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Original Investigation

Oral Calcitriol for Reduction of Proteinuria in Patients With IgA Nephropathy: A Randomized Controlled Trial

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Background: Vitamin D has shown efficacy in the reduction of proteinuria in patients with chronic kidney disease. This study aimed to determine the effect of calcitriol on urinary protein excretion in patients with immunoglobulin A (IgA) nephropathy.

Study Design: Open-label, non–placebo-controlled, randomized study.

Setting & Participants: 50 patients with IgA nephropathy were enrolled. The main criterion for inclusion was urinary protein excretion >0.8 g/d after renin-angiotensin system–inhibitor treatment for at least 3 months.

Intervention: Patients were randomly assigned (1:1) to receive 2 doses (0.5 μg) of calcitriol per week or no treatment for 48 weeks.

Outcomes: The primary end point was to compare change in 24-hour urinary protein excretion from baseline to last measurement during treatment.

Measurements: Every 8 weeks, there was measurement of 24-hour urinary protein excretion, serum calcium, serum phosphorus, serum creatinine, and intact parathyroid hormone.

Results: Measurement of the primary end point showed changes in urinary protein excretion of +21% (from 1.29 to 1.58 g/24 h; 95% CI, −9% to +52%) in the control group and −19% (from 1.60 to 1.30 g/24 h; 95% CI, −42% to +4%) in the calcitriol-treated group. There was a significant decrease in proteinuria in the calcitriol-treated group compared with the control group (difference between groups, 41%; 95% CI, 5%-79%; $P = 0.03$). The secondary end point of achieving at least a 15% decrease in proteinuria was attained by 7 of 24 (29%) controls and 17 of 26 (65%) of those treated with calcitriol ($P = 0.02$). No significant differences were observed in decrease in estimated glomerular filtration rate and change in blood pressure between the 2 groups. The incidence of recorded adverse events was similar between the 2 groups.

Limitations: Small and non–placebo-controlled study.

Conclusions: The addition of calcitriol to a renin-angiotensin system inhibitor resulted in a safe decrease in proteinuria in patients with IgA nephropathy.

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INDEX WORDS: Immunoglobulin A (IgA) nephropathy; proteinuria; calcitriol; renin-angiotensin system.

Immunoglobulin A (IgA) nephropathy is the most common form of primary glomerulonephritis globally.[1] Several studies have indicated that a proportion (6%-43%) of patients with IgA nephropathy reach end-stage kidney disease within 10 years.[2-4] Clinical risk factors for progression are identified as hypertension, proteinuria, decreased kidney function, and histologic lesions at presentation.[2,3,5]

Although there is no universally accepted optimal therapy for IgA nephropathy, currently established treatments include full renin-angiotensin system (RAS) inhibition and optimal blood pressure control for patients with proteinuria and/or hypertension. However, a substantial risk of progression remains even when these therapies are used.[6-8] Corticosteroid treatment is controversial,[9,10] and widespread use of this approach in clinical practice is limited by toxicity.

Recent studies have shown broad-ranging activities of vitamin D that extend beyond the regulation of calcium and phosphorus metabolism mediated by the vitamin D receptor. These so-called noncalcemic activities include regulation of renal and cardiovascular functions and modulation of immune responses.[11] Experimental data have indicated that vitamin D analogues mediate a decrease in albuminuria and slow the progression of kidney injury through activation of the vitamin D receptor in several animal models of kidney disease.[12-14] The effects of vitamin D analogues are thought to target the nuclear factor κB pathway and the RAS.[15,16]

The VITAL (Selective Vitamin D Receptor Activator [Paricalcitol] for Albuminuria Lowering) Study conducted by de Zeeuw et al[17] investigated the effects

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of selective vitamin D receptor activation by paricalcitol for a decrease in albuminuria in patients with type 2 diabetes. This study showed that the addition of 2 μg/d of paricalcitol to RAS inhibition safely decreased residual albuminuria in patients with diabetic kidney disease and resulted in a beneficial decrease in residual renal risk in patients with diabetes.[17]

However, the effects of this strategy in patients with IgA nephropathy are unknown. A previous small (n = 10) noncontrolled trial reported that twice-weekly oral doses of calcitriol produced a modest antiproteinuric effect that was accompanied by a decrease in serum transforming growth factor β (TGFβ).[18] However, the study design and small sample size used render the data inconclusive, and the efficacy of vitamin D or its analogues in patients with IgA nephropathy remains to be investigated in a large randomized controlled trial.

In this study, a randomized trial was carried out to investigate the efficacy of calcitriol in the reduction of proteinuria in patients with IgA nephropathy who were receiving stable treatment with an angiotensin-converting enzyme (ACE) inhibitor and/or angiotensin receptor blocker (ARB). Furthermore, the effects of calcitriol on estimated glomerular filtration rate (eGFR) and blood pressure were examined.

METHODS

Study Participants

Patients with biopsy-confirmed IgA nephropathy were enrolled from the IgA follow-up team in Peking University Institute of Nephrology. Patients 18 years and older with persistent proteinuria with protein excretion >0.8 g/d after optimal blood pressure control and full RAS inhibition for at least 3 months (in 3 consecutive samples monthly, and the last value was used as baseline calculation), eGFR (calculated by using the 4-variable MDRD [Modification of Diet in Renal Disease] Study equation[19]) >15 mL/min/1.73 m^2, and serum calcium levels <2.45 mmol/L were eligible for inclusion. Patients receiving treatment with corticosteroids or other immune suppressant drugs and those with other severe coexisting diseases, such as chronic liver disease, myocardial infarction, cerebrovascular accident, or malignant hypertension, were excluded. The study protocol was approved by an independent ethics committee at Peking University First Hospital, and written informed consent was obtained from all patients.

Treatment Regimen

This was an open-label randomized controlled trial of calcitriol in patients with biopsy-confirmed IgA nephropathy. The randomization sequence was computer generated by the statistician and preserved in a sealed envelope. Randomization was carried out by non–trial-associated staff. Patients in the study were assigned (1:1) to calcitriol or no treatment for 48 weeks. Patients received calcitriol (F. Hoffmann-La Roche, Ltd, Swiss, www.roche.com.cn), 0.5 μg, 2 times per week with at least 3 days between 2 doses. Patients were asked to report their pill consumption for evaluation of treatment adherence. Patients were recalled every 8 weeks for clinical evaluation and measurement of serum intact parathyroid hormone (iPTH), calcium, phosphorus, creatinine, and proteinuria. The calcitriol dose was maintained in the absence of adverse effects and a corrected serum calcium level <2.45 mmol/L. However, the calcitriol dose was immediately decreased or discontinued if corrected serum calcium level was >2.45 mmol/L. Adjustment for iPTH level was permitted according to the standard therapy guideline. In this study, no calcitriol dosage adjustments were required in response to iPTH level fluctuation. During the course of study, neither the ACE-inhibitor nor the ARB dose was changed. In the event of a requirement for intensification of blood pressure therapy, other antihypertensive treatments were initiated or increased in dose.

End Points

The difference in change in proteinuria between the baseline measurement and last study evaluation (48 weeks in study completers) between the 2 groups was predefined as the primary end point. Secondary efficacy measures were recorded from baseline to the last measurement during treatment and included the proportion of patients achieving at least a 15% decrease in proteinuria, an end point used in prior studies.[20] Mean change in eGFR and blood pressure was recorded as an additional efficacy measure. Proteinuria was determined by the pyrogallol red–molybdate method.

Statistical Analysis

The intention-to-treat data set included all randomly assigned patients who received at least one study treatment and had at least one postrandomization follow-up visit. The last value for patients who did not reach the final visit was carried forward for calculation. All patients received at least a single dose of study medication (calcitriol) and were included in the analysis as described. Continuous variables are reported as mean ± standard deviation. Categorical variables are reported in terms of frequency and percentage. The primary end point was comparison of change in proteinuria between the baseline measurement and last evaluation between the 2 groups. Absolute proteinuria changes were calculated by using the last measurement of 24-hour protein excretion minus the baseline measurement of proteinuria. The percentage of change in proteinuria was calculated by dividing the change in absolute proteinuria by the baseline measurement of proteinuria. The difference in changes between 2 groups was analyzed by t test. Changes in proteinuria over time between the 2 groups also were compared using analysis of variance for repeated measures. Analysis of variance and repeated-measures analyses also were used to analyze change from baseline in other continuous efficacy variables. Treatment group differences in response rates were assessed using Fisher exact test. Differences in the incidence of adverse events between treatment groups and other categorical variables were assessed using Fisher exact test. We calculated that a total sample size of 44 patients was needed for at least 80% power to detect an absolute difference in proteinuria of protein excretion of 0.3 ± 0.5 g/d from baseline to last measurement during treatment between the calcitriol treatment group and control group at a 2-sided significance level of 0.05.[20] A 10% dropout rate was considered and a total of 50 patients was needed. All statistical analyses were conducted using SAS, version 8.2 (www.sas.com), at a significance level of $P < 0.05$.

RESULTS

Demographic Data

Of 164 patients screened for eligibility, 50 were enrolled. All patients finished at least one visit after baseline. Four of these patients completed only 2-5 study visits. Three women became pregnant during the study period, and one of these women (in the calcitriol-treated group) discontinued treatment. All 3