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Antiproteinuric effect of oral paricalcitol in chronic kidney disease

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Background. Proteinuria is a marker of cardiovascular and renal disease in patients with chronic kidney disease (CKD), and reduction in proteinuria has been associated with improved cardiovascular and renal outcomes. While active vitamin D and its analogs have been shown to have renal protective effects in animals, these hormones have not been shown to reduce proteinuria in CKD patients.

Methods. In three double-blind, randomized, placebo-controlled studies to evaluate the safety and efficacy of oral paricalcitol, 220 CKD stage 3 and 4 patients with secondary hyperparathyroidism (SHPT) were randomized to oral paricalcitol ($N = 107$, mean dose 9.5 μg/week) or placebo ($N = 113$) and followed for up to 24 weeks. In conjunction with other safety measures, proteinuria was measured by dipstick and read by an automated reader at the beginning and end of trial. We subsequently analyzed the dipstick data to evaluate the effect of paricalcitol on proteinuria.

Results. At baseline, proteinuria was present in 57 patients randomized to oral paricalcitol and 61patients randomized to placebo (NS). At the final visit, 29/57 (51%) of the paricalcitol patients compared to 15/61 (25%) placebo patients had reduction in proteinuria, $P = 0.004$ (odds for reduction in proteinuria 3.2 times greater for paricalcitol patients, 95% CI 1.5–6.9). For the patients who had both proteinuria at baseline and parathyroid hormone (PTH) suppression (end point defined as 2 consecutive ≥30% decreases in iPTH from baseline), 27/51 (53%) patients had a reduction in the proteinuria in the paricalcitol group and 0/7 (0%) had a reduction in proteinuria in the placebo group. Reduction of proteinuria favored patients on paricalcitol, regardless of age, sex, race, diabetes mellitus, hypertension, or use of therapies to block the renin-angiotensin-aldosterone system (RAAS).

Conclusion. Our results demonstrate that the reduction in proteinuria was associated with paricalcitol treatment, and the reduction in proteinuria was independent of concomitant use of agents that block the RAAS. Paricalcitol as a potential pharmacologic means of reducing proteinuria in CKD patients warrants further investigation.

Key words: paricalcitol, chronic kidney disease, proteinuria, vitamin D.

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Proteinuria is not only a capital sign of kidney disease, but also a marker of chronic kidney disease (CKD) progression, and a marker of cardiovascular disease and death [1]. Moreover, reduction in proteinuria has been linked to improvement in both cardiovascular and renal outcomes [2] and, therefore, strategies that reduce proteinuria are considered beneficial.

Blood pressure reduction using inhibitors of the renin-angiotensin-aldosterone system (RAAS), namely angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) is currently the standard of care for reducing proteinuria and improving cardiovascular and renal outcomes [3]. However, active vitamin D and its analogs also have unique effects on the kidney that involve the renin-angiotensin-aldosterone system [4], and these agents have demonstrated renal protective effects in animal studies [5]. Additionally, studies in CKD patients suggest a role of active vitamin D in abrogating renal disease [6] and providing cardiovascular protection [7, 8]. Despite the use of agents that inhibit RAAS, renal and cardiac disease tend to progress in CKD patients and this progression seems to correlate with residual proteinuria [2, 9, 10]. If, in fact, active vitamin D affects proteinuria reduction, this finding would warrant further investigation as a potential novel therapy, along with preexisting therapies that could provide additional cardiovascular and renal protective benefits in CKD patients. In this report, we evaluated the effect of paricalcitol compared to placebo on proteinuria (originally examined as a safety measure) in predialysis CKD patients with secondary hyperparathyroidism (SHPT).

METHODS

Patients and study design

Results from three double-blind, randomized, placebo-controlled trials comparing paricalcitol capsule and

placebo for the suppression of parathyroid hormone (PTH) in 220 patients who were enrolled at 46 sites in the United States and Poland between April 3, 2002 and March 3, 2004, were examined. Across these trials, 107 patients were randomly assigned to the paricalcitol capsule group and 113 were randomly assigned to placebo group.

The inclusion/exclusion criteria were identical for all three trials. Eligible patients were men and women ≥18 years of age who had been in the care of a physician ≥2 months for CKD prior to entry into the study, and had not been on active vitamin D therapy for at least 4 weeks prior to the screening visit. Patients were required to have an average of 2 consecutive iPTH values of ≥150 pg/mL, 2 consecutive serum calcium levels between 8.0 to 10.0 mg/dL, 2 consecutive serum phosphorus levels of ≤5.2 mg/dL within 4 weeks prior to treatment, and patients who had an estimated glomerular filtration rate (eGFR) of 15 to 60 mL/min and who were not expected to begin dialysis for at least 6 months.

Because the study was designed to evaluate the efficacy of oral paricalcitol on PTH control, proteinuria was not considered to be an inclusion or exclusion criteria. Patients were randomized to either oral paricalcitol or placebo, and were followed for up to 24 weeks. In two trials a three-times-weekly (TIW) dosing regimen was used, and the initial dose was 2 or 4 μg depending on baseline iPTH levels (2 μg if iPTH was ≤500 pg/mL and 4 μg if iPTH was >500 pg/mL). In the third trial a once-daily (QD) dosing regimen was used, and the initial dose was 1 μg if iPTH was ≤500 pg/mL and 2 μg if iPTH was >500 pg/mL. Doses thereafter were titrated in 2 μg (TIW regimen) or 1 μg (QD regimen) increments based on PTH, calcium, and phosphorus values. Principal investigators made every attempt to maintain a stable dose of all concurrent medications, including ACEi and ARB use, during the treatment phase. All patients signed informed consent prior to enrollment, and the study was approved by the local Institutional Review Board of each participating center.

All blood and urine tests were performed in a central laboratory (Covance, Indianapolis, IN, USA). For each patient, GFR was estimated using the modified MDRD study formula [$GFR = 170 \times (S_{cr})^{-0.999} \times (Age)^{-0.167} \times (0.762$ if patient is female$) \times (1.180$ if patient is black$) \times (BUN)^{-0.170} \times (Alb)^{+0.318}$ [11]. As part of the urinalysis, semiquantitative dipstick proteinuria was measured using IRIStrips™ (Roche Diagnostics Corporation, Indianapolis, IN, USA) at baseline (prior to study drug administration) and at the end of the study (final visit). Urine dipstick results were analyzed using an automated reader (IRIS CHEMSTRIP reader Model 500, International Remote Imaging Systems, Inc., Chatsworth CA) and were reported as negative, trace, 1+, 2+ and 3+. Reduction of proteinuria was not a pre-specified end-point, therefore urine protein/creatinine ratios were not measured, nor urine specimens archived for future measurements.

Statistical analyses

The primary analysis consisted of a comparison of the proportion of paricalcitol and placebo patients who had dipstick proteinuria at baseline that subsequently experienced a decrease from baseline using Fisher's exact test. The proportion of paricalcitol and placebo patients that experienced a decrease from baseline in proteinuria were compared using Fisher's exact test within subpopulations of age, race, sex, baseline diabetes mellitus status, baseline hypertension status, and use of ACEi/ARB. The Breslow-Day test was performed to compare the odds ratio (for paricalcitol patients to placebo patients) of a decrease in proteinuria across subpopulations of age, race, sex, baseline diabetes mellitus status, baseline hypertension status, and use of ACEi/ARB.

Response to PTH suppression was defined a priori as two consecutive reductions in iPTH of at least 30% from baseline. The proportion of paricalcitol and placebo patients that experienced a decrease from baseline in proteinuria were compared within the set of patients with PTH response and the set of patients without PTH response using Fisher exact test. A comparison of the odds ratio (for paricalcitol patients to placebo patients) for a decrease in proteinuria between the two sets of patients was performed with a Breslow-Day test.

For patients who had dipstick proteinuria at baseline, mean change from baseline to final visit in eGFR, mean change from baseline to weeks 7, 15, and final visit in systolic and diastolic blood pressure were compared between the paricalcitol and placebo treatment groups using a one-way analysis of variance (ANOVA) with treatment group as the factor.

A test for an association between baseline iPTH and baseline proteinuria was performed using a linear model with baseline iPTH as a continuous response variable and baseline proteinuria as a discrete factor.

RESULTS

Of the 220 subjects enrolled in three studies, 195 subjects had tests for dipstick urinalysis at the beginning and the end of study. Baseline and demographic characteristics of these 195 patients who received oral paricalcitol or placebo are shown in Table 1 and reveal no major differences between groups. The mean dose of oral paricalcitol was 9.5 μg/week.

Effect of oral paricalcitol on dipstick proteinuria

Shifts in urine protein from baseline to final visit are shown in Figure 1. The percent of patients who experience