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Original Articles

Effects of paricalcitol on calcium and phosphate metabolism and markers of bone health in patients with diabetic nephropathy: results of the VITAL study

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ORIGINAL ARTICLE

ABSTRACT

Background. Chronic kidney disease (CKD) is associated with elevations in serum phosphate, calcium–phosphorus product and bone-specific alkaline phosphatase (BAP), with attendant risks of cardiovascular and bone disorders. Active vitamin D can suppress parathyroid hormone (PTH), but may raise serum calcium and phosphate concentrations. Paricalcitol, a selective vitamin D activator, suppressed PTH in CKD patients (stages 3 and 4) with secondary hyperparathyroidism (SHPT) with minimal changes in calcium and phosphate metabolism.
Methods. The VITAL study enrolled patients with CKD stages 2–4. We examined the effect and relationship of paricalcitol to calcium and phosphate metabolism and bone markers in a *post hoc* analysis of VITAL. The study comprised patients with diabetic nephropathy enrolled in a double-blind, placebo-controlled, randomized trial of paricalcitol (1 or 2 μg/day). Urinary and serum calcium and phosphate, serum BAP, and intact PTH (iPTH) concentrations were measured throughout the study.
Results. Baseline demographics and calcium, phosphate, PTH (49% with iPTH <70 pg/mL), and BAP concentrations were similar between groups. A transient, modest yet significant increase in phosphate was observed for paricalcitol 2 μg/day (+0.29 mg/dL; $P < 0.001$). Dose-dependent increases in serum and urinary calcium were observed; however, there were few cases of hypercalcemia: one in the 1-μg/day group (1.1%) and three in the 2-μg/day group (3.2%). Significant reductions in BAP were observed that persisted for 60 days after paricalcitol discontinuation ($P < 0.001$ for combined paricalcitol groups versus placebo). Paricalcitol dose-dependent reductions in iPTH were observed. Paricalcitol in CKD patients (±SHPT) was associated with modest increases in calcium and phosphate.
Conclusion. Paricalcitol reduces BAP levels, which may be beneficial for reducing vascular calcification.
Trial registration. Trial is registered with ClinicalTrials.gov, number NCT00421733.

INTRODUCTION

Alterations in serum phosphate and calcium levels in chronic kidney disease (CKD) are associated with an elevated risk of secondary hyperparathyroidism (SHPT), bone abnormalities, cardiovascular disease (CVD) and death [1–4]. Indeed, high normal serum phosphorus is associated with cardiovascular events and mortality [3, 5–8], even among individuals without preexisting CKD or CVD [8–10]. Similarly, observational studies have demonstrated that elevated serum calcium levels are associated with increased mortality, though the strength

and consistency of this relationship are weaker than that for phosphorus [4, 7]. Thus, aberrant phosphate and calcium homeostasis may be important contributors to complications of CKD.

Changes in circulating markers of bone turnover may also be prognostic of early mortality in CKD. Increases in bone-specific alkaline phosphatase (BAP) levels, a marker of high-turnover bone disease, have been observed in patients with CKD and are a strong predictor of cardiovascular morbidity and mortality in CKD [11, 12]. BAP levels are increased by parathyroid hormone (PTH), which may further contribute to increased serum phosphorus levels.

Vitamin D is an important regulator of PTH, serum phosphorus and calcium and is an independent predictor of early survival in patients on dialysis and in patients with CKD stages 2-5 [13, 14]. Normalization of levels of calcitriol, the natural activator of the vitamin D receptor (VDR), has been proposed as a means of reducing renal and cardiovascular complications [15]. In observational studies of patients with SHPT, calcitriol lowered PTH levels and improved survival [16, 17]. Calcitriol has also been shown to lower BAP levels [18]. However, the benefits of calcitriol were observed at the expense of increased serum calcium and phosphate levels [16, 17]. Higher serum calcium and phosphate levels are associated with vascular calcification. Thus, while active vitamin D treatment exhibits certain benefits on PTH and possibly bone metabolism, safety concerns of elevated phosphate levels and hypercalcemia have been raised [19].

Paricalcitol is a vitamin D analog and selective activator of the VDR that is currently approved to prevent or treat SHPT associated with CKD stages 3–5 [20]. In preclinical studies, therapeutic doses of paricalcitol had little effect on calcium and phosphate metabolites [21, 22]. In clinical studies of paricalcitol in patients with SHPT in CKD stages 3–5, paricalcitol showed potent suppression of intact PTH (iPTH) and reductions in BAP levels [19, 23]. Some observational studies have shown that the use of paricalcitol is associated with improved survival compared with the use of calcitriol or with no use of vitamin D [24–26].

As the potential benefits of paricalcitol on cardiovascular health and survival may be independent of the presence of CKD or SHPT, it is important to determine the effects of paricalcitol across a broad range of CKD severity and PTH values. We therefore explored the effects of paricalcitol on calcium and phosphate metabolism and bone markers in the VDR Activator for Albuminuria Lowering (VITAL) study, which randomized patients with diabetic nephropathy, CKD stages 2–4, and PTH concentrations of 35–500 pg/mL to treatment with 1 or 2 μg/day of paricalcitol or placebo for 24 weeks.

SUBJECTS AND METHODS

Study design and methodology

The study design and methodology have been described in detail elsewhere [15, 27]. Briefly, male and female patients ≥20 years old with type 2 diabetes and nephropathy (estimated glomerular filtration rate (eGFR) between 15 and 90 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio between 100 and 3000 mg/g at first morning void) receiving stable doses of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for 3 months or more were eligible. Patients with a serum PTH concentration between 35 and 500 pg/mL and a serum calcium concentration of <9.8 mg/dL were eligible.

This was a *post hoc* analysis of patients enrolled in the Phase 2 VITAL study [15, 27], which had a randomized, double-blind, placebo-controlled, multicenter design. The study was conducted with institutional review board approval and in accordance with the Declaration of Helsinki. Eligible patients were randomized in a 1:1:1 manner to placebo, paricalcitol 1 μg/day and paricalcitol 2 μg/day. The study included a 3-week screening phase followed by a 24-week randomized treatment period and a 60-day follow-up period after treatment withdrawal. Clinical assessments for this analysis included measurements of iPTH (using the DPC Immulite intact PTH assay [28]), calcium, phosphate and BAP concentrations. Calcium-containing phosphate binders were permitted, if required to control hyperphosphatemia, provided that the type of phosphate binder was not changed and was continued throughout the duration of the study (screening through follow-up phases). Blood was drawn for assessments of serum iPTH, calcium and phosphate concentrations at baseline (fasted), every 4 weeks during the randomization period (nonfasted) and 30 and 60 days (fasted) after treatment withdrawal. Urinary calcium and phosphate excretion and serum BAP concentration were measured at baseline, at the end of the 24-week randomization period and 60 days after treatment withdrawal. Hypercalcemia was defined by two or more consecutive visits with serum calcium concentration (corrected for albumin level) >10.5 mg/dL (2.62 mmol/L) after the first dose of study drug. Paricalcitol dose reductions from once daily (q.d.) to three times weekly (t.i.w.) were instituted for iPTH <15 pg/mL, calcium >11.0 mg/dL or two consecutive serum calcium measurements >10.5 but ≤11.0 mg/dL.

Statistical methods

Data for all baseline variables were summarized using descriptive statistics. Least squares mean changes in phosphate, calcium and iPTH concentrations from baseline to last on-treatment measurement and to 60 days after treatment withdrawal were analyzed by analysis of covariance (ANCOVA). Repeated measures analyses were used to evaluate mean changes in phosphate, calcium and iPTH concentrations from baseline over the treatment period. The mean percentage change in BAP concentration to last on-treatment measurement or 60 days after treatment withdrawal was analyzed by ANCOVA. Spearman's rank correlation coefficients were used to investigate the relationship in the change from baseline to final on-treatment observation between iPTH and BAP concentrations. Multiple regression analysis was used to examine the effects of covariates on the change from baseline to final on-treatment observation in BAP. Path analysis, a multivariable statistical method that utilizes regression models to analyze relationships between correlated variables [29–31], was used to evaluate the direct and indirect effects of

paricalcitol on the reduction in BAP after controlling for its therapeutic effects on lowering iPTH. For effects of treatment on BAP analyses, patients were stratified by subgroups based on the median baseline iPTH concentration (~70 pg/mL). One subgroup included patients with an iPTH level of <70 pg/mL, and the other subgroup included patients with an iPTH level of ≥70 pg/mL.

RESULTS

Patient characteristics and disposition

Two hundred eighty-one patients were randomized. Demographic and baseline characteristics are summarized in Table 1. The demographic characteristics were similar among the treatment groups. At baseline, calcium, phosphate and BAP concentrations did not differ significantly among the groups. Other clinical and biochemical characteristics were also comparable among the groups and have been described in detail elsewhere [15, 27].

Patient disposition has been reported in detail previously [15]. The average weekly dose of paricalcitol was 12 µg in the 2-µg/day group and 6 µg in the 1-µg/day group. No patient receiving placebo required a dose reduction from q.d. to t.i.w. during the treatment period, compared with 13 (14%) and 40 (42%) patients in the 1- and 2-µg/day groups, respectively. The majority of dose reductions were the result of iPTH concentration <15 pg/mL (88% of the reductions in the 2-µg/day group; 85% of the reductions in the 1-µg/day group).

Effects on phosphorus and calcium concentrations

The mean change from baseline to last on-treatment measurement and 60 days after treatment is shown for serum phosphorus and calcium in Figure 1A and B, respectively. A statistically significant increase in serum phosphate concentration was observed only for the paricalcitol 2-µg/day group

Table 1. Patient demographics and baseline characteristics

Parameter	Placebo (n = 93)	Paricalcitol 1 µg/day (n = 93)	Paricalcitol 2 µg/day (n = 95)	Total (N = 281)
Age, mean ± SD, years	65 ± 11	64 ± 10	65 ± 10	64 ± 10
Male:female, %	65:35	71:29	73:27	69:31
Race, n (%)				
White	72 (77)	63 (68)	66 (70)	201 (72)
Black	11 (12)	15 (16)	14 (15)	40 (14)
Asian	10 (11)	14 (15)	15 (16)	39 (14)
Other	0	1 (1)	0	1 (<1)
Blood pressure, mean ± SD, mm Hg				
SBP	142 ± 17	142 ± 18	141 ± 16	142 ± 17
DBP	73 ± 12	73 ± 12	73 ± 9	73 ± 11
UACR, mg/g, median (IQR)	642 [263, 1128]	626 [288, 1225]	597 [246, 1172]	612 [260, 1184]
eGFR, mean ± SD,mL/min/1.73 m^2	39 ± 17	40 ± 15	42 ± 18	40 ± 17
Serum iPTH, mean ± SD, pg/mL % with iPTH <70 pg/mL	105 ± 91 53	97 ± 77 44	91 ± 65 49	98 ± 78 49
Phosphorus, mean ± SD				
Serum, mg/dL	3.8 ± 0.6	3.9 ± 0.5	3.8 ± 0.6	3.9 ± 0.6
Urinary, g/24 h	0.7 ± 0.3	0.7 ± 0.3	0.7 ± 0.5	0.7 ± 0.4
Calcium, mean ± SD				
Serum, mg/dL	9.3 ± 0.4	9.3 ± 0.4	9.4 ± 0.4	9.3 ± 0.4
Urinary, mg/24 h	38.0 ± 37.8	36.0 ± 33.8	47.0 ± 48.6	40.4 ± 40.8
Serum BAP, mean ± SD, U/L	26 ± 10	25 ± 13	25 ± 11	25 ± 11

DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone; IQR, interquartile range; PTH, parathyroid hormone; SBP, systolic blood pressure; SD, standard deviation; UACR, urinary albumin-to-creatinine ratio.

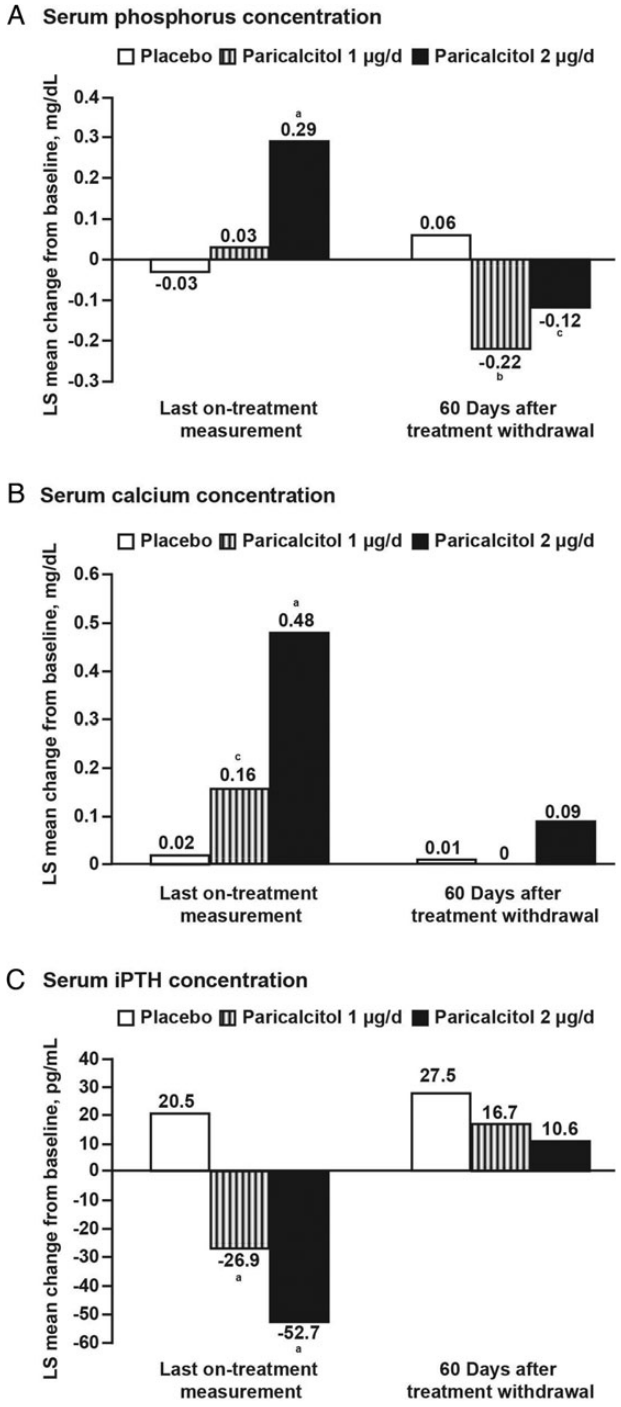

FIGURE 1: Mean change from baseline in (**A**) serum phosphorus, (**B**) calcium and (**C**) iPTH concentrations to last on-treatment measurement and 60 days after treatment withdrawal. iPTH, intact parathyroid hormone; LS, least squares. [a]P < 0.001 versus placebo. [b]P = 0.001 versus placebo. [c]P < 0.05 versus placebo.

at last on-treatment assessment (+0.29 mg/dL; P < 0.001 versus placebo). The change in serum phosphorus was transient, with the increase most evident in the first 12 weeks of treatment with paricalcitol 2 µg/day, followed by a gradual return toward baseline (Figure 2). The mean decreases in 24-h urinary phosphorus excretion from baseline to last on-treatment assessment were 0.03 g for placebo, 0.10 g for paricalcitol

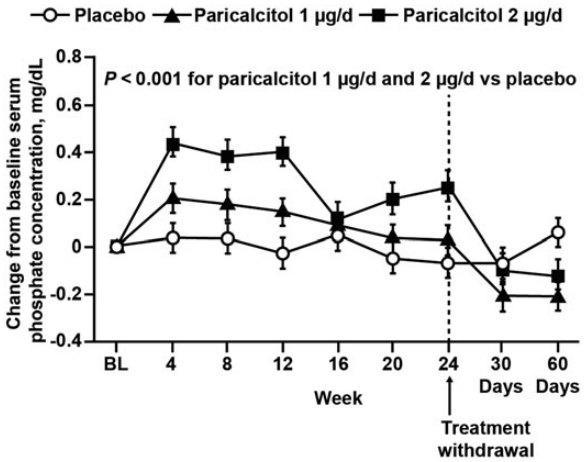

FIGURE 2: Mean change from baseline in serum phosphateconcentration during treatment and 60 days after treatmentwithdrawal. Data are shown as the mean change ± standard deviation. BL, baseline.

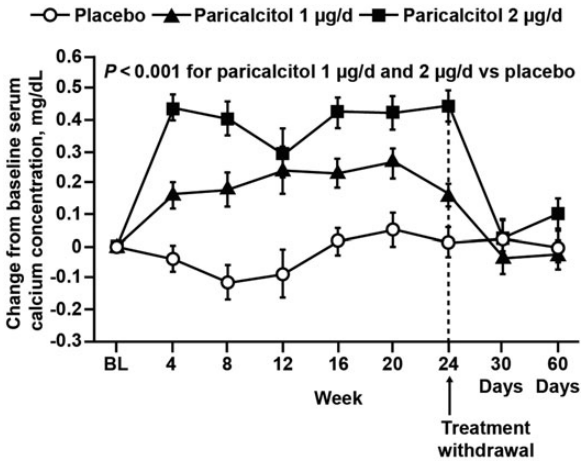

FIGURE 3: Mean change from baseline in serum calcium concentration during treatment and 60 days after treatment withdrawal. Data are shown as the mean change ± standard deviation. BL,baseline.

1 µg/day and 0.07 g for paricalcitol 2 µg/day (P values were not significant for all comparisons with placebo). Following treatment withdrawal, the serum phosphorus concentration decreased to below baseline in the paricalcitol groups (paricalcitol 1 µg/day, P = 0.001 versus placebo; paricalcitol 2 µg/day, P = 0.034 versus placebo).

There was a dose-dependent increase in serum calcium concentration in the paricalcitol treatment groups from baseline to last on-treatment measurement (Figure 1B and 3). Increases from baseline in serum calcium were observed for the paricalcitol 1-µg/day (0.16 mg/dL; P = 0.039 versus placebo) and 2-µg/day groups (0.48 mg/dL; P < 0.001 versus placebo). Hypercalcemia (at least two consecutive monthly calcium concentration values >10.5 mg/dL) occurred in only three patients (3.2%) in the paricalcitol 2-µg/day group and one patient (1.1%) in the paricalcitol 1-µg/day group. Increases in 24-h urinary calcium excretion from baseline to last on-treatment assessment paralleled changes in serum calcium, with 19.73-

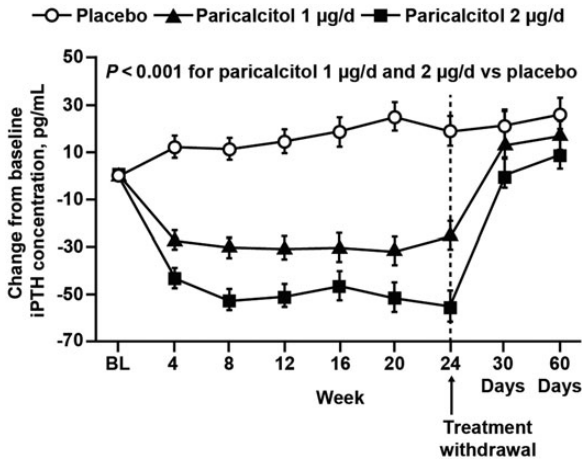

FIGURE 4: Mean change from baseline in iPTH concentration during treatment and 60 days after treatment withdrawal. Data are shown as the mean change ± standard deviation. BL, baseline; iPTH, intact parathyroid hormone.

mg (P = 0.003 versus placebo) and 26.12-mg increases (P < 0.001 versus placebo) for the paricalcitol 1- and 2-µg/day groups, respectively. Serum calcium concentrations returned to baseline after withdrawal of active treatment.

Effects on intact parathyroid hormone concentration

The mean change from baseline to last on-treatment assessment and 60 days after treatment is shown for iPTH in Figure 1C. In placebo-treated patients, iPTH levels increased to 20.5 pg/mL at the end of treatment and 27.5 pg/mL at 60 days after treatment. In the active treatment groups, there was a dose-dependent reduction in iPTH, with a 26.9-pg/mL decrease in the 1-µg/day group (20.9% reduction; P < 0.001 versus placebo) and a 52.7-pg/mL reduction in the 2-µg/day group (48.9% reduction; P < 0.001 versus placebo). The mean change in iPTH concentration over time for the three groups is shown in Figure 4. In patients in the placebo group, iPTH progressively increased over time. In contrast, a clear dose-dependent suppression of iPTH was observed with paricalcitol. As indicated above, the majority of dose reductions were attributed to an iPTH concentration of <15 pg/mL. After treatment withdrawal, iPTH concentration returned to baseline in the paricalcitol groups.

Effects on bone-specific alkaline phosphatase concentration

The mean percentage change from baseline to last on-treatment assessment and 60 days after treatment is summarized for the three treatment groups in Figure 5. BAP levels were significantly reduced in both paricalcitol groups at the last on-treatment measurement [1 µg/day, 26% reduction (P < 0.001 versus placebo); 2 µg/day, 27% reduction (P < 0.001 versus placebo)]. BAP levels remained suppressed 60 days after treatment withdrawal despite iPTH levels returning to baseline for both active groups during that time period.

The mean BAP levels were significantly lower among patients with baseline levels of iPTH <70 pg/mL when

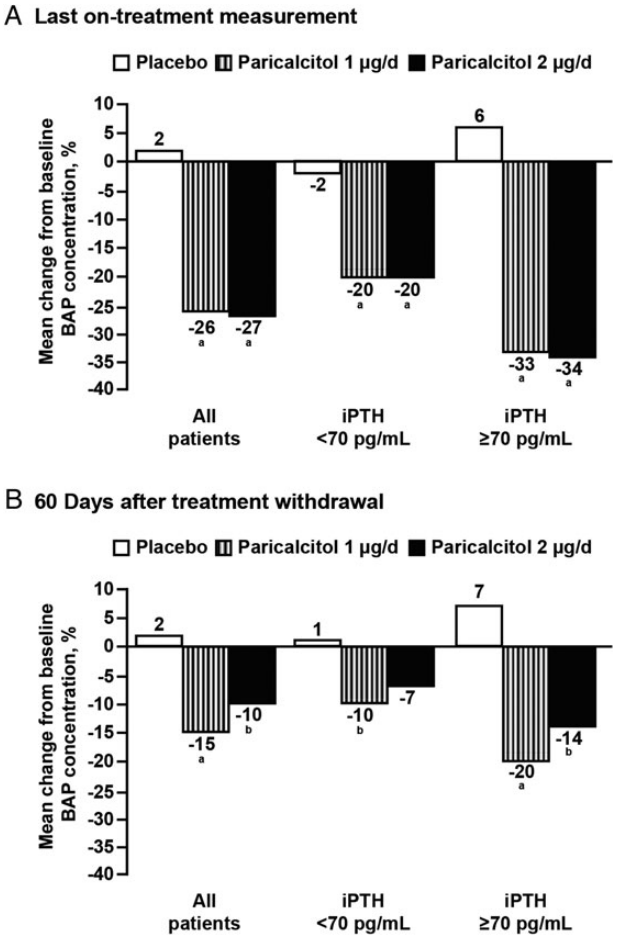

FIGURE 5: Mean percentage change from baseline in BAP concentration to **(A)** last on-treatment measurement and **(B)** 60 days after treatment withdrawal, by baseline iPTH. BAP, bone-specific alkaline phosphatase; iPTH, intact parathyroid hormone. [a]P ≤ 0.001 versus placebo. [b]P < 0.05 versus placebo.

compared with patients with baseline levels of iPTH ≥70 pg/mL. Treatment with paricalcitol reduced BAP levels by 20% (P ≤ 0.001) at the last on-treatment assessment among patients with iPTH level <70 pg/mL and by 33% (P ≤ 0.001) among patients with iPTH level ≥70 pg/mL, whereas treatment with placebo had no effect.

Scatter plots for the change from baseline to last on-treatment values between iPTH and BAP for all groups are shown in Figure 6. There was a significant correlation for both paricalcitol groups, with Spearman's rank correlation coefficients of 0.27 (P = 0.017) and 0.45 (P < 0.001), respectively, for the 1- and 2-µg/day groups. In the subgroup of patients with a baseline iPTH level of ≥70 pg/mL, a significant correlation coefficient was found only in the paricalcitol 2-µg/day group (0.36, P = 0.035).

Path analysis revealed that the BAP reduction associated with paricalcitol was mediated by a significant direct effect (P < 0.001) independent of iPTH responses. The indirect effect of iPTH reduction on BAP reduction accounted for 35% of the total BAP-lowering effect of paricalcitol (P < 0.001), compared with 65% of the total for a direct effect of paricalcitol on BAP

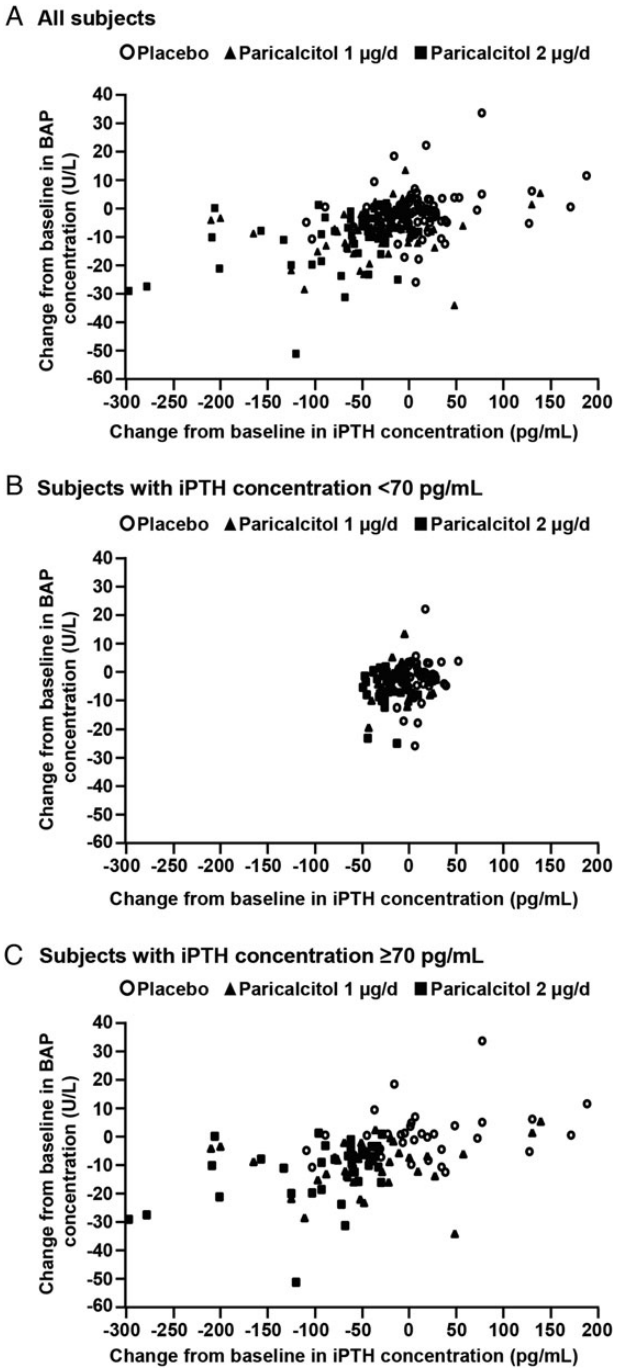

FIGURE 6: Scatter plots of the change from baseline in BAPconcentration versus change from baseline in iPTH concentration,by baseline iPTH concentration. Changes from baseline to last on-treatment values for iPTH and BAP are shown for **(A)** all subjects, **(B)** subjects with iPTH concentration <70 pg/mL and **(C)** subjects with iPTH concentration ≥70 pg/mL. BAP, bone-specific alkaline phosphatase; iPTH, intact parathyroid hormone.

concentration. In regression analysis, significant effects of baseline BAP and treatment were observed, but there were no significant associations between changes in BAP and other tested covariates: age (<65, ≥65 years), gender, race, baseline iPTH levels (<70, ≥70 pg/mL), 25(OH) vitamin D levels (<15, ≥15 ng/mL), baseline eGFR, baseline urinary calcium levels, baseline urinary albumin-to-creatinine ratio and days of treatment exposure.

DISCUSSION

This is the first report of changes in calcium and phosphate metabolism and bone biochemical markers in a large cohort of patients receiving paricalcitol 2 µg/day. We observed modest increases in serum calcium concentration accompanied by increases in urinary calcium excretion, with few cases of hypercalcemia: one in the 1-µg group (1.1%) and three in the 2-µg group (3.2%). Small, transient increases in serum phosphorus concentration were observed. An accompanying increase in urinary phosphorus excretion was not observed, but such an increase could have been missed because we did not control dietary phosphorus intake and did not monitor cumulative phosphorus excretion. We also observed significant reductions in BAP concentration, the majority of which were attributed to a direct effect of paricalcitol on BAP. A lower BAP concentration may be beneficial in decreasing vascular calcification and adverse cardiovascular events. Reductions in BAP persisted for at least 60 days after paricalcitol discontinuation. This trial also confirmed the PTH-lowering effects of paricalcitol among patients with a broad range of CKD severity and baseline PTH values and refuted previous suggestions that VDRA agents have no significant effect on PTH [32].

Although no active comparator was included in the VITAL study, selective activation of VDR with paricalcitol has previously been shown to have a lower magnitude of effect on serum calcium and phosphorus relative to calcitriol [16, 33–36]. However, at least one study in hemodialysis patients suggested that alfacalcidol and paricalcitol do not elicit significantly different effects on the activation of VDR [37]. Approximately 3 and 1% of patients treated with paricalcitol 2 and 1 µg/day, respectively, experienced hypercalcemia (at least two consecutive monthly calcium concentration values >10.5 mg/dL). Observations in the VITAL cohort are similar to previous findings for paricalcitol treatment in patients with SHPT. In a study by the primary author, incidence of hypercalcemia (two consecutive biweekly serum calcium concentrations >10.5 mg/dL) with paricalcitol was 2%, an incidence not different from placebo treatment [19]. In contrast, a study of calcitriol in nondialyzed CKD patients reported a 15% rate of hypercalcemia (first uncorrected serum calcium >10.2 mg/dL) [16]. In a comparative trial of hemodialysis patients with SHPT randomized to calcitriol or paricalcitol, calcitriol was associated with a significantly greater incidence of the composite endpoint of hypercalcemia (two consecutive serum calcium concentrations >11.5 mg/dL) and/or four consecutive calcium-phosphorus product (Ca × P) values >75 mg^2/dL^2, wherein calcium and phosphorus values were determined twice weekly (33 versus 18%; P = 0.008) [36]. Furthermore, there was a numerically greater incidence of elevated calcium (two consecutive values >10.5 mg/dL) in the calcitriol group (14.3%) compared with the paricalcitol group (7.7%); however, the difference was not statistically significant

(P = 0.115) [36]. Taken together, the incidence of hypercalcemia with paricalcitol seems to be favorable relative to calcitriol [16, 33, 35]. A randomized trial comparing these agents in patients with stage 3 and 4 CKD is ongoing and will be completed in 2012.

Hyperphosphatemia is an important cause of/contributor to vascular calcification [38]. Indeed, excess bone resorption observed in patients with CKD further contributes to vascular calcification [39]. In the current analysis, we observed small, transient increases in serum phosphorus concentration at the higher dose of paricalcitol. In a trial comparing high doses of paricalcitol with comparable doses of calcitriol in patients on hemodialysis, paricalcitol increased phosphorus and Ca × P levels less than calcitriol, suggesting less of an effect on gut absorption of calcium and phosphate and bone resorption [34]. Other studies have also shown lower gut absorption and bone resorption of calcium and phosphate with paricalcitol use relative to calcitriol use in hemodialysis patients [40, 41].

An association between bone turnover abnormalities, an increase in calcium and phosphate available for deposit in soft tissues and vascular calcification have been demonstrated [39, 42]. Increased BAP concentrations correlate with higher bone turnover. Other investigators have reported reductions in BAP concentration with calcitriol [18] and later with paricalcitol [19, 23]. Our findings in the VITAL cohort confirm the actions of paricalcitol in suppressing BAP and suggest that the majority of the suppression was a direct effect of paricalcitol, while one-third was attributed to a lower PTH level. Indeed, the effect of paricalcitol on BAP persisted for at least 60 days after treatment discontinuation, even though iPTH levels returned to baseline within 30 days. These results suggest that paricalcitol may directly suppress bone turnover.

This study has several limitations. First, this manuscript includes both prespecified endpoints and a *post hoc* analysis. Measurements of changes from baseline in calcium and phosphate metabolites and BAP were prespecified; however, additional *post hoc* analyses were performed. Second, in the VITAL trial, when iPTH levels were suppressed <15 pg/mL or calcium levels were >10.5 mg/dL, the dose of paricalcitol was decreased. While this is similar to usual clinical practice and reflects prudent care, it likely reduced the incidence of hypercalcemia we observed. Third, there was no active control arm (e.g., calcitriol), so any comparisons between paricalcitol and other vitamin D analogs were based on historical data. Fourth, while we observed significant suppression of BAP concentration, the duration of the study was not sufficiently long enough to assess the clinical significance in terms of hard outcomes (e.g., cardiovascular events, bone disorders, survival).

The potential clinical value of selective activation of the VDR for patients with diabetic nephropathy was addressed by de Zeeuw et al. in the main VITAL publication [15]. Clearly, an unmet need exists for drug strategies aimed at preventing kidney failure in the ever-growing type 2 diabetes population. Paricalcitol has been extensively used clinically since its introduction more than a decade ago and is well characterized in pre-dialysis and dialysis patients. Further, observational studies have suggested a survival benefit among patients receiving long-term treatment with paricalcitol [19, 24–26]. The current analysis is important because paricalcitol doses up to 2 μg/day for 6 months in patients with a broad range of CKD severity and PTH levels had limited effects on serum calcium and phosphate. As a result, long-term paricalcitol use would not appear to adversely affect mortality through mechanisms related to hypercalcemia and hyperphosphatemia. In addition to having limited effects on serum calcium and phosphates, paricalcitol decreased BAP, a surrogate marker of bone turnover. Reductions in bone turnover may have protective implications for vascular calcification.

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CONFICT OF INTEREST STATEMENT

D.C. is a consultant and speaker and has received honoraria from AbbVie. D.A. and M.A. are AbbVie employees and own AbbVie stock. E.R. is a consultant for and has received honoraria from AbbVie, Daiichi-Sankyo and Roche. D.d.Z. is a consultant for and has received honoraria (to employer) from AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Novartis, Noxxon Pharma, HemoCue and Reata Pharmaceuticals.

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ORIGINAL ARTICLE

Association of URG11 and Twist with clinical pathological characteristics and prognosis in patients with IgA nephropathy

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ABSTRACT

Background. Our previous studies demonstrated that URG11 is involved in hypoxia-induced tubular epithelial–mesenchymal transition and the development of kidney fibrosis in cellular and animal models. The objective of this study was to determine the expression levels of URG11 in kidneys with IgA nephropathy (IgAN), and the association of URG11 with various clinical parameters.

Methods. We analysed the degree of expression and localization of URG11 in biopsies from kidneys with IgAN, and correlated their immunostaining levels with various clinical and histological parameters. We also analysed the correlation between the expression of URG11 and Twist in the renal interstitium with renal survival.

Results. URG11 was strongly expressed in the cytoplasm of tubular epithelial cells obtained from kidneys of patients with IgAN. However, there was little positive staining for URG11 in the renal tubules of normal kidneys ($P = 0.024$). URG11 protein levels in the tubulointerstitium were inversely correlated with estimated glomerular filtration rates (eGFRs) ($r = -0.305$, $P = 0.038$) and the percentage of tubulointerstitial fibrosis ($r = 0.350$, $P = 0.023$). Moreover, a high level of URG11 correlated with the activation of Twist expression and E-cadherin repression in patients with IgAN ($P = 0.000$ and 0.041, respectively). Multivariate analyses indicated that a combination of high URG11 and Twist expression was an independent prognostic factor [relative ratio, RR 4.738 (95% CI: 1.040, 21.591), $P = 0.044$] of IgAN.

Conclusions. Our findings suggest that URG11 staining in renal biopsy specimens might be a novel histological marker for progression in IgAN patients.