate biochemi-

given cinacalcet alone and those given cinacalcet together with vitamin D sterols. One patient in each group was withdrawn from the study because of hypocalcemia.
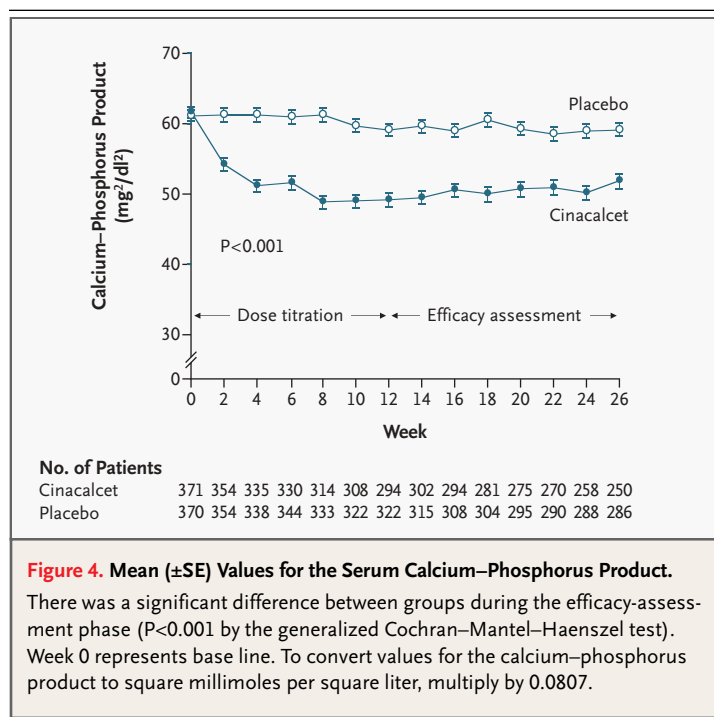
Variable	
Overall	7.3 (4.8–11.1)
Sex	
Female	8.8 (4.1–19.0)
Male	6.0 (3.7–9.8)
Race	
White	6.2 (3.7–10.3)
Black	7.3 (3.4–15.6)
Age	
<65 yr	7.0 (4.2–11.5)
≥65 yr	6.3 (3.2–12.3)
Duration of dialysis	
<1 yr	3.4 (1.6–7.2)
1–5 yr	9.9 (5.3–18.7)
>5 yr	3.7 (2.0–6.8)
Parathyroid hormone level	
300–500 pg/ml	6.1 (3.8–9.7)
501–800 pg/ml	20.1 (6.5–62.4)
>800 pg/ml	9.3 (1.2–70.1)
Calcium level	
≤10.2 mg/dl	6.5 (4.1–10.2)
>10.2 mg/dl	9.4 (3.5–25.5)
Phosphorus level	
≤6.0 mg/dl	6.4 (3.8–10.8)
>6.0 mg/dl	7.3 (3.8–13.9)
Calcium–phosphorus product	
≤60 mg^2/dl^2	5.9 (3.6–9.6)
>60 mg^2/dl^2	13.6 (5.9–31.4)
Diabetes	
Yes	6.4 (3.3–12.3)
No	6.9 (4.1–11.8)
Vitamin D sterol use	
Yes	6.2 (4.1–9.6)
No	6.8 (2.1–22.8)

0.1   1.0   10.0   100.0

Placebo Better ← → Cinacalcet Better

Figure 3. Stratified Analysis of the Likelihood of Achieving a Parathyroid Hormone Level of 250 pg per Milliliter or Less in the Cinacalcet Group as Compared with the Placebo Group.

The analysis was adjusted for the base-line parathyroid hormone level and the calcium–phosphorus product. Values in parentheses are confidence intervals.

cal control and progression of bone disease.[28,30] Such derangements are also associated with an increased risk of death, increased arterial stiffness, and calcification of the coronary arteries, aorta, and cardiac valves.[6-10] Vitamin D sterols had been withheld from 20 percent of our patients at study entry owing to elevated levels of serum phosphorus, calcium, or both. Thus, the fact that cinacalcet lowers parathyroid hormone levels while reducing serum calcium and phosphorus levels represents a potentially important therapeutic development.

Stratified analysis demonstrated the effectiveness of cinacalcet across a broad range of demographic subgroups and base-line characteristics. Decreases in parathyroid hormone levels during cinacalcet therapy did not differ according to the dose of vitamin D sterols. Although definitive studies are needed to assess the role of cinacalcet as primary therapy, a subgroup of patients receiving cinacalcet as primary treatment appeared to have a response. Because their mechanisms of action differ, cinacalcet and vitamin D may have additive effects that act to lower parathyroid hormone levels, but this possibility will require further study.

Treatment with cinacalcet was generally well tolerated. Episodes of nausea and vomiting occurred

Figure 4. Mean (±SE) Values for the Serum Calcium–Phosphorus Product.
There was a significant difference between groups during the efficacy-assessment phase ($P<0.001$ by the generalized Cochran–Mantel–Haenszel test). Week 0 represents base line. To convert values for the calcium–phosphorus product to square millimoles per square liter, multiply by 0.0807.

bone histologic features, bone mass, arterial and soft-tissue calcification, arterial stiffness, and cardiovascular events in these six-month clinical trials. Longer studies will be required to address these skeletal and cardiovascular issues adequately. Nevertheless, the effectiveness of cinacalcet in lowering parathyroid hormone levels and its favorable effect on biochemical variables that have been associated with adverse clinical outcomes represent noteworthy findings.

By directly targeting the molecular mechanism that regulates the secretion of parathyroid hormone, the calcimimetic agent cinacalcet provides a novel therapeutic approach for controlling secondary hyperparathyroidism in patients with chronic kidney disease. The use of treatment strategies that include cinacalcet may make it possible to achieve the more stringent therapeutic guidelines now recommended for managing secondary hyperparathyroidism.[31]

more often in cinacalcet-treated patients but were generally mild to moderate in severity and transient. Serum calcium values below the normal range were rarely associated with symptoms of hypocalcemia and were readily managed by means of adjustments in the doses of calcium-containing phosphate binders, vitamin D sterols, or both.

In contrast to earlier trials,[21-23] our study included a larger number of patients, higher maximal doses of cinacalcet, demographically diverse subjects, and a longer duration of follow-up. Thus, our approach more closely approximates clinical practice, since the management of secondary hyperparathyroidism spans a wide range of disease severity over extended periods of time. Our study nonetheless has certain limitations. Although parathyroid hormone levels decreased and disturbances in calcium and phosphorus metabolism improved, we did not assess the effect of these changes on

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<div align="center">**APPENDIX**</div>

In addition to the authors, the following investigators participated in the Cinacalcet North American Study: S. Acchiardo (Memphis, Tenn.), M. Anger (Thornton, Colo.), J. Anzalone (Wenatchee, Wash.), J. Arruda (Chicago), M. Belledonne (Rockville, Md.), J. Brennan (Fort Worth, Tex.), D. Bushinski (Rochester, N.Y.), E. Brown (Stamford, Conn.), P. Campbell (Edmonton, Canada), R. Clark (Lafayette, La.), L. Cohen (Cincinnati), C. Corpier (Dallas), R.M. Culpepper (Mobile, Ala.), M. Curzi (Walnut Creek, Calif.), J. Diego (Miami), M. Faber (Detroit), G. Fadda (San Diego, Calif.), A. Fine (Winnipeg, Canada), D. Fischer (Cincinnati), L. Garret, Jr. (Raleigh, N.C.), M. Germain (W. Springfield, Mass.), Y. Jean-Claude (New York), M. Kaplan (Nashville), M. Koren (Jacksonville, Fla.), K.S. Kant (Cincinnati), A. Kshirsagar (Chapel Hill, N.C.), M. Joy (Chapel Hill, N.C.), J. Lewis (Birmingham, Ala.), J. Lindberg (New Orleans), B. Ling (Asheville, N.C.), N.D. Makoff (Los Angeles), N.E. Mansour (Memphis, Tenn.), B. Michael (Philadelphia), S. Mischel (Hammond, Ind.), G. Nassar (Houston), N. Pokroy (Las Vegas), R. Provenzano (Detroit), S.N. Rahman (Houston), R. Raja (Philadelphia), S. Rosansky (Columbia, S.C.), C. Shadur (Des Moines, Iowa), D.

Sherrard (Seattle), M. Silver (Cleveland), S. Soroka (Halifax, Canada), D. Spiegel (Denver), S. Sprague (Evanston, Ill.), R. Sreedhara (New Port Richey, Fla.), C. Stehman-Breen (Seattle), J.R. Sterrett (Paterson, N.J.), J. Strom (Boston), K. Tucker (Simi Valley, Calif.), I. Wahba (Portland, Oreg.), D. Wombolt (Norfolk, Va.), S. Zeig (Pembroke Pines, Fla.).

In addition to the authors, the following investigators participated in the Cinacalcet European and Australian Study: A. Albertazzi (Modena, Italy), A. Alvestrand (Huddinge, Sweden), U. Bahner (Würzburg, Germany), J. Barata (Amadora, Portugal), J. Berglund (Danderyd, Sweden), Y. Berland (Marseilles, France), H.S. Brink (Enschede, the Netherlands), G. Cancarini (Brescia, Italy), G. Cannella (Genoa, Italy), F. Caravaca (Badajoz, Spain), J. Chanard (Rheims, France), G. Civati (Milan, Italy), P. Conlon (Dublin, Ireland), H. Deuber (Erlangen, Germany), A. Disney (Woodville, S.A., Australia), A. Ferreira (Vila Franca de Xira, Portugal), R. Fiedler (Halle/Salle, Germany), J. Frazão (Porto, Portugal), H. Geiger (Frankfurt, Germany), P. Gerlag (Veldhoven, the Netherlands), R. Gokal (Manchester, United Kingdom), A. Gomes da Costa (Lisbon, Portugal), M. González (Barcelona, Spain), E. Hagen (Amersfoort, the Netherlands), W. Höerl (Vienna, Austria), H. Holzer (Graz, Austria), B. Hutchison (Nedlands, W.A., Australia), E. Imbasciati (Lodi, Italy), M. Jadoul (Brussels, Belgium), P. Jaeger (Nice, France), D. Johnson (Woolloongabba, Qld., Australia), P. Kerr (Clayton, Vic., Australia), R. Kramar (Wels, Austria), M. Laville (Lyons, France), A. Martín-Malo (Córdoba, Spain), G. Mayer (Innsbruck, Austria), G. Mellotte (Dublin, Ireland), U. Neyer (Feldkirch, Austria), K. Ølgaard (Copenhagen, Denmark), P. Ponce (Corroios, Portugal), H. Reichel (Villingen-Schwenningen, Germany), E. Ritz (Heidelberg, Germany), J. Rodicio (Madrid), H. Saha (Tampere, Finland), G. Stein (Jena, Germany), H.K. Stummvoll (Linz, Austria), C. Tielemans (Brussels, Belgium), V. Torregrosa (Barcelona, Spain), P. Ureña-Torres (Aubervilliers, France), M. Van den Dorpel (Rotterdam, the Netherlands), Y. Vanrenterghem (Leuven, Belgium), R. Walker (Parkville, Vic., Australia), B. Wikström (Uppsala, Sweden), M. Wilkie (Sheffield, United Kingdom).

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