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Brief Communication

Oral Paricalcitol Reduces the Prevalence of Posttransplant Hyperparathyroidism: Results of an Open Label Randomized Trial

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Postkidney transplant hyperparathyroidism is a significant problem. Vitamin D receptor agonists are known to suppress parathyroid hormone (PTH) secretion. We examined the effect of oral paricalcitol on posttransplant secondary hyperparathyroidism by conducting an open label randomized trial in which 100 incident kidney transplant recipients were randomized 1:1 to receive oral paricalcitol, 2 μg per day, for the first year posttransplant or no additional therapy. Serial measurements of serum PTH, calcium and bone alkaline phosphatase, 24-h urine calcium and bone density were performed. The primary endpoint was the frequency of hyperparathyroidism 1 year posttransplant. Eighty-seven patients completed the trial. One-year posttransplant, 29% of paricalcitol-treated subjects had hyperparathyroidism compared with 63% of untreated patients ($p = 0.0005$). Calcium supplementation was discontinued in two control and 15 treatment patients due to mild hypercalcemia or hypercalcuria. Paricalcitol was discontinued in four patients due to hypercalcuria/hypercalcemia and in one for preference. Two subjects required decreasing the dose of paricalcitol to 1 μg daily. Hypercalcemia was asymptomatic and reversible. Incidence of acute rejection, BK nephropathy and renal function at 1 year were similar between groups. Moderate renal allograft fibrosis was reduced in treated patients. Oral paricalcitol is effective in decreasing posttransplant hyperparathyroidism and may have beneficial effects on renal allograft histology.

Key words: Bone disease, hyperparathyroidism, kidney transplant, paricalcitol, vitamin D receptor agonist

Abbreviations: BAP, bone alkaline phosphatase; CKD, chronic kidney disease; FGF 23, fibroblast growth factor 23; GFR, glomerular filtration rate; IFTA, interstitial fibrosis and tubular atrophy; MDRD, modification of diet in renal disease; PTH, parathyroid hormone; VDR, vitamin D receptor

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Introduction

For patients with end-stage renal disease, kidney transplantation offers the best longevity and quality of life (1,2). Over the past several decades there has been remarkable improvement in short-term survival, whereas long-term morbidity and premature mortality postkidney transplantation remain a challenge (3). Kidney transplant recipients are at increased risk of cardiovascular disease (4), infections (5), neoplasia (6) and bone fractures (7). Bone mineral loss following transplantation of up to 7% has been observed in the first 6 months posttransplant and 1–2% annually thereafter in subjects receiving corticosteroid containing anti-rejection therapy (8). Posttransplant hyperparathyroidism, which occurs in 40–60% of kidney transplant recipients 1 year posttransplant, and in 20–40% of patients in long-term follow-up, contributes to this bone loss (9). Severe hyperparathyroidism necessitates parathyroidectomy in 2–5% of transplant recipients (10). Parathyroidectomy posttransplant is associated with allograft dysfunction (11).

Vitamin D receptor (VDR) agonists suppress parathyroid hormone (PTH) (12). Alfacalcidol and calcitriol administered for short durations following transplantation suppress PTH and preserve bone mineral density (13,14). Alfacalcidol also confers a survival advantage in dialysis patients (15). Paricalcitol-treated dialysis patients have reduced mortality compared to patients receiving calcitriol or no VDR therapy (16).

Most transplant patients have reduced renal function following transplantation and a high incidence of hyperparathyroidism that is similar to that found in patients with CKD stage 3–4. The safety of sustained use of VDR agonists is not known in the kidney transplant population. Given this, we conducted a randomized open label trial to evaluate the efficacy and safety of oral paricalcitol in reducing the prevalence of hyperparathyroidism in kidney transplant recipients 1 year after transplantation.

Methods

Study design

Prospective open label parallel two-arm trial with an efficacy endpoint. The Mayo Clinic Institutional Review Board approved the trial and it was registered at Clincaltrials.gov (NCT00587158). A data safety and monitoring board met every 6 months to review the adverse events.

Patient enrollment

One hundred patients were randomized 1:1. Eligible patients were: adults (≥18-years old), receiving their first or second compatible renal transplant and eligible for the corticosteroid avoidance immunosuppression protocol offered at Mayo Clinic. Exclusion criteria were: prior hypercalcemia, total 25-hydroxyvitamin D <10 ng/mL, recipients of multiple organs, or receiving a calcimimetic agent prior to transplant. All patients provided informed consent.

Randomization and intervention

Randomization occurred on Day 3 posttransplant. The randomization tables were generated at the trial onset by the statistician. Randomization was stratified on recipient gender and donor type. Alemtuzumab (30 mg single dose) and 1–4 doses of methylprednisolone (total dose <950 mg) were given for induction. Maintenance immunosuppression consisted of tacrolimus and mycophenolate mofetil. Patients in the treatment group started paricalcitol, 1 μg/day orally, on Day 3-posttransplant. This dose was increased on Day 15 posttransplant to 2 μg/day orally if no hypercalcemia developed. A calcium carbonate supplement containing 500 mg of elemental calcium was administered twice a day to patients in both groups.

The study concluded 1 year posttransplant, or if the patient declined further study participation, underwent a parathyroidectomy, lost the allograft or died. The patients were followed by the standard Mayo Clinic posttransplant practice.

Study end points

The primary study endpoint was hyperparathyroidism 1 year posttransplant. Hyperparathyroidism was defined as the need for a parathyroidectomy during the first year or PTH >65 pg/mL in the absence of hypocalcemia at the 1 year posttransplant protocol visit. Several secondary end points were defined *a priori* (Supplementary Table 1).

Measurement of PTH

Serum PTH concentration was measured by the Roche modular intact PTH assay (Roche Diagnostics Corp, Indianapolis, IN). The reference range for this assay is 15–65 pg/mL in healthy subjects.

Measurement of renal allograft function

Renal function was assessed by nonradioactive iothalamate GFR or creatinine clearance at the early posttransplant period (3 weeks) and end of the study (1 year) (17). More frequent estimates of GFR were made using the four-variable MDRD equation (18). We performed protocol allograft kidney biopsies at the time of implantation, 3–4 months posttransplant and at 1 year posttransplant as is the standard practice in our transplant program.

Renal histology

Specialist renal pathologists who were unaware of the patients' treatment allocation evaluated the renal allograft biopsies. Histological findings were scored according to the Banff '97 scheme (19). For details see the Supplementary Appendix.

Safety measures

Serum and 24-h urine calcium were measured at predefined intervals (Supplementary Appendix).

Statistical analysis

Data are presented as mean (±standard deviation) for normally distributed data and median (IQR) when highly skewed. Differences in proportions were assessed by the Fischer exact test. Statistical differences in means were assessed by Student's t-test when data were normally distributed or by the Wilcoxon test when the data were highly skewed. Analyses for the primary end point were performed by the intention-to-treat principle (all 100 patients who were randomized) where the last observation was carried forward for missing values. The per protocol population included patients who had a normal study completion visit whether or not they continued on therapy. STATA 12® (Stata Corp, College Station, TX, USA) and SAS 9.2 (SAS Institute, Cary, NC, USA) programs were used for the analyses.

Results

Patient characteristics

Baseline characteristics of the study cohort are shown in Table 1. The flow of patients through the trial is shown in Figure 1. The trial was conducted between January 2007 and November 2011.

Parathyroid, calcium/phosphorous and bone indices

Serum PTH concentration declined in both paricalcitol-treated and control (untreated) groups following transplantation. The trends in serum PTH concentrations are shown in Figure 2A. PTH concentrations were similar for the two groups at baseline but were lower in the paricalcitol group at 3-weeks, 3-months and 1 year posttransplant by a sequentially increasing margin. Two patients in the control group required parathyroidectomy. At the conclusion of the study, 15 patients (29%) in the paricalcitol group had hyperparathyroidism compared to 31 patients (63%) in the control group ($p = 0.0005$). The relative risk reduction of hyperparathyroidism was 54% and absolute risk reduction was 34% for the paricalcitol group. For the per-protocol population, hyperparathyroidism was present in 28% versus 61% (treatment vs. control, $p = 0.0013$). Paricalcitol-treated patients had, on average, serum PTH concentrations that were one-half of those seen in the untreated group.

Table 1: Baseline parameters of the study patients

	All patients (N = 100)	Control arm (N = 49)	Therapy arm (N = 51)
Age mean (±SD) years	48.1 (10.1)	47.7 (10.0)	48.5 (10.3)
Males N (%)	66 (66)	33 (67.3)	33 (64.7)
Caucasian race N (%)	91 (91)	42 (85.7)	49 (96.1)
Diabetes N (%)	22 (22)	12 (24.5)	10 (19.6)
Cause of ESRD			
APKD	30 (30)	14 (28.6)	16 (31.4)
Diabetic	18 (18)	10 (20.4)	8 (15.7)
GN	33 (33)	17 (34.7)	16 (31.4)
HTN	4 (4)	1 (2.0)	3 (5.9)
Other	15 (15)	7 (14.3)	8 (15.7)
Living donor	96 (96)	48 (98)	48 (94.1)
First transplant N (%)	97(97.0)	47 (95.9)	50 (98.0)
Preemptive transplant N (%)	51 (51)	24 (48.9)	57 (52.9)
Duration of dialysis months	0 [0, 10]	0 [0, 10]	0 [0, 9]
Duration of dialysis months (excluding preemptives)	11 [5, 26]	11 [6, 21]	11 [5, 27]
Pre Tx PTH (pg/mL)	206 [130, 295]	233 [136, 341]	171 [128, 278]

Trends in serum calcium, phosphorus and the calcium X phosphorus product are shown in Table 2. Trends in urine calcium excretion are shown in Figure 2B. In the paricalcitol group, median urine calcium excretion was higher than in the control group by 3 weeks posttransplant and remained so throughout the study period but did not exceed 250 mg/day.

Mean hip and lumbar spine t-scores, changes in mean t-scores and proportions of subjects with osteopenia of hip and lumbar spine at 3 weeks and 1 year posttransplant were similar in the two groups (Table 2). Trends in serum bone alkaline phosphatase (BAP) levels are shown in Figure 2C. After adjusting for baseline levels there was no significant difference in BAP between the groups overtime.

Trends in transplant outcomes, renal function and graft histology

One patient, in the treatment group died from a nondrug-related cause. Death occurred 8 days posttransplant and was attributed to disruption of the vascular anastomosis. No other graft losses occurred. There were five biopsy-proven rejection episodes in the control group and four in the paricalcitol group ($p = 0.68$) in the 100 study patients during the study period. All rejection episodes responded to treatment. One patient in the paricalcitol arm developed polyomavirus (BK) nephropathy. This was detected on a surveillance biopsy at 4 months and resolved (negative blood PCR and stable graft function) with decreased immunosuppression and cidofovir infusions.

The measured and estimated glomerular filtration rates were similar for paricalcitol and control groups at 21, 90 and 365 days posttransplantation (Table 2 and Figure 3A and B). Histological abnormalities at implantation and 1 year posttransplant are summarized in Table 2. IFTA (ci > 0 and/or ct > 0) at time zero or 12 months did not differ between the groups and was within ranges previously reported from our center (20). Control group patients had higher frequency of moderate to severe interstitial fibrosis (ci ≥ 2) however, and numerically higher frequency of inflammation (i or t >0) at 1 year than the paricalcitol group (10.5% vs. 0% $p = 0.04$) and (24% vs. 11% $p = 0.13$), respectively. Proteinuria at 1 year was no different between groups (Table 2).

Adverse events

No patient developed clinical urolithiasis or severe hypercalcemia (total serum calcium >11 mg/dL with symptoms). No patient had notable nephrocalcinosis. Mild hypercalcemia occurred at some time posttransplant in 20% of paricalcitol-treated patients and 6% of controls. Significant hypercalciuria (24-h urine calcium >500 mg/24 h) occurred in four patients in the paricalcitol group. No serious adverse events were attributed to the study medication, and of the adverse events recorded; only mild, reversible hypercalcemia and hypercalciuria were attributed to paricalcitol. Calcium supplementation was discontinued in 15 (29%) treatment patients and 2 (4%) control patients due to hypercalcemia or hypercalcuria. In 5 (10%) patients, paricalcitol was discontinued. In one patient this was at the request of the patient's primary care physician. The patient had a history of seizure disorder and the physician did not want the patient receiving unnecessary medications. In two cases, paricalcitol was reduced from 2 to 1 μg/day. A complete list of serious adverse events and adverse events is provided in Table 3. A higher proportion of paricalcitol treated patients reported an adverse event (69% vs. 41% $p = 0.009$) and serious adverse event (53% vs. 33% $p = 0.05$).

Discussion

In this randomized controlled trial, we observed a greater reduction in PTH concentrations and a significantly lower prevalence of hyperparathyroidism (29% vs. 63%) at 1 year

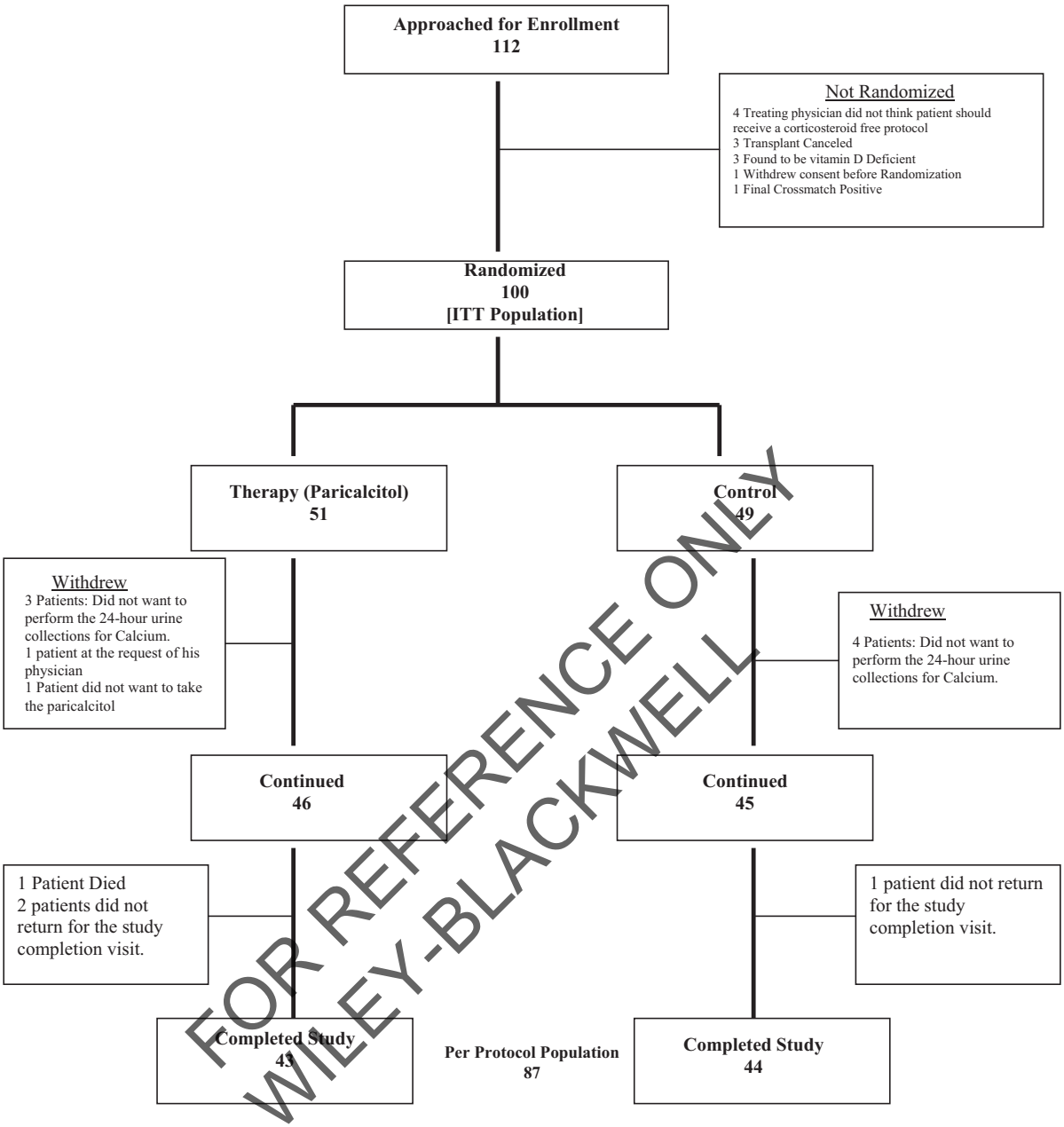

Figure 1: Diagram showing the flow of patients through the trial. ITT = intention to treat.

following transplantation in paricalcitol-treated patients. In the paricalcitol-treated group, the median serum PTH concentration was about one-half of that observed in the control group (42 vs. 85 pg/mL). The trend-lines of the two groups for serum PTH concentration continued to diverge between 3 weeks and 1 year suggesting that further prolongation of VDR agonist therapy might be associated with additional benefit compared to no active therapy. Overall, paricalcitol effected a 54% relative risk reduction of hyperparathyroidism at 1 year posttransplant. This is similar to the salutary effect of paricalcitol on hyperparathyroidism in stage 3–4 CKD (21).

Bone density at both hip and lumbar spine increased in both groups of patients from immediately posttransplant to 1 year, although osteopenia (t-score <-1.5) at hip and lumbar spine remained frequent (20–30%) at 1 year posttransplant. Despite the reduced frequency of persistent hyperparathyroidism in the paricalcitol group, we did not detect a difference in the proportion of patients with osteopenia or a

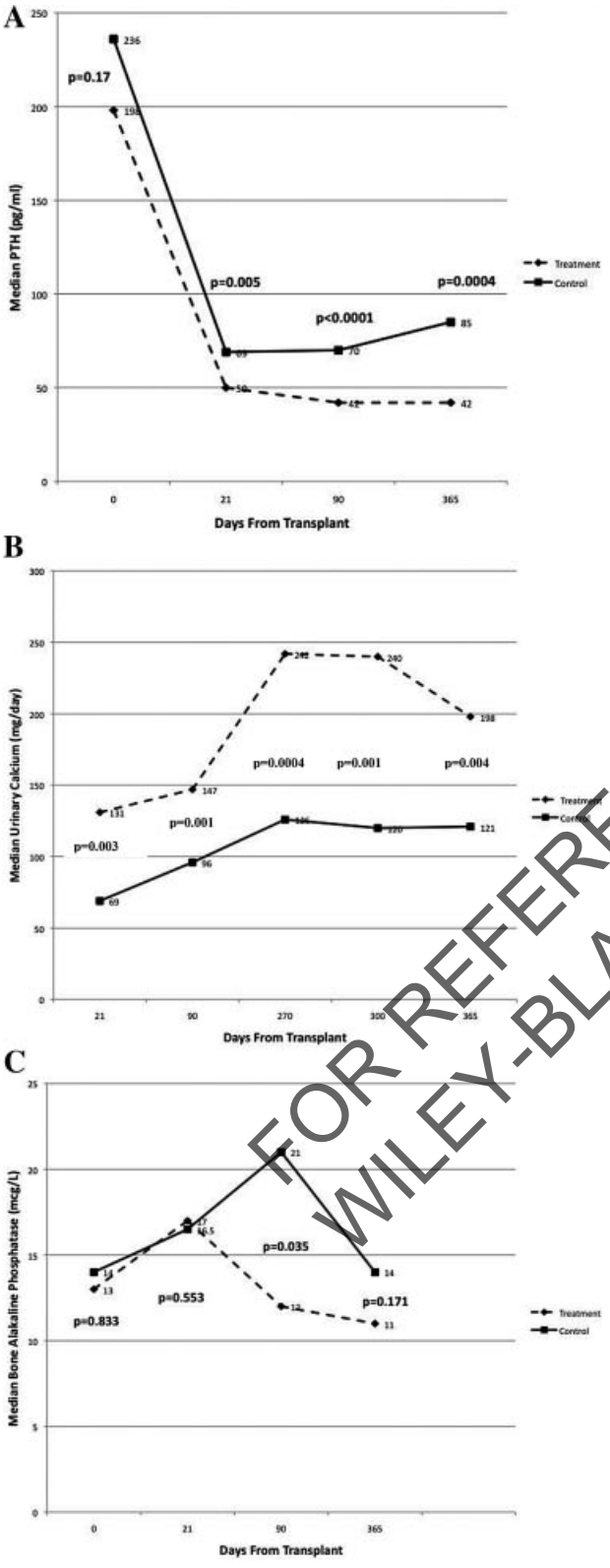

Figure 2: The change in (A) median parathyroid levels (B) 24-h urine calcium levels, (C) bone alkaline phosphatase at various time points during the study. p-Values are between groups (treatment vs. control).

change in bone mineral density between the groups. The lack of an observed difference in bone density in this cohort may indicate that suppression of secondary hyperparathyroidism by VDR agonist therapy does not exert a beneficial effect on posttransplant bone re-modeling in the context of corticosteroid-free immunosuppression. The possibility that the VDR agonist's effect on fibroblast growth factor 23 (FGF 23) levels in this setting could also be a factor and may explain the trend of lower phosphorus in the treatment arm (22). A larger trial with a longer period of therapy and follow-up will be necessary to accurately assess the potential effect of PTH suppression by VDR agonist therapy on long-term bone integrity in transplant recipients. The measurement of FGF 23 levels will also be of high interest in elucidating the effect of VDR agonist therapy on bone health.

The safety of paricalcitol therapy following kidney transplantation has not been stringently evaluated prior to the current study. We demonstrated that paricalcitol was well tolerated and did not cause serious adverse events with careful monitoring. A dose of 2 μg daily accompanied by oral calcium supplementation was associated with mild hypercalcemia and increased urine calcium excretion in some subjects. These events were readily reversible by withdrawal of calcium supplement and, in some cases, discontinuation of paricalcitol. Reintroduction of paricalcitol at a lower dose was possible following reversal of hypercalcemia. Importantly, hyperphosphatemia and raised calcium X phosphorous product did not occur in paricalcitol-treated patients and, in fact, there was a trend towards lower serum phosphorus concentration in the treated group throughout the first posttransplant year. This may also point to the role of FGF 23 modulation in this patient population (22). Monitoring of urine calcium excretion during VDR agonist therapy is of specific importance in the setting of kidney transplantation given recent reports highlighting the link between nephrocalcinosis in transplant biopsies and reduced GFR and increased interstitial fibrosis (23). In this study, an increase in urinary calcium was apparent in the paricalcitol group compared to controls from as early as 3-weeks. In general, however, severe hypercalcuria was not observed and group median levels remained below 250 mg/day. This emphasizes however the importance of careful monitoring of this therapy in the transplant population. Reassuringly, we did not observe clinical allograft urolithiasis in any subject and histological evidence of significant nephrocalcinosis was not observed in any of the 1 year biopsies.

Renal function measured by iothalamate clearance or creatinine clearance was no different between groups. The lack of difference in the measured GFR is contrary to previous reports in which paricalcitol was associated with a decrease in estimated GFR (24). This may be a consequence of the regular urinary calcium estimation with the accompanying adjustment in dose to avoid protracted hypercalcemia and hypercalcuria. Our observations indicate

Table 2: Clinical parameters of the study patients at different time points

	All patients	Treatment	Control	p-Value
Renal allograft function				
3-week uGFR (±SD) mL/min	58.9 (14.1)	60.5 (14.2)	57.3(14.0)	0.33
3-week cGFR (±SD) mL/min/1.73 m^2	50.9(14.4)	53.1 (15)	48.7 (13.7)	0.22
1-year uGFR (±SD) mL/min	65.4(17.0)	65.7(18.8)	65.0(15.5)	0.88
1-year cGFR (±SD) mL/min/1.73 m^2	54.3(14.3)	55.3(16.9)	53.3(11.5)	0.55
Delta cGFR (±SD) mL/min/1.73 m^2	5.0(12.7)	3.7(13.2)	6.4(12.3)	0.44
Delta uGFR (±SD) mL/min	8.4(14.9)	6.5(15.3)	10.3 (14.5)	0.33
3-week CrCl (±SD) mL/min/1.73 m^2	54.1(16.7)	46.7(15.1)	58.5(16.7)	0.22
1-year CrCl (±SD) mL/min/1.73 m^2	75.2(27.6)	65.0(22.1)	83.1(29.9)	0.22
Delta CrCl (±SD) mL/min/SA	19.5(24.2)	20.6(19.9)	18.9(27.8)	0.88
eGFR 3 weeks (±SD) mL/min/1.73 m^2	45.1 (12.9)	45.0 (15.4)	45.3(10.0)	0.99
eGFR 3 months (±SD) mL/min/1.73 m^2	47.5(13.1)	48.0(12.3)	47.0(14.0)	0.77
eGFR 1-year (±SD) mL/min/1.73 m^2	52.0 (14.7)	51.2(15.4)	52.7(14.1)	0.66
Delta eGFR (±SD)mL/min/1.73m^2	6.8(12.9)	6.2(10.4)	7.4(15.1)	0.66
24-h urine protein 3-weeks (±SD) mg/day	186 [117, 398]	169 [106, 421]	195 [117, 398]	0.83
24-h urine protein 1-year (±SD) mg/day	98 [58, 203]	91 [51, 177]	118 [66, 242]	0.21
24-h urine albumin 3-weeks (±SD) mg/day	27 [7, 90]	9 [5, 59]	90 [22, 285]	0.002
24-h urine albumin 1-year (±SD) mg/day	12 [0.1, 45]	11 [0.1, 31]	21 [0.1, 45]	0.66
Serum calcium and phosphorus:				
Serum calcium at 3 weeks (±SD) mg/dL	9.8 (0.5)	9.8(0.6)	9.8 (0.5)	0.99
Serum calcium at 3 months (±SD) mg/dL	9.7 (0.6)	9.8 (0.6)	9.3(0.5)	0.11
Serum calcium at 1-year (±SD) mg/dL	9.8(0.5)	9.9(0.5)	9.7(0.5)	$<$0.001
Serum phosphorus at 3 weeks (±SD) mg/dL	3.1(0.7)	3.0(0.8)	3.1(0.7)	0.44
Serum phosphorus at 3 months (±SD) mg/dL	3.0(0.7)	2.9(0.6)	3.2(0.7)	0.11
Serum phosphorus at 1-year (±SD) mg/dL	3.3(0.6)	3.2(0.6)	3.5(0.6)	0.11
Calcium phosphorus product 21 days (±SD)	30(7)	29 (7)	31 (7)	0.33
Calcium phosphorus product 90 days (±SD)	29 (7)	28 (5)	30 (7)	0.22
Calcium phosphorus product 365 days (±SD)	33 (6)	32 (6)	33 (7)	0.22
Total 25-hydroxyvitamin D at transplant (±SD) ng/mL	36 (14)	35 (13)	36 (14)	0.66
Total 25-hydroxyvitamin D at 365 days (±SD) ng/mL	37 (13)	38(14)	37 (12)	0.55
Bone density				
Lumbar spine T score at 21 days mean (±SD)	−0.73(1.38)	−0.82(1.43)	−0.63(1.34)	0.54
Lumbar spine T score at 365 days mean (±SD)	−0.38(1.35)	−0.52(1.44)	−0.25(1.26)	0.36
Delta lumbar Spine T score mean (±SD)	0.35(0.52)	0.35(0.58)	0.35(0.45)	0.98
Hip T score at 21 days mean (±SD)	−0.82(1.15)	−0.96(1.14)	−0.69(1.14)	0.27
Hip T score at 365 days mean (±SD)	−0.63(1.15)	−0.74(1.20)	−0.52(1.10)	0.39
Delta hip T score mean (±SD)	0.18(0.32)	0.21(0.36)	0.15(0.27)	0.41
Osteopenia of the hip at baseline N (%)[a]	25(29.4)	12(28.6)	13 (30.2)	0.99
Osteopenia of the hip at 1-year N (%)[a]	21(25.3)	12 (29.3)	9(21.4)	0.45
Osteopenia of the lumbar spine at baseline N (%)[a]	21(25.0)	12(29.3)	9 (20.9)	0.44
Osteopenia of the lumbar spine at One-year N (%)[a]	21(25.3)	12(29.3)	9 (21.4)	0.44
Renal allograft histology				
Acute cellular rejections[b]	9 (9.0)	4 (7.8)	5 (10.2)	0.68
BK nephropathy	1 (1.0)	1 (2.0)	0 (0.0)	
Any inflammation at 12 months N (%)	13 (17.1)	4 (10.5)	9 (23.7)	0.22
IFTA at time 0 N (%)	16 (19.5)	8 (20.5)	8 (18.6)	1.00
IFTA at 1-year N (%)	44 (57.9)	21 (55.3)	23 (60.5)	0.82
Progression of IFTA N (%)	38 (52.8)	18 (51.4)	20 (54.1)	1.00
ci $>$ 0 time 0 N (%)	5 (6.0)	3 (7.5)	2 (4.7)	0.67
ci $>$ 0 one year N (%)	38 (50)	19 (50)	19 (50)	1.00
ci $\geq$ 2 time 0 N (%)	0 (0)	0 (0)	0 (0)	
ci $\geq$ 2 one year N (%)	4 (5.3)	0 (0)	4 (10.5)	0.04

[a]Osteopenia defined as t score ≤ -1.5.
[b]Includes borderline changes.

that oral paricalcitol can be administered up to 2 μg daily following kidney transplantation in the context of careful monitoring of serum calcium and with dose adjustments as needed without deleterious effects on renal function. In our opinion the routine use of a calcium supplement with paricalcitol may not be advisable in kidney transplant recipients given the episodes of hypercalcemia and hypercalcuria. Nonetheless adequacy of dietary calcium intake should be evaluated to avoid dietary calcium insufficiency that may have negative implications for bone health (25).

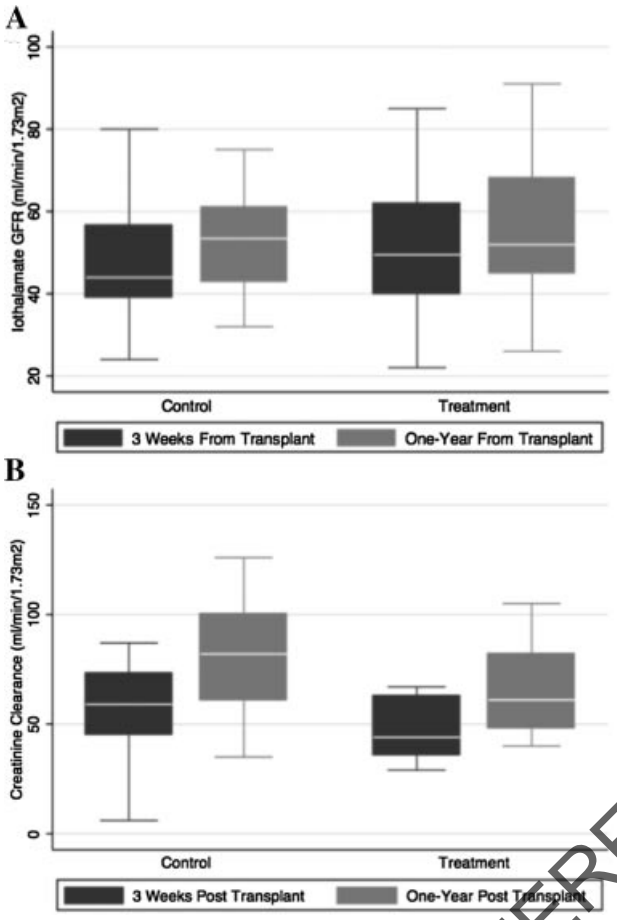

Figure 3: Box plots showing (A) iothalamate measured GFR and (B) creatinine clearance at dismissal from the early posttransplant clinic and 1-year posttransplant.

The increased numbers of S/AE reported in the paricalcitol arm were driven mainly by vascular complications (two pulmonary emboli, one vertebral artery dissection and two foot ulcers) and infections (primarily urinary tract). None of these were deemed to be related to the study drug. Surgical complications were more frequent in the control arm. It should be noted that this was an open label trial and, consequently there may have been an element of over-reporting in the therapy arm. Nonetheless, such findings warrant further investigation in prospective, double blind trials.

There has been considerable interest in recent years in the potential reno-protective effects of VDR agonist therapy in the setting of chronic kidney disease with evidence at preclinical and clinical level of anti-inflammatory, anti-fibrotic and anti-proteinuria effects (26). In contrast to results reported for subjects with type 2 diabetes mellitus and albuminuria (27), we did not observe lower protein excretion among paricalcitol-treated transplant recipients compared to controls 1 year posttransplant. Nonetheless, it remains possible that prolonged paricalcitol therapy will be associated with attenuation of proteinuria in transplants that develop chronic injury during long-term follow-up. Of further interest in this regard, while mild interstitial fibrosis was present in about half of all 1 year biopsies in both study groups, moderate interstitial fibrosis (ci $>$ 2) was observed in 4/38 biopsies in the control group, but was absent in the paricalcitol group ($p = 0.04$). Of the four cases with moderate fibrosis in the control group, three had prior acute cellular rejections. To be noted is that in the treatment arm there were four acute cellular rejections and one case of BK nephropathy and none of these had moderate or severe fibrosis at 1 year. Tacrolimus exposure between treatment and control groups was similar (Supplementary Figure 1). This finding is in keeping with reported effects of

Table 3: Description of adverse events and serious adverse Events by system organ class (SOC)

SOC	All patients	Control	Treatment
Blood and lymphatic system disorders	Neutropneic fever 1*		Neutropneia 1*
Cardiac disorders	Afib 2	MI 1*	Orthostasis 1*
	Orothostasis 1*	Afib1*	Afib 1
	MI*		
Endocrine disorders	PTDM 6	PTDM 2	PTDM 4
Gastrointestinal disorders	Nausea, vomiting 1	Nausea/Vomiting 1*	Diarrhea 2
	Diarrhea 3	Diarrhea 1	
General disorders and administration site conditions	Fever 2	Fever 1*	Fever 1*
	Headache 1		Headache 1*
	Malaise 1		Malaise 1*
Hepatobiliary disorders	Liver cirrhosis		Liver cirrhosis 1*
Immune system disorders	Allergy to bactrim 1	Allergy to IVIg 1*	Allergy to bactrim 1
Metabolism and nutrition disorders	Allergy to IVIg		
	Gout1	Hyperkalemia 1*	Hyperkalemia 1*
	Hyperkalemia 2		Gout 1
	Symptomatic		Symptomatic
	Hypomagnesemia1		Hypomagnesemia1

(*Continued*)

Table 3: Continued

SOC	All patients	Control	Treatment
Musculoskeletal and connective tissue disorders	Fell in bathroom 1		Fell in bathroom 1
	Bone fracture 1		Bone fracture 1*
	Rt leg radicular pain 1		Rt leg radicular pain 1*
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Incidental RCC 2*	Breast CA 1*	Incidental RCC 2*
	Breast CA 1*		
Nervous system disorders	Seizure 1*		Seizure 1*
Psychiatric disorders	Depression1*	Depression1*	Paranoia 1*
	Paranoia 1*		
Renal and urinary disorders	AKI 2*	AKI 1*	AKI 1*
	Bladder urgency 1	GN 1	Bladder urgency 1
	GN2	Hydronephrosis 1*	GN 1
	Ureteral stensosis 5*		Hydronephrosis 4*
Surgical and medical procedures	Bilateral native nephrectomy 5	Bilateral native nephrectomy 1*	Bilateral native nephrectomy 4*
	Abdominal wall hematoma 1	Biopsy complication 1*	Hernia repair 4*
	Hernia repair 4	Surgical incision pain 1	Hysterectomy 1*
	Hysterectomy 1		MVA 1*
	MVA 1		Re-operation 1
	Re-operation 1		Ureteral revision 2*
Vascular disorders	PE 2*		PE 2*
	PVD 2*		PVD 2*
	Anastomotic rupture 1*		Anastomotic rupture 1*
	Vertebral artery dissection 1*		Vertebral artery dissection 1*
Injury, poisoning and procedural complications	Biopsy complication*	Biopsy Complication*	Chylous ascitis*
	Chylous ascitis*	Hematoma*	Lymphocele 2*
	Hematoma*	Surgical Incision Pain*	Ureteric revision 2*
	Lymphocele 4*	Lymphocele 2*	Wound complication 1*
	Surgical incision pain*	Ureteric revision 2*	
	Ureteric revision 4*	Wound complication 5 (2*)	
	Wound complication 6 (3*)		
Infections and infestations	Bacteremia 1*	Bacteremia 1*	BK nephropathy 1
	BK nephropathy 1	BK viremia 4	Bronchitis 1*
	Bronchitis 1*	CMV viremia 1*	C Diff 2 (1*)
	C diff 2 (1*)	Pneumonia 2 (1*)	CMV viremia 3 (1*)
	CMV 4(1*)	Pyelonephritis 1	Gastroenteritis 1*
	Gastroenteritis 1*	TB 1*	Herpes Zoster 1
	Herpes Zoster 1	URI 1*	Penumonia 1
	Pneumonia 3 (1*)		Scrotal cellulitis 1*
	Pyelnoephritis 1		Sinusitis 1
	Scrotal cellulitis 1*		Wound infection 2*
	Sinusitis 1		UTI 15 (*5)
	TB 1*		
	URI 1*		
	Wound infection 2*		
	UTI 15 (*5)		

*SAE, (*n) number qualifying as SAE within the diagnosis.
MI, myocardial infarction; IVIg, intravenous immunoglobulin, PTDM, posttransplant diabetes mellitus; TB, active tuberculosis; URI, upper respiratory infection; CA, cancer.

paricalcitol in inhibiting interstitial fibrosis in animal models of kidney injury (28). In the analysis of 1 year histology, there was a numerically lower frequency of tubulo-interstitial inflammation in the paricalcitol group compared to controls (10.5% vs. 23.7%, $p = 0.13$). The overall number of biopsies with inflammation however was small precluding adequate assessment of the difference. It is, however, of particular interest given the reported immune modulating effects of VDR therapy (29). The frequency of cellular inflammation at 1 year posttransplant in the control group is

higher than has been previously observed in our program (20,30)—possibly as a consequence of the corticosteroid free immunosuppression regimen used in this study. Although this trial was not designed to robustly address the potential for paricalcitol therapy to modulate interstitial inflammation and fibrosis in kidney transplants, it does provide impetus for further, long-term studies to determine whether VDR agonist therapy mediates favorable effects on chronic allograft damage. There were no graft losses not due to patient death, and no differences were observed in the frequency of acute rejection episodes during the first year posttransplant.

The strengths of our study include follow-up and care by a small group of transplant nephrologists and surgeons using protocol-based posttransplant care; the performance of protocol renal biopsies at the time of transplant and 1 year later; the accurate measurement of GFR by iothalamate methods and collection of 24-h urine specimens for measurement of urinary calcium and protein. The limitations of the study include the predominance of living kidney donor recipients and a low representation of non-Caucasians. Although this may limit the applicability of our findings to populations other than the one studied, the increased homogeneity of the cohort limits unknown confounders.

In conclusion, in a randomized trial of paricalcitol compared to no additional therapy in kidney transplant recipients, the frequency of posttransplant hyperparathyroidism at 1 year was reduced by more than half. With appropriate monitoring of urine and serum calcium, paricalcitol can be administered to kidney transplant recipients with preservation of renal function. Longer term studies of posttransplant VDR agonist therapy are required to determine whether suppression of hyperparathyroidism is associated with significant benefits for bone and cardiovascular health and whether putative salutary influences on renal integrity occur.

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Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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Supporting Information

Additional supporting information may be found in the online version of this article.

Figure S1: Trough tacrolimus levels posttransplant.

Supplementary Methods: Assessment of Renal Histology and Safety Measures

Table S1: Secondary endpoints