Efficacy and Safety of Paricalcitol Therapy for Chronic Kidney Disease: A Meta-Analysis

Jun Cheng,* Wen Zhang,† Xiaohui Zhang,* Xiayu Li,* and Jianghua Chen*

Summary

Background and objectives Observational data indicate that newer vitamin D compounds such as paricalcitol can suppress serum intact parathyroid hormone (iPTH) and reduce proteinuria in patients with CKD. To systematically evaluate the efficacy and safety of paricalcitol for CKD, we conducted a meta-analysis of the published randomized controlled trials (RCTs).

Design, setting, participants, & measurements MEDLINE, Embase, the Cochrane Library, and article reference lists were searched for RCTs that compared paricalcitol with placebo in the treatment of patients with stage 2–5 CKD. The quality of the studies was evaluated using the Jadad method. The results are summarized as risk ratios (RRs) for dichotomous outcomes or mean differences for continuous outcomes.

Results Nine studies (832 patients) were included. Compared with placebo, paricalcitol suppressed serum iPTH (RR, 6.37; 95% confidence interval [95% CI], 4.64–8.74; P<0.001) and reduced proteinuria (RR, 1.68; 95% CI, 1.25–2.25; P<0.001). Compared with the control group, the RR for hypercalcemia associated with paricalcitol use was 2.25 (95% CI, 0.81–6.26; P=0.12). Patients receiving paricalcitol therapy did not have an increased risk of endocrine system and cardiovascular system adverse effects (RR, 1.07; 95% CI, 0.84–1.36; P=0.58).

Conclusions We confirm that paricalcitol suppresses iPTH and lowers proteinuria in patients with stage 2–5 CKD without an increased risk of adverse events. A trend toward increased hypercalcemia did not reach statistical significance, but may be clinically relevant. A randomized trial is needed to determine if paricalcitol affects the development of ESRD or mortality.


Introduction

Secondary hyperparathyroidism (SHPT) is a complication of CKD. Elevations in serum intact parathyroid hormone (iPTH) concentration are observed early in the development of CKD (1,2). The prevention and treatment of SHPT are important because imbalances in mineral metabolism imbalances are associated with increased rates of mortality and morbidity rates in CKD patients (3,4).

The pathogenesis of SHPT is complex; however, a deficiency in 1,25-dihydroxyvitamin D3 (calcitriol) is taken as a major contributing factor. Calcitriol synthesis decreases in direct response to the decline in kidney function. Calcitriol has a direct inhibitory effect on pre-parathyroid hormone gene transcription, and a deficiency in this hormone results in a cascade of events that include decreased calcium absorption and an increase in parathyroid hormone (PTH) production (5).

Interventions that are widely used to improve biochemical markers of mineral metabolism and bone include calcium supplements, phosphate binders, and active vitamin D compounds. Vitamin D therapy has historically been based on alfacalcidol or calcitriol, both of which suppress SHPT (6).

Because of the marked effect of calcitriol in increasing the risk of hypercalcemia and hyperphosphatemia during SHPT (3,7), the need to improve our therapies for SHPT has led to the search for vitamin D analogs.

Two epidemiologic studies (8,9) revealed a potentially important systemic role for a new vitamin D analogs paricalcitol in patients with CKD. The first study (8) revealed that the use of paricalcitol was associated with an adjusted 16% survival benefit compared with the use of calcitriol. The second randomized controlled trial (RCT) (9) showed that the addition of 2 μg/d paricalcitol to renin-angiotensin system (RAS) blockers safely lowered residual albuminuria in patients with diabetic nephropathy.

Although in clinical trials emerging evidence in patients with CKD showed that paricalcitol suppressed PTH and reduced albuminuria, this agent may also increase calcium and phosphorus levels and other serious adverse events that are associated with poorer cardiovascular and mortality outcomes (10–12). However, a large RCT or a comprehensive meta-analysis on this issue is currently lacking.

*Kidney Disease Center of the First Affiliated Hospital, Medical School of Zhejiang University, Hangzhou, China; and †Department of Nephrology of Hangzhou Red Cross Hospital, Hangzhou, China

Correspondence: Dr. Chen Jianghua, Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou, Zhejiang Province, P.R. China, 310003. Email: chenjianghua@zju.edu.cn
We present the results of a systematic review summarizing currently available evidence from RCTs on the effects of paricalcitol in patients with renal disease.

Materials and Methods

Inclusion Criteria
To be selected for analysis, a study had to meet all of the following criteria: (1) the study was an RCT for treating patients with stage 2–5 CKD; (2) the study compared paricalcitol agents (any dose, type) with placebo/no treatment; and (3) the first period of available randomized, cross-over studies was included. A study was excluded if the RCT did not assess the effects of different treatment regimens for CKD on PTH or proteinuria.

Search Strategy
Electronic searches were performed using MEDLINE (1966–2010) and Embase (1988–2010). The Cochrane Controlled Trials Register (CCTR-Specialized Renal Registry) available on compact disc was also searched. The following medical subject heading terms and text words were used: vitamin D compounds, paricalcitol, CKD, proteinuria, RCTs, and clinical trials. Reference lists from identified articles were also searched. Abstracts presented at the American Society of Nephrology, National Kidney Foundation, European Dialysis and Transplant Association, and World Congress of Nephrology meetings from 2005 to 2010 were searched for additional unpublished data.

The titles and abstracts of the articles from these searches were independently analyzed by two of the authors (J. Cheng and W. Zhang) to ascertain inclusion criteria conformity. The full text of an article was carefully reviewed if screening of its title and abstract was unclear with regard to its admissibility.

Study Validity Assessment
We evaluated the quality of the included studies in terms of allocation concealment and intention-to-treat analysis, blinding of investigators, participants and outcome assessors, and completeness of follow-up, as well as the Jadad scale score (13–15).

Data Extraction
Data extraction was performed on full-text copies of all included trials by the two reviewers independently, using data extraction forms developed for this purpose. Data were extracted from all included trials with respect to patient characteristics of the study sample, the study drugs, doses, baseline characteristics of the trials, follow-up, and the following reported outcomes: (1) number of patients whose PTH was reduced by at least 30% from the maximum baseline at the end of treatment, (2) number of patients who had a reduction in proteinuria (defined as having at least a 10% decrease in proteinuria at the end of treatment), (3) number of patients with hypercalcemia (defined by serum Ca levels >11.0 mg/dl), (4) serum phosphorus levels at the end of treatment, and (5) treatment-related adverse events.

Any additional information required from the original investigators was requested by written correspondence, and if relevant information was obtained in this manner, this was included in the review. If an outcome was reported at more than one time point for a single study, the longest period of follow-up was used.

Statistical Analyses
Dichotomous outcome data from individual trials were analyzed using the risk ratio (RR) measure and its 95% confidence intervals (95% CIs). For continuous outcomes, the difference in means and 95% CIs at the end of treatment were calculated for individual trials, and the mean difference was used as a summary estimator.

To determine the robustness of our pooled effects, we compared our primary analysis with random-effects models (16–18). All statistical analyses were performed using Review Manager 5.1 statistical software (Cochrane Collaboration, Oxford, UK) for the meta-analysis.

Results

Trial Flow and Study Characteristics
The combined search of MEDLINE, Embase, and CCTR, which also included some hand-searching of relevant nephrology journals, retrieved 255 citations. After discarding a number of duplicates retrieved by individual searches and reviewing all titles and abstracts, many studies were excluded because they were not RCTs, did not investigate any of the outcomes of interest to this study, or were animal or basic research studies or review articles. Overall, this analysis included nine trials that enrolled a total of 832 patients (9,19–27) (Figure 1). Of the 10 included articles, those by Coyne et al. (19) and Agarwal et al. (25) were from the same clinical trials.

The details of the interventions, baseline characteristics of the populations, study period, concomitant drugs, follow-up, and primary outcome in the RCTs included in our analysis are summarized in Table 1.

Quality Assessment
The quality of the included studies was assessed independently by two of the authors (W. Zhang and J. Cheng) using the Jadad score, which ranged from 0 to 5 points. Study quality generally was good; all studies had a Jadad score >3 (Table 1). Participants and investigators were blinded in all trials. Two of the studies met allocation concealment criteria (22%), and five studies met the intention-to-treat analysis criteria (55.6%).

Effects on Proteinuria
Four studies of nine RCTs were undertaken to prospectively test the effectiveness of paricalcitol in reducing residual albuminuria in a total of 469 patients with CKD who were receiving stable treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) (9,25–27). In these studies, 285 patients were assigned to the treatment groups and 184 patients received placebo.

None of the RCTs provided data on daily proteinuria at the end of treatment. However, four RCTs showed that a number of patients had a reduction in proteinuria. Fishbane et al. (26) used a 10% decrease in proteinuria as the end point. de Zeeuw et al. (9) used a change in proteinuria of at least –15% as a result. Alborzi et al. (27) and Agarwal et al.
provided the data on albuminuria before and after paricalcitol treatment. Therefore, we used a reduction in proteinuria >10% from baseline value as our study end point.

The study by Agarwal et al. (25) indicated that treatment with 1 mg of oral paricalcitol once daily associated with ACE inhibitor/ARB–reduced proteinuria in patients with stage 3 and 4 CKD with SHPT more than placebo. The study by Alborzi et al. (27) enrolled patients with stage 3 and 4 CKD who were treated with 1 μg of oral paricalcitol once daily, whereas the studies by de Zeeuw et al. (9) and Fishbane et al. (26) enrolled patients with stage 2–4 CKD with an iPTH level ≥20 ng/L and ≤250 ng/L (26) or 35–500 ng/L (9) who were treated with 1 μg or 2 μg of oral paricalcitol once daily. The dose of paricalcitol may have influenced the effectiveness of the reduction in residual albuminuria. We used subgroup analyses to decrease clinical heterogeneity. A subgroup analysis of 1 μg of oral paricalcitol treatment indicated that paricalcitol treatment was beneficial for reducing proteinuria (defined by reaching at least a 10% decrease in proteinuria at the end of treatment) compared with the control group. Similar results were obtained in the subgroup analysis of 2 μg of oral paricalcitol treatment versus the control group.

Overall, according to this analysis, in which the weight of individual studies was taken into account, oral paricalcitol treatment (1 or 2 μg/d) induced a reduction in proteinuria compared with the control group. Because of heterogeneity, we used a random-effects model to pool the data (RR, 1.68; 95% CI, 1.25–2.25; P<0.001) (heterogeneity χ²=8.17; P=0.15; Figure 2).

Effects on PTH

Five studies assessed PTH (defined as reaching at least a 30% reduction from the maximum baseline at the end of treatment) in a total of 563 patients (19,21–24). Two hundred and ninety-nine patients were assigned to the treatment groups and 264 patients were assigned to the control groups. All studies used one (21,22) or two (19,23–25) consecutive 30% decreases from baseline in iPTH levels as the primary end point. We used subgroup analyses to decrease clinical heterogeneity. An analysis of the effect of treatment with paricalcitol on the reduction in PTH is plotted in Figure 3. The pooled risk ratio for a decrease in PTH was statistically significant (RR, 6.37; 95% CI, 4.64–8.74; P<0.001; Figure 3).

Overall, our meta-analysis indicated that treatment with paricalcitol agents had a significant effect on PTH compared with the control group and induced a greater reduction in PTH.

Effects on Serum Ca Levels and Serum Phosphorus Levels

Five studies involving 644 patients have been published on the effect of paricalcitol therapy on serum Ca levels in patients with CKD (9,19,20,22,24). Three-hundred and ninety-four patients were assigned to the treatment groups and 250 patients were assigned to the placebo groups. Five studies on paricalcitol therapy were small sample trials that reported a number of patients with hypercalcemia (defined as serum Ca levels >11.0 mg/dl) at the end of treatment with paricalcitol.

According to our meta-analysis, in which the weight of individual studies was taken into account, we found that the RR for hypercalcemia associated with paricalcitol use was 2.25 (5 trials; 644 patients; RR, 2.25; 95% CI, 0.81–6.26; P=0.12; Figure 4).

Although we contacted the investigators of the individual studies, inadequate data were available for serum phosphorus. Only one study (21) reported end of treatment serum phosphorus. Five of nine studies reported no effects on serum phosphorus after paricalcitol therapy and thus were not in a extractable format for this meta-analysis (20–24).

Adverse Effects of Treatment

For paricalcitol treatments groups versus control groups, six studies of nine RCTs reported treatment-related adverse effects and serious adverse events of treatment (9,20,22,23,26,27). The numbers of adverse events was similar between the different study arms (6 trials; 452 patients; RR, 1.07; 95% CI, 0.84–1.36; P=0.72) (heterogeneity χ²=6.53; P=0.59; Figure 5). However, only five studies...
<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Baseline Kidney Disease</th>
<th>Drugs</th>
<th>Baseline Characteristics</th>
<th>Follow-Up</th>
<th>Primary Outcome</th>
<th>No. of Participants (Intervention/Control)</th>
<th>Sum of Jadad Score</th>
<th>ITT</th>
<th>Location Concealment</th>
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<tbody>
<tr>
<td>Moe et al. (20)</td>
<td>CKD stage 5 HD patients</td>
<td>Intravenously at doses 4 μg; 3 times weekly</td>
<td>Placebo iPTH level &lt;200 pg/ml; age &gt;18 yr</td>
<td>12 wk</td>
<td>Assessments of immune function</td>
<td>16/15</td>
<td>3</td>
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<td>Martin et al. (21)</td>
<td>CKD stage 5 HD patients</td>
<td>Intravenously at doses ranging from 0.04 to 0.24 μg/kg; 3 times weekly</td>
<td>Placebo iPTH levels &gt;400 pg/ml; serum calcium between 8.0 and 10.0 mg/dl; age 22–90 yr</td>
<td>12 wk</td>
<td>A decrease in iPTH of at least 30%</td>
<td>40/38</td>
<td>3</td>
<td>No</td>
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<td>Llach et al. (22)</td>
<td>CKD stage 5 HD patients</td>
<td>Intravenously at doses ranging from 0.04 to 0.24 μg/kg; 3 times weekly</td>
<td>Placebo iPTH level &gt;300 pg/ml; age &gt;18 yr</td>
<td>4 wk</td>
<td>A 30% reduction from maximum baseline in iPTH</td>
<td>22/13</td>
<td>3</td>
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<td>Unknown</td>
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<td>Greenbaum et al. (23)</td>
<td>CKD stage 5 HD patients</td>
<td>Intravenously at doses of 0.04 μg/kg if iPTH level &gt;500 pg/ml; 0.08 g/kg if iPTH level &gt;500 pg/ml</td>
<td>Placebo iPTH level ≥300 pg/ml; age &gt;18 yr</td>
<td>12 wk</td>
<td>2 consecutive 30% decreases from baseline in iPTH levels</td>
<td>15/14</td>
<td>4</td>
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<td>Ross et al. (24)</td>
<td>CKD stage 5 HD or PD patients</td>
<td>2 μg or 4 μg paricalcitol once a week</td>
<td>Placebo iPTH level ≥300 pg/ml; serum calcium level of 8.0–10.5 mg/dl</td>
<td>12 wk</td>
<td>2 consecutive 30% decreases from baseline in iPTH levels</td>
<td>61/27</td>
<td>4</td>
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<td>Unknown</td>
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<td>Coyne et al. (19)</td>
<td>CKD stages 3 and 4</td>
<td>Oral paricalcitol mean dosage 9.5 μg/wk</td>
<td>Placebo iPTH ≥150 pg/ml; eGFR between 15 to 60 ml/min; age ≥18 yr</td>
<td>24 wk</td>
<td>2 consecutive 30% decreases from baseline in iPTH levels</td>
<td>107/113</td>
<td>3</td>
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<td>de Zeeuw et al. (9)</td>
<td>CKD stages 2–4 (type 2 diabetes)</td>
<td>Oral 1 μg or 2 μg paricalcitol once daily</td>
<td>Placebo</td>
<td>UACR of 11–339 mg/mmol and eGFR of 15–90 ml/min, and stable doses of ACE inhibitors or ARBs for ≥3 mo</td>
<td>60 d</td>
<td>Change in UACR during treatment</td>
<td>184/88</td>
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<td>Agarwal et al. (25)</td>
<td>CKD stages 3 and 4</td>
<td>Oral paricalcitol mean dosage 9.5 μg/wk</td>
<td>Placebo</td>
<td>iPTH ≥150 pg/mL; eGFR between 15 and 60 ml/min; age ≥18 yr</td>
<td>24 wk</td>
<td>Proteinuria</td>
<td>57/61</td>
<td>3</td>
<td>Yes</td>
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<td>Fishbane et al. (26)</td>
<td>CKD stages 2–4</td>
<td>Oral paricalcitol 1 μg once daily</td>
<td>Placebo</td>
<td>Proteinuria &gt;0.4 g/d; eGFR of 15–90 ml/min; iPTH level ≥20 pg/ml and &gt;250 pg/mL; age 18–85 yr</td>
<td>6 mo</td>
<td>Change in UACR during treatment</td>
<td>28/27</td>
<td>5</td>
<td>Yes</td>
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<td>Alborzi et al. (27)</td>
<td>CKD stages 3 and 4</td>
<td>Oral 1 μg or 2 μg paricalcitol once daily</td>
<td>Placebo</td>
<td>age ≥18 yr; eGFR &gt;30 ml/min; a stable dose of an ACE inhibitor/ARB for 1 mo</td>
<td>1 mo</td>
<td>Proteinuria</td>
<td>16/8</td>
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RCT, randomized controlled trial; ITT, intention-to-treat analysis; HD, hemodialysis; iPTH, intact parathyroid hormone; PD, peritoneal dialysis; eGFR, estimated GFR; UACR, urine albumin/creatinine ratio; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
listed these adverse events and serious adverse events in detail (9,20,22,23,26). Events in the placebo group included upper respiratory tract infection, cough, pain, and abdominal cramps. In the paricalcitol group, adverse effects included headache, rash, edema, and vomiting. Serious adverse events such as coronary artery disease, cerebrovascular accident, and ARF were seen in the placebo group and in the paricalcitol group. According to our meta-analysis, there was a nonsignificant difference between the paricalcitol treatment groups and control groups with respect to cough, edema, decreased iPTH, and cardiovascular events (Figure 6).

Sensitivity Analyses and Publication Bias

Our analyses were robust in both the choice of models and the statistical methods. The substitution of a random-effects model for a fixed model did not change our initial qualitative interpretation of the pooled treatment effect of
paricalcitol on iPTH and proteinuria. Nine studies were inadequate to detect publication bias.

Discussion
This study reviewed existing RCTs to evaluate the effect of the new vitamin D compound, paricalcitol, in the treatment of patients with CKD and ESRD. The results suggest that paricalcitol suppressed iPTH and lowered proteinuria in patients with CKD without an increased risk of adverse events. Although we also found a trend toward increased hypercalcemia, this did not reach statistical significance but may be clinically relevant.

Evidence-based recommendations for the management of CKD using vitamin D compounds have been published (28–30) and the data of 76 trials suggest that the value of vitamin D treatment in patients with CKD remains uncertain. The study by Palmer et al. (28–30) included treatment with calcitriol and the newer vitamin D compounds paricalcitol, maxacalcitol, and doxercalciferol, which led to greater clinical heterogeneity. However, it is still controversial whether any type of vitamin D therapy is beneficial in CKD patients. Two recent epidemiologic studies (8,9) revealed a potentially important systemic role for paricalcitol in patients with CKD. These studies increased our interest in paricalcitol. We identified nine RCTs that evaluated the effects of the newer vitamin D compound, paricalcitol, on PTH and proteinuria in nearly 832 participants. Overall, paricalcitol therapy was well tolerated with minimal side effects, and may effectively decrease PTH by 30%. In fact, some head-to-head studies also suggest that paricalcitol reduces PTH levels more rapidly, with fewer episodes of hyperphosphatemia, than calcitriol (31).

Two RCTs showed that bone-specific alkaline phosphatase levels decreased in the paricalcitol group and...
increased in the placebo group in dialysis patients (19,23). Bone-specific alkaline phosphatase is one of the markers of bone turnover. The reductions in PTH with paricalcitol treatment were accompanied by changes in the bone turnover biomarkers, alkaline phosphatase, suggesting normalization of a high bone turnover (32).

This meta-analysis also showed that paricalcitol treatment reduced the severity of urinary protein excretion. No

**Figure 6.** Detailed comparison of paricalcitol versus controls on number of patients with adverse events.
studies have compared native vitamin D for the reduction of proteinuria and similar benefits may be seen with native or other newer vitamin D compounds.

The test for heterogeneity was not powerful enough due to the small number of studies included in the meta-analysis. It is possible that the different study end points with regard to reduction in proteinuria from baseline caused this clinical heterogeneity.

Paricalcitol seems to have many mechanisms of action for lowering of PTH, because activation of the vitamin D receptor intervenes in pathways with well known associations with the regulation of calcium and phosphorus and bone mineralization. However, the mechanisms of action of paricalcitol involved in the reduction of proteinuria are unclear. Results of experimental studies suggest that renoprotection by reducing proteinuria is caused by suppression of renin transcription (33), reduction in podocyte injury, antiproliferative effects, or antifibrotic effects, or a combination of these effects (34).

Effective treatments that decrease proteinuria seem to protect renal function, slowing the subsequent loss in GFR (35). Evidence-based recommendations for the management of CKD show that effective therapies include ACE inhibitors and ARBs. However, there is clearly a need for additional effective treatments if a decrease in the incidence of progressive renal disease and ESRD is to be achieved. Paricalcitol may be an important adjunctive treatment, providing optimum management of renal osteodystrophy, with little hypercalcemia, and lowering of residual albuminuria. Therefore, it is suggested that paricalcitol may have a wider therapeutic window for patients with stage 2–5 CKD.

Although our meta-analysis provides recommendations for paricalcitol treatment in CKD patients, our meta-analysis has several limitations that should be considered. First, the dose and type of drug (intravenous vitamin D and oral treatment; i.e., the agents used in the paricalcitol treatment group) were different. In addition, the primary end points of the studies were different. The different study end points with regard to reduction in proteinuria and PTH from baseline caused clinical heterogeneity. Because the study periods were not long enough to evaluate this slowly progressive chronic disease, some studies only assessed proteinuria but did not assess the true outcome of renal death (defined as ESRD). Long-term follow-up studies that treat the true outcome might yield different results. Finally, most of the studies included patients who were receiving concomitant drugs, such as RAS blockers. Although we included studies in which patients received these concomitant drugs for both the intervention and control groups, studies to assess the effect of paricalcitol agents alone in patients who are not receiving concomitant therapy are needed.

Findings from this meta-analysis suggest that paricalcitol significantly reduced proteinuria and PTH with few adverse events in patients with renal disease. A trend toward increased hypercalcemia with paricalcitol therapy did not reach statistical significance but may be clinically relevant. The significant limitations of this meta-analysis as outlined above must be stressed when evaluating these results in a clinical context. A randomized trial is needed to determine whether paricalcitol affects the development of ESRD or mortality.

Disclosures
None.

References


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J. Cheng and W.Z. contributed equally to this work.

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