

Oral Paricalcitol for the Treatment of Secondary Hyperparathyroidism in Patients on Hemodialysis or Peritoneal Dialysis

Edward A. Ross^a Jin Tian^b Hanna Abboud^c Richard Hippensteel^b
Joel Z. Melnick^b Rajendra S. Pradhan^b Laura A. Williams^b L. Lee Hamm^d
Stuart M. Sprague^e

^aDivision of Nephrology, Hypertension, and Transplantation, University of Florida, Gainesville, Fla.,

^bAbbott Laboratories, Abbott Park, Ill., ^cDivision of Nephrology, University of Texas Health Science Center, San Antonio, Tex., ^dSection of Nephrology and Hypertension, Tulane University School of Medicine, New Orleans, La., and ^eDivision of Nephrology and Hypertension, Evanston Northwestern Healthcare Northwestern University Feinberg School of Medicine, Evanston, Ill., USA

Key Words

Paricalcitol · Secondary hyperparathyroidism · Chronic renal failure · Chronic renal insufficiency

Abstract

Background/Aims: Secondary hyperparathyroidism is a common complication of chronic kidney disease, resulting from inactivation of vitamin D receptor signaling and phosphate retention. Selective activation of vitamin D receptors with intravenous paricalcitol significantly reduced parathyroid hormone (PTH) levels with no significant hypercalcemia or hyperphosphatemia in predialysis and hemodialysis (HD) patients. This study investigates the effects of oral paricalcitol to reduce PTH in patients receiving chronic HD and peritoneal dialysis (PD). **Methods:** Eighty-eight patients were randomized in double-blind fashion to receive paricalcitol or placebo for 12 weeks. The dose of the study drug was adjusted weekly using the previous week's intact PTH (iPTH)

level as well as calcium and Ca × P product levels. The primary end points were efficacy (two consecutive iPTH decreases of ≥30%) and safety (two consecutive calcium measurements >11.0 mg/dl). Markers of biochemical bone activity were followed. **Results:** Demographic characteristics were similar between treatment groups. The mean paricalcitol doses (three times a week) over the entire treatment period for subjects with baseline iPTH ≤500 pg/ml and iPTH >500 pg/ml were 3.9 and 7.6 μg, respectively. A statistically significant decrease in iPTH was seen after week 1, with a mean 30% reduction occurring by week 3. A significantly greater proportion of both HD and PD paricalcitol subjects [83% (33/40) and 100% (18/18), respectively] achieved two consecutive ≥30% decreases in iPTH. The treatment groups were not statistically different in regard to the hypercalcemia safety end point. Phosphate binder use and mean serum phosphorus levels were not different between the treatment groups. The markers of bone activity improved in the treated subjects and worsened in those on placebo. **Conclusion:** Paricalcitol provides a rapid and sustained reduction of PTH in both HD and PD patients with minimal effect on serum calcium and phosphorus and no significant difference in adverse events as compared with placebo.

Conflicts of Interest: E.A.R., L.L.H., and S.M.S. have received speaker's honoraria from Abbott Laboratories; J.T., R.H., J.Z.M., R.S.P., and L.A.W. are employees of Abbott Laboratories.

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Edward A. Ross, MD
Division of Nephrology, Hypertension, and Transplantation
University of Florida, Box 100224
Gainesville, FL 32610-0224 (USA)
Tel. +1 352 392 4007, Fax +1 352 392 3581, E-Mail Rossea@medicine.ufl.edu

Introduction

Secondary hyperparathyroidism (SHPT), characterized by elevated parathyroid hormone (PTH) levels and parathyroid gland hyperplasia, is a common complication of chronic kidney disease (CKD). The pathogenesis is mainly attributed to diminished calcitriol synthesis and phosphate retention, both of which are the result of decreased functional kidney mass. The therapeutic goal is to prevent or to delay the development of potentially irreversible nodular parathyroid hyperplasia and bone mineral disease, thereby preserving normal bone health and decreasing long-term morbidity and mortality. Treatment of SHPT in dialysis patients includes phosphate control (via dietary restriction and the use of phosphate binders) and active vitamin D and calcimimetic therapy [1–4].

Phosphorus control via dietary restriction and the use of phosphate binders is widely accepted in nephrology practice. However, studies performed in dialysis patients have failed to demonstrate conclusively a reduction in morbidity or mortality through control of phosphorus by these means. Further, most data indicate that fewer than 30% of the dialysis patients are able to maintain phosphorus in the suggested target range [5]. Calcimimetic therapy (e.g., cinacalcet) can lower the PTH levels by targeting the molecular mechanism that regulates the secretion of PTH [6]; however, calcimimetics do not correct inactivation of the vitamin D receptor (VDR) transcription pathways, but instead may exacerbate it [7]. Calcitriol [1,25-(OH)₂D₃], an endogenous VDR activator (VDRA), decreases synthesis and secretion of PTH by a direct inhibitory mechanism acting on parathyroid gland cells and by increasing the sensitivity of the parathyroid gland to calcium; however, calcitriol treatment also significantly increases intestinal absorption of calcium and phosphorus, causing hypercalcemia and/or hyperphosphatemia via VDRA-enhanced intestinal calcium absorption [8] or bone resorption [9].

Intravenous paricalcitol (Zemlar[®] Injection), a selective VDRA, has been extensively used for the prevention and treatment of SHPT associated with CKD stage 5 in patients receiving chronic hemodialysis (HD) [10]. Clinical studies in HD subjects have shown that intravenous paricalcitol significantly reduced PTH levels with no significant difference between paricalcitol and placebo in the incidence of hypercalcemia [11]. There have been no double-blind, placebo-controlled, randomized studies examining the effect of any vitamin D therapy in treating peritoneal dialysis (PD) patients with SHPT. An oral for-

mulation of paricalcitol (Zemlar[®] Capsules) is approved and is marketed in the USA and Spain for prevention and treatment of SHPT in patients with CKD stages 3–4 [12]. Oral paricalcitol was developed to provide a convenient, alternative therapy, particularly for PD patients, in whom regular intravenous administration of paricalcitol is not practical. This report describes the results from a prospective, placebo-controlled, 12-week, multicenter study that evaluates safety and efficacy of oral paricalcitol in CKD stage 5 patients with SHPT receiving either HD or PD. A placebo arm was chosen to provide the best measure of a treatment effect of, as well as the maximum ability to distinguish adverse effects caused by paricalcitol.

Patients and Methods

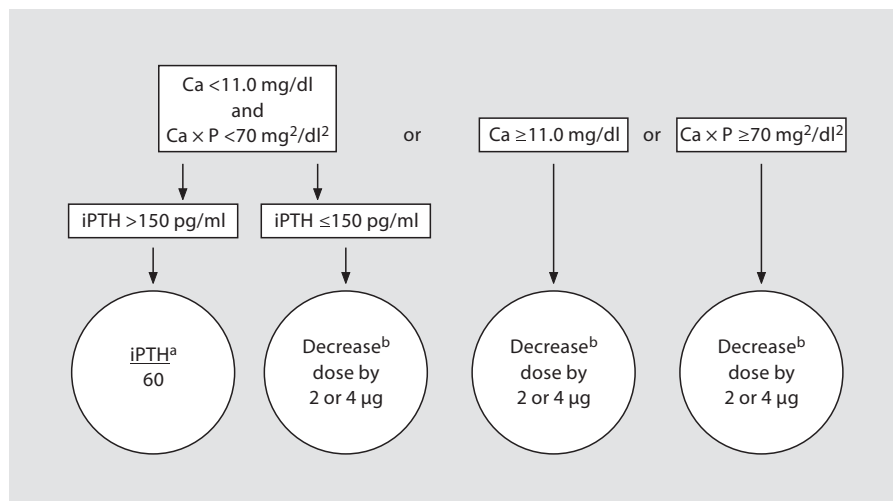
This study was conducted using a randomized, double-blind design in accordance with International Committee on Harmonization, Good Clinical Practices, and all applicable local regulations. The randomization schedule was computer generated by Abbott Laboratories (Abbott Park, Ill., USA) for each site before the study began.

Study Design and Eligibility Criteria

Eligible subjects were ≥ 18 years of age and on HD three times per week or daily PD (continuous cycling PD and/or continuous ambulatory PD) for at least 2 months prior to the screening phase. Exclusion criteria were acute renal failure during the 3 months prior to the screening phase, clinically significant chronic gastrointestinal or liver disease, malignancy, human immunodeficiency virus infection, active granulomatous disease (e.g., tuberculosis, sarcoidosis), current pregnancy or breast-feeding at the time of screening, a history of hypersensitivity to vitamin D, or a partial parathyroidectomy within 1 year of the screening phase. Subjects also were excluded, if they received medications that potentially could affect the calcium or bone metabolism (e.g., calcitonin, bisphosphonates, cinacalcet, maintenance intravenous or oral glucocorticoids), or if there was a history of drug or alcohol abuse within 6 months prior to the screening phase. Subjects with evidence of poor compliance with diet, medication, or HD/PD that might interfere with adherence to the protocol were excluded at the discretion of the investigator. Subjects who had participated in any investigational drug or device study within 4 weeks prior to the treatment phase also were excluded. Subjects who had been taking a phosphate binder had to have been on a stable regimen for ≥ 4 weeks before the screening visit. Aluminum-containing phosphate binders were not allowed to be used for >3 weeks during the study; subjects on aluminum-containing phosphate binders >3 weeks within 3 months of the screening phase also were excluded. If PD subjects had active peritonitis within 1 month prior to the screening visit or >1 episode of peritonitis within 4 months of the screening visit, they were excluded.

There were three phases to this study: screening, pretreatment, and treatment. Subjects were screened for a serum calcium level ≤ 10.5 mg/dl and a calcium-phosphorus product (Ca \times P) ≤ 65 mg²/dl² and could be rescreened once, if needed. The sub-

Fig. 1. Schematic of three times per week paricalcitol dose adjustments for treatment weeks 2–12. ^a Rounded down to the nearest even number. ^b PD patients came to the clinics once a week during this study, so the site made every effort to contact patients within 48 h, instructing the subject to reduce the dose by 2 or 4 μg at their next dosing day and then maintain that dose for the remainder of the week and for an additional 2 weeks; HD patients' doses were adjusted by 2 or 4 μg at the first HD session of the next treatment week, and the dose was maintained for 2 weeks. If a subject was dose reduced to 0 μg , study drug could be restarted at 2 μg after serum Ca <11.0 mg/dl, Ca \times P <70 mg^2/dl^2 , and iPTH >150 pg/ml.



jects entered the pretreatment phase within 14 days of screening procedures. Pretreatment lasted for 4–8 weeks, during which time phosphate binder therapy, if needed, was stabilized. Dialysate calcium concentrations were to be maintained at 2.5 mEq/l throughout the study. During pretreatment, subjects who were receiving vitamin D therapy prior to enrollment completed 4–8 weeks of washout before stabilization of any phosphate binder therapy. A chemistry evaluation was drawn weekly, preferably on the same day of the week, beginning with pretreatment week 1 for serum calcium, phosphorus, intact PTH (iPTH), and albumin. In HD subjects, evaluations were drawn prior to dialysis at the second HD session of the week. Serum phosphorus levels were kept at a level deemed appropriate by the investigator.

For entry into the treatment phase, the subjects were required to have an iPTH level ≥ 300 pg/ml, a serum calcium level of 8.0–10.5 mg/dl, and Ca \times P product level ≤ 65 mg^2/dl^2 . The treatment phase lasted for 12 weeks. A complete chemistry and hematology evaluation was drawn at treatment week 1 prior to first dose of the study drug and at the final visit; bone-specific alkaline phosphatase (BSAP), osteocalcin, collagen C-telopeptides (CTX), and tartrate-resistant acid phosphatase isoform 5b (TRAP-5b) were biochemical bone markers measured prior to study drug and at the final visit. Weekly visits during the treatment phase consisted of a chemistry evaluation and dispensing of study drug, along with new dosing instructions based on the previous week's chemistry evaluation. HD subjects received their study drug three times per week after HD, no more frequently than every other day. PD subjects self-administered their study drug three times per week on Monday, Wednesday, and Friday, preferably at night before going to sleep, and were seen weekly during the treatment phase for chemistry evaluation and new dosing instruction, if any.

Dosing of Oral Paricalcitol

The results from previous [unpublished] clinical studies were used to develop a pharmacokinetic/pharmacodynamic model that described relationships between paricalcitol systemic drug exposure, serum iPTH, calcium, and phosphorus. Using this model, a Monte Carlo clinical trial simulation experiment was conducted to simulate different dosing strategies (initial dose and

dose titration) which were evaluated for efficacy and safety outcomes. Simulations for each dosing regimen were performed in 20 replicates with 100 subjects in each replicate. The results of these modeling and trial simulation experiments were then used to determine the protocol for this study. Initial and subsequent study drug doses were calculated using the previous week's iPTH/60 (rounded down to the nearest even number) as well as calcium and Ca \times P product (fig. 1) and the investigator's judgment. The simulations predicted that 81 and 1.5% of the paricalcitol subjects, respectively, would achieve the efficacy end point (two consecutive $\geq 30\%$ reductions in iPTH from baseline) and the safety end point (two consecutive elevations in serum calcium >11.0 mg/dl).

Objectives

The primary efficacy end point was the achievement of two consecutive $\geq 30\%$ decreases in iPTH from baseline. The secondary efficacy analyses were the absolute and percent changes from baseline in iPTH and markers of bone turnover. The primary safety analysis explored the development of clinically meaningful hypercalcemia (≥ 2 consecutive calcium measurements >11.0 mg/dl following the first dose of study drug). The secondary safety analyses were an assessment of adverse events, as well as the change from baseline in hematology and chemistry laboratory variables, including serum total calcium, serum phosphorus, albumin, and Ca \times P product.

Laboratory Procedures

Covance Central Laboratory Service (Indianapolis, Ind., USA) served as a central laboratory that performed testing for all sites. The serum iPTH levels were measured using the Nichols Advantage[®] iPTH assay (Nichols Institute Diagnostics, San Clemente, Calif., USA; reference range 10–65 pg/ml). The serum calcium levels were corrected for serum albumin (if <4.0 g/dl).

Statistics

The primary efficacy analysis compared the proportion of subjects in the paricalcitol and placebo groups achieving two consecutive decreases of $\geq 30\%$ from baseline in iPTH using Fisher's

Table 1. Demographics (all treated subjects)

Characteristic	Paricalcitol (n = 61)	Placebo (n = 27)
Sex		
Female	24 (39)	5 (19)
Male	37 (61)	22 (81)
Race		
Asian	3 (5)	0 (0)
Black	23 (38)	17 (63)
Other	1 (2)	0 (0)
White	34 (56)	10 (37)
Tobacco use		
Nonsmoker	27 (44)	11 (41)
Smoker (includes ex-smokers)	34 (56)	16 (59)
Alcohol use		
Nondrinker	37 (61)	12 (44)
Drinker (includes ex-drinkers)	24 (39)	15 (56)
Age group		
<65 years	45 (74)	18 (67)
≥65 years	16 (26)	9 (33)
<75 years	57 (93)	26 (96)
≥75 years	4 (7)	1 (4)
Age, years		
Mean ± SE	57.0 ± 1.62	56.4 ± 2.48
Median	57.0	58.0
Range	29–92	31–78
Time since 1st dialysis, years		
Mean ± SE	3.19 ± 0.385	3.41 ± 0.628
Median	2.20	2.20
Range	0.3–13.6	0.3–10.5
Time since 1st HD, years	(n = 42)	(n = 20)
Mean ± SE	3.16 ± 0.426	3.75 ± 0.741
Median	2.25	2.70
Range	0.3–13.5	0.6–10.5
Time since 1st PD, years	(n = 19)	(n = 7)
Mean ± SE	3.27 ± 0.821	2.46 ± 1.190
Median	2.20	1.00
Range	0.4–13.6	0.3–9.0

No statistically significant differences were detected between treatment groups for any of the baseline demographic data.

Figures in parentheses are percentages.

exact test. Baseline laboratory values were defined as the last value obtained in the pretreatment phase. A sample size of 78 subjects was expected to provide a 2:1 ratio of 46 paricalcitol and 23 placebo subjects providing 97% power at a 0.05 significance level to detect a difference in the response rates between the treatment groups, assuming a rate of 12% for placebo and 60% for paricalcitol. Assessments of time to response (two consecutive ≥30% decreases in iPTH from baseline) and duration of response were performed using Kaplan-Meier analyses.

The mean changes from baseline to the final visit for biochemical bone markers were compared between paricalcitol and pla-

cebo groups using a one-way ANOVA with treatment as the factor. Baseline and final visit BSAP measurements were categorized as low, normal, or high (based on normal ranges provided by Covance). The number of subjects that shifted from one category at baseline to a different category at the final visit, or remained in the same category for both visits, was summarized for each treatment group.

The percentage of subjects with ≥2 consecutive calcium measurements >11.0 mg/dl following the first dose of study drug was compared between the paricalcitol and placebo groups using Fisher's exact test. For the last on-treatment visit and longitudinal assessments, the mean change from baseline in iPTH, calcium, phosphorus, and Ca × P product was compared between paricalcitol and placebo groups using a one-way ANOVA with treatment as the factor. Treatment-emergent adverse events were summarized by body system and Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) according to the COSTART V adverse-event-coding dictionary. Comparisons of the percentage of subjects experiencing an adverse event between paricalcitol and placebo groups were performed using Fisher's exact test.

All statistical tests were two-tailed, and p values ≤0.05 were considered statistically significant. Data were summarized and analyzed using SAS/STAT® version 8.2 (SAS Institute, Cary, N.C., USA).

Results

Between October 2004 and September 2005, a total of 88 subjects (62 HD and 26 PD) were randomized to paricalcitol or placebo in a 2:1 ratio (61 paricalcitol and 27 placebo) at 15 investigative sites. Eighteen percent (11/61) of the paricalcitol-treated subjects and 22% (6/27) of the placebo subjects were terminated prematurely from the study. The primary efficacy end point was evaluated in subjects who had a baseline iPTH and at least two iPTH measurements on treatment [58 (40 HD and 18 PD) paricalcitol-treated and 24 (19 HD and 5 PD) placebo subjects]. The demographic characteristics were similar between the treatment groups (table 1). No statistically significant differences were found between the treatment groups in other pretreatment body measures, including height, weight, temperature, systolic and diastolic blood pressures, and resting heart rate (data not shown). At baseline, 53 (87%) paricalcitol-treated subjects and 26 (96%) placebo-treated subjects were receiving phosphate binders. Less than half of the subjects in both treatment groups [38% (23/61) paricalcitol, 44% (12/27) placebo] received Ca-based binders. At the final visit, phosphate binder usage was unchanged from baseline for the majority of subjects in both treatment groups (paricalcitol 87%, placebo 77%), regardless of binder type.

Concerning the primary study end point, a significantly greater proportion of subjects in the paricalcitol

Table 2. Change from baseline to last on-treatment visit in iPTH (all treated patients)

	All patients		HD		PD	
	paricalcitol (n = 60)	placebo (n = 26)	paricalcitol (n = 42)	placebo (n = 20)	paricalcitol (n = 18)	placebo (n = 6)
iPTH, pg/ml						
Mean baseline	721.4	626.8	657.7	567.8	870.1	823.3
Mean last on-treatment value	474.3	754.3	486.4	701.2	445.9	931.3
Mean Δ from baseline (SE)	-247.2* (37.56)	127.5 (57.06)	-171.3* (38.92)	133.4 (56.40)	-424.2* (79.21)	108.0 (137.19)
Mean % Δ from baseline (SE) ^a	-27.8* (5.53)	20.4 (8.40)	-21.0* (7.09)	22.4 (10.27)	-43.9* (7.17)	14.1 (12.42)

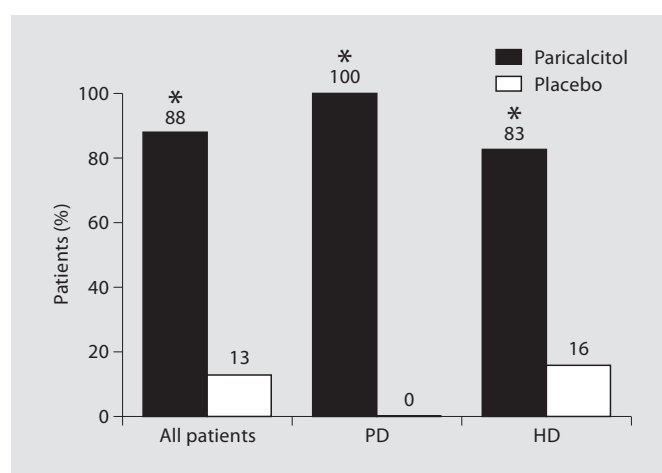
SE = Standard error.

^a Represents the mean of individual subject % Δ value from baseline.* $p < 0.001$ between paricalcitol and placebo groups using ANOVA.

group achieved two consecutive $\geq 30\%$ decreases from baseline in iPTH as compared with subjects in the placebo group (fig. 2). Regardless of dialysis modality, a significantly greater percentage of paricalcitol-treated subjects achieved the efficacy end point (HD 83 vs. 16%, PD 100 vs. 0%). Robustness of the paricalcitol effect was observed in that a significantly greater percentage of subjects in the paricalcitol group (67%) achieved four consecutive $\geq 30\%$ decreases from baseline in iPTH as compared with subjects in the placebo group (0%). Similarly, significant mean percent reductions from baseline to last on-treatment visit (table 2) in iPTH were experienced by paricalcitol-treated subjects (-27.8%) as compared with an increase in the placebo group (20.4%). A post hoc analysis found that 72% of the subjects achieved an iPTH < 300 pg/ml, though this iPTH goal was not part of the study design.

Statistically significant mean reductions from baseline in iPTH were observed at each visit of the treatment phase for the paricalcitol-treated subjects (range from -133.8 to -325.0 pg/ml) as compared with mean increases from baseline in iPTH (range from 4.6 to 138.8 pg/ml) observed for the placebo-treated subjects (fig. 3a). A statistically significant difference also was observed between the paricalcitol and placebo groups in mean percent change in iPTH from baseline to each scheduled visit of the treatment phase after week 1, with a mean 30% reduction occurring by week 3.

Kaplan-Meier analyses were performed to assess time to and duration of iPTH response for paricalcitol-treated subjects. The estimated probability of achieving the first of two consecutive 30% decreases from baseline iPTH was found to be 59, 69, and 86% by week 3 (day 21), week 6 (day 42), and week 9 (day 63), respectively (fig. 4a). The estimated probability of maintaining a 30% or more de-

**Fig. 2.** Percentage of patients who achieved two consecutive $\geq 30\%$ decreases in iPTH from baseline by group. * $p < 0.001$.

crease in iPTH for at least 1 and 2 months was found to be 78 and 59%, respectively (fig. 4b).

The differences between the treatment groups in mean change from baseline to the final visit in all of the biochemical bone activity markers (BSAP, osteocalcin, CTx, and TRAP-5b) were statistically significant (table 3). The paricalcitol group experienced mean decreases, while the placebo group experienced mean increases in all of the biochemical bone activity markers. Shift analyses revealed that more paricalcitol-treated subjects (45%, 13/29) experienced normalization of their high baseline BSAP as compared with the placebo subjects (11%, 1/9) and that no subjects in either treatment group experienced low serum BSAP levels (table 4).

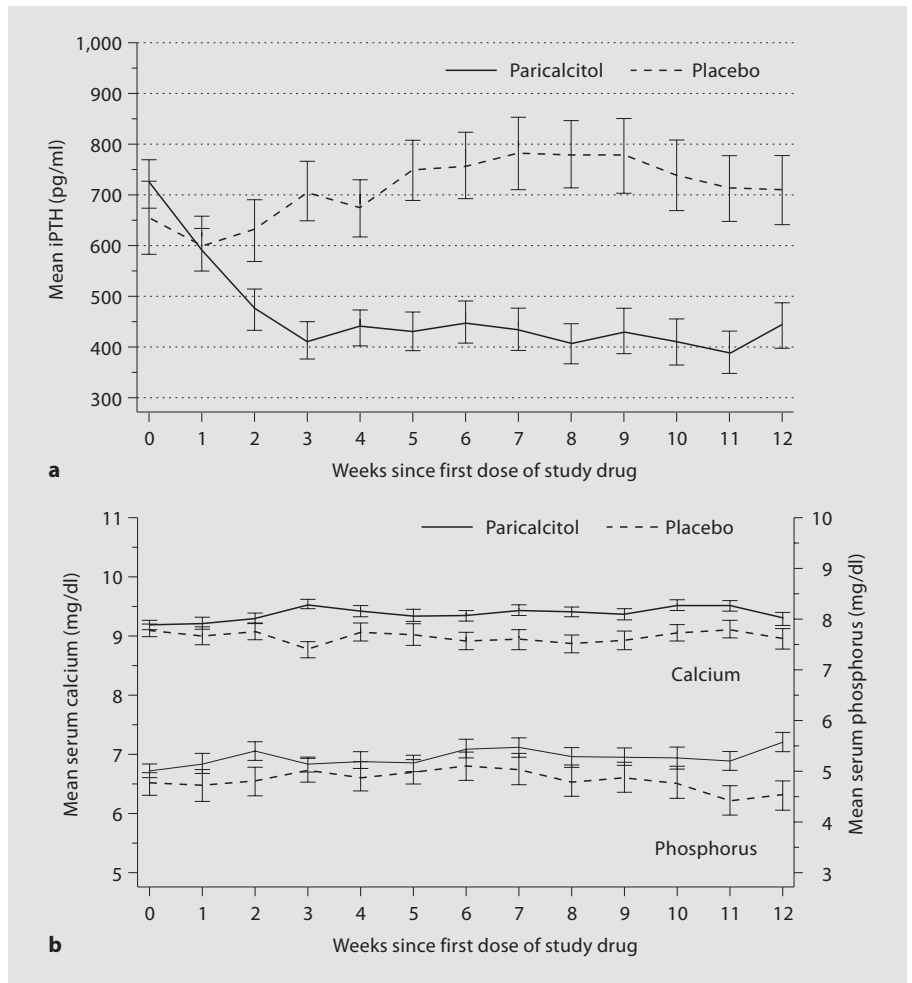


Fig. 3. a Observed mean values of iPTH over time during the treatment phase. Values were statistically significant at each time point. **b** Observed mean values of serum calcium and phosphorus during treatment phase. Calcium values were statistically significant at each time point, except for weeks 1, 2, and 5. No difference was detected in serum phosphorus values during the treatment phase.

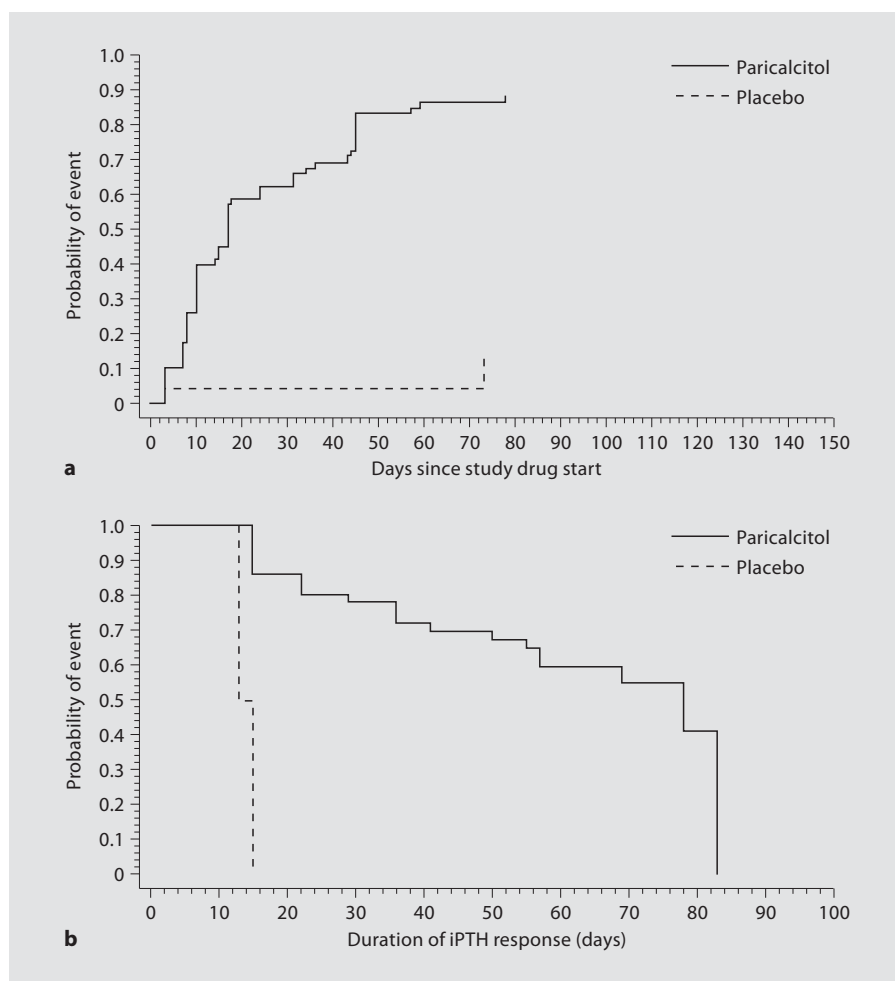
No statistically significant difference was observed between the treatment groups in the proportion of subjects who developed clinically meaningful hypercalcemia (≥ 2 consecutive calcium measurements >11.0 mg/dl; 1/61 or 2% paricalcitol subjects and 0/26 or 0% placebo subjects). The mean serum calcium levels remained in the normal range throughout the treatment phase for both treatment groups and increased minimally during treatment in the paricalcitol group, with a minimal decrease in the placebo group, reaching statistical significance at various weeks (fig. 3b). A statistically significant difference was observed between treatment groups for the mean change in serum calcium at the last on-treatment visit. A mean decrease (-0.22 mg/dl) was observed in the placebo group, and a mean increase (0.17 mg/dl) was observed in the paricalcitol group.

No statistically significant differences were observed between the treatment groups for mean changes from

baseline to any of the scheduled visits of the treatment phase or last on-treatment visit for phosphorus. This is clinically meaningful, given the association between increases in serum phosphorus and mortality. The mean $\text{Ca} \times \text{P}$ product levels remained <55 mg^2/dl^2 throughout the treatment phase. Primarily driven by the small decreases in serum calcium in the placebo group and by the small increases in the paricalcitol group, a significant difference was observed between the treatment groups for mean changes from baseline to the last on-treatment visit for $\text{Ca} \times \text{P}$ product (from 45.38 to 52.94 mg^2/dl^2 and from 42.96 to 44.83 mg^2/dl^2 for the paricalcitol and placebo groups, respectively; $p = 0.029$). Evaluations of adverse clinical events and other laboratory parameters revealed no pattern of changes as a result of paricalcitol treatment.

The mean weekly dose was highest (33.6 μg) at week 1 and decreased over time to the lowest value (13.8 μg) at week 12. These mean doses were consistent with the study

Fig. 4. a Kaplan-Meier curve of time to response in iPTH (1st of 2 consecutive $\geq 30\%$ reductions from baseline). **b** Kaplan-Meier curve of duration of iPTH response from 1st of 2 consecutive $\geq 30\%$ reductions from baseline.



protocol which used the formula $iPTH/60$ and rounding down to the nearest even microgram. We examined the individual doses and found that the majority of doses (530/713 or 74%) received by paricalcitol subjects were based on the formula of $iPTH/60$. Of the remaining 183 doses, 49% (90/183) were lower and 27% (49/183) were higher than a ratio of $iPTH/60$, and 24% (44/183) were withheld. To calculate a monthly ratio of $iPTH$ to study drug dose, the average monthly dose of study drug was calculated and was compared to the $iPTH$ at the start of the month. Paricalcitol-treated subjects received a mean ratio of $iPTH/90$ for month 1, of $iPTH/82$ for month 2, and of $iPTH/105$ for month 3. The mean monthly ratios for the placebo group were $iPTH/67$, $iPTH/62$, and $iPTH/77$, consecutively. The mean dose over the entire treatment period was $3.9 \mu\text{g}$ three times per week for subjects with baseline $iPTH \leq 500 \text{ pg/ml}$ and $7.6 \mu\text{g}$ three times per week for subjects with baseline $iPTH > 500 \text{ pg/ml}$.

Discussion

The use of compounds that activate VDR pathways has been the mainstay for treating SHPT and is essential for achieving normal bones and parathyroid glands [13], prevents bone mineral loss and also associates with a survival benefit [14]. However, nonselective activation of VDR pathways can cause hypercalcemia and hyperphosphatemia by enhanced intestinal absorption of calcium and phosphorus [15] which is associated with increased mortality in dialysis patients [16]. Ideally, management of SHPT in dialysis patients should control PTH levels, while maintaining serum calcium and phosphorus within the normal range, and correct active vitamin D deficiency and inactivation of VDR pathway transcription.

As a selective activator of VDR pathways, previous studies have shown that oral paricalcitol in predialysis patients and intravenous paricalcitol in HD patients pro-

Table 3. Change in biochemical bone activity markers from baseline to final visit (all treated patients)

Variable	Paricalcitol	Placebo	p
Serum BSAP, $\mu\text{g/l}$			
Number of patients	55	23	
Baseline value	34.9	30.0	
Change from baseline to final visit	-10.52 (1.875)	9.91 (2.899)	<0.001
Serum osteocalcin, ng/ml			
Number of patients	54	24	
Baseline value	273	247	
Change from baseline to final visit	-31.2 (17.77)	95.0 (26.7)	<0.001
CTx, pg/ml			
Number of patients	33	18	
Baseline value	3,002	2,834	
Change from baseline to final visit	-694.6 (153)	576 (207)	<0.001
TRAP-5b, U/l			
Number of patients	48	18	
Baseline value	5.84	5.74	
Change from baseline to final visit	-1.28 (0.31)	0.39 (0.51)	0.006

Values are expressed as mean (standard error).

Table 4. Categorical shifts in BSAP from baseline to final visit (n, % in category at baseline excluding missing values)

	Final visit							
	paricalcitol-treated group (n = 61)				placebo-treated group (n = 27)			
	low	normal	high	missing	low	normal	high	missing
Baseline								
Low	0	0	0	0	0	0	0	0
Normal ^a	0	25 (96)	1 (4)	1	0	11 (79)	3 (21)	2
High	0	13 (45)	16 (55)	1	0	1 (11)	8 (89)	1
Missing	0	1	0	3	0	0	0	1

^a Reference ranges adjusted for age and gender.

vide a rapid and sustained reduction of PTH with minimal effect on serum calcium and phosphorus. The results of our study demonstrate that in dialysis subjects receiving oral paricalcitol the mean reduction in PTH was significantly greater as compared with placebo as early as week 2 and was 30% less than baseline beginning at week 3. Of the subjects receiving paricalcitol, 88% achieved the protocol-defined efficacy end point of two consecutive $\geq 30\%$ decreases in iPTH. Importantly 72% of the subjects achieved an iPTH < 300 pg/ml, even though this goal was not part of the study design.

The reductions in PTH with oral paricalcitol are accompanied by changes in biomarkers for bone turnover, suggesting normalization of a high bone turnover, but without significant difference for the incidence of hypercalcemia, hyperphosphatemia, or elevated $\text{Ca} \times \text{P}$ product. For subjects with elevated BSAP at baseline, therapy with paricalcitol normalized levels in 45% of them as compared with 11% of those receiving placebo. None of the paricalcitol-treated subjects experienced low BSAP levels, suggesting that none of the subjects developed adynamic bone disease and which is consistent with paricalcitol's in vitro anabolic effects on bone [17, 18]. Strati-

fied analyses demonstrate that paricalcitol is equally effective across all studied subpopulations, including HD and PD subjects. Treatment with oral paricalcitol is well tolerated. There are no statistically significant or clinically important differences between paricalcitol and placebo in the types and incidences of adverse events.

Paricalcitol's selective activation of VDR pathways in the parathyroid gland or in other tissues over that in the intestine and bone can minimize hypercalcemia and hyperphosphatemia while significantly reducing PTH in dialysis patients with SHPT. The difference between the treatment groups in mean change from baseline to the last on-treatment visit in calcium, while statistically significant, was not clinically meaningful. A small mean increase in serum calcium was observed in the paricalcitol group, while a small mean decrease was observed in the placebo group. The small mean decrease in calcium observed in the placebo group is consistent with the pathogenesis of SHPT and VDR inactivation and reflects the disease state in this population. Tissue and gene selectivity of paricalcitol thus allows for a greater therapeutic index for PTH reduction and may explain the previous observations of improved survival [16] and reduced morbidity [19].

The dosing regimen for oral paricalcitol in HD and PD subjects used in this pivotal study was based on pharmacometric modeling and simulations of the data from earlier studies. Initial doses were determined using the formula of baseline $iPTH/60$ up to a maximum dose of 32 μg . Subsequent doses were based also on $iPTH/60$, in conjunction with serum Ca and P measurements. As $iPTH$ approaches the target range, individualized dose adjustments may be necessary to achieve a stable $iPTH$. Our study suggests that in situations in which monitoring of $iPTH$, Ca, or P occurs less frequently than once per

week, a more modest ratio for initial and subsequent doses may be warranted. Indeed, dose alterations to optimize the $iPTH$ or to control the metabolic parameters were reflected in ratios as low as $iPTH/105$.

A limitation of these studies is the 12-week duration. While previous studies have revealed that a decreased PTH level is associated with improved bone morphology, future studies should investigate the long-term effect of paricalcitol on outcomes related to mineral and bone disorders of CKD. Finally, additional studies are needed to assess potential differences between vitamin D sterols.

The findings of these studies provide evidence that initial dosing and subsequent dose titration of oral paricalcitol based on the severity of SHPT is a safe and efficacious approach to managing SHPT. In addition, treatment with oral paricalcitol leads to significant decreases in bone biochemical markers relative to placebo, suggesting correction of high-turnover bone disease associated with SHPT. Oral paricalcitol is shown to be efficacious and well tolerated in the treatment of SHPT in both HD and PD patients.

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