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CINACALCET IMPROVES BONE DENSITY IN POST KIDNEY TRANSPLANT HYPERPARATHYROIDISM

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Abstract

The recent availability of cinacalcet has provided a possible alternative to parathyroidectomy in kidney transplant patients with persistent hyperparathyroidism, but its effect on bone mass density (BMD) is unknown. From our database containing 163 kidney transplants performed at our center from 1999–2007, we compared recipients who received cinacalcet for persistent hypercalcemia and hyperparathyroidism following renal tx (n=8; CIN) with up to 2 other post tx patients matched for age, sex, race, and graft function (n=15; CON). The outcome of the study was BMD changes from baseline to 12, 24, and 36 months post renal tx. Repeated Measures Mixed model was used to assess the difference of BMD change between two groups. Cinacalcet therapy was started at a median of 9 months (range; 1, 24 months) post tx with a mean dose 56±29 mg/d (mean duration; 1.6 years, range; 1, 2.1). Cinacalcet therapy was associated with significant reduction of serum calcium compared to control. Cinacalcet therapy was associated with greater BMD increase at the hip over the 36-month post transplant period. Cinacalcet was well tolerated. Our results suggest that cinacalcet may have a small but favorable effect on bone density following kidney transplantation.

INTRODUCTION

The prolonged hyperparathyroidism (HPT) and hypercalcemia in post kidney transplant recipients are associated with increased bone turnover and bone mass density (BMD) loss¹, worse graft outcome, and greater cardiovascular morbidity and mortality.² Recently, studies using cinacalcet, a calcimimetic agent, after renal transplantation have shown a decline in PTH and calcium levels.^{3–6} It has also been suggested that cinacalcet may have a beneficial

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effect on preserving BMD in kidney transplant recipients, but these studies have been limited by the small size, short study duration, and lack of control treatment groups.⁷⁻⁹ The primary aim of this study was to determine the impact of cinacalcet on BMD measurement in spine, hip, and forearm in kidney graft recipients after up to two years of treatment. The secondary endpoints of the study were to determine the safety of cinacalcet and its effect on metabolic indices.

PATIENTS AND METHODS

Patients

This is a single-center retrospective analysis of prospective data involving 163 patients who have undergone kidney transplantation at the National Institutes of Health (NIH) between 1999 and 2007. All protocols required bone density measurement by dual-energy X-ray absorptiometry (DEXA) scans at baseline and annually following transplant. We reviewed our database to identify those who had been treated with cinacalcet for persistent hypercalcemia >10 mg/dL and increased parathyroid hormone levels >100 pg/mL. We excluded those who had <12 months of cinacalcet therapy, history of parathyroidectomy, and missing DEXA results. A total of 17 patients out of 163 patients at the NIH received cinacalcet therapy. Of these, nine patients were excluded for reasons listed above. After selecting 8 study patients (CIN), we then identified 1 to 2 age-, sex-, and race-matched controls (CON, n=15) per CIN in our NIH cohort. The primary outcome of the study was change of spine, hip, and forearm BMD from baseline to 12, 24, and 36 months post kidney transplantation. Secondary endpoints included actual values of relevant laboratory measurements at baseline and 1, 6, 12, 24 and 36 months, including serum creatinine, calcium, phosphorus, PTH, and alkaline phosphatase throughout the study period.

Statistical analysis

The changes of spine, hip, and forearm BMD from baseline were calculated at 12, 24, and 36 months post kidney transplantation. Repeated Measures Mixed Models (Proc Mixed SAS) were used to compare BMD changes and laboratory values between the two groups. All models included actual values at baseline, treatment, time, and interaction of treatment and time. Repeated Measures Mixed Models were also used to assess the actual level of laboratory variables between two groups at baseline and 1, 6, 12, 24 and 36 months. For each mixed model, an unstructured covariance structure was utilized and the least square means were estimated and compared at each time point. A random slope model (Proc Mixed) was also used to compare the slopes from month 12 to month 36 in the two groups and to test whether the slopes in each group were equal to zero. Statistical significance was assigned if *P* was less than 0.05. Data processing and statistical evaluations were completed by using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

The baseline and demographic characteristics of the cinacalcet and control groups are described in Table 1. The CIN group had a significantly longer duration of dialysis treatment preceding kidney transplantation compared to CON (*P* =0.002). In addition to methylprednisolone, the induction therapy included antithymocyte globulin, alemtuzumab, and daclizumab. Our patients were most commonly maintained on tacrolimus monotherapy. Other maintenance therapy regimen included combination of tacrolimus and mycophenolate mofetil, sirolimus and mycophenolate mofetil, and tacrolimus and sirolimus. By design, CIN patients had greater steroid burden during the study period.

The baseline and fourth-month post kidney transplant laboratory values are shown in Table 1. Cinacalcet therapy was initiated at a median of 9 months (range: 1, 24) post kidney transplant with a mean dose of 56 ± 29 mg/d. Four patients started cinacalcet within the first six months following the transplant and four patients began cinacalcet therapy between 12 and 24 months post transplant. The mean duration of cinacalcet therapy was 1.6 years (range; 1, 2.1 years).

Figure 1 shows the least square means of laboratory values estimated from mixed models. Both groups exhibited stable renal graft function over the three-year period. The most significant laboratory change associated with cinacalcet therapy was decrease in serum calcium, compared to the control group (Figure 1). The baseline bone density and T scores were not significantly different in both groups at the time of transplantation (Table 2). After adjusting for the baseline levels, the mixed model analysis suggested that the CIN patients had greater gain of BMD at several sites of hip over time (Figure 2 and Table 3). The absolute changes were small, however, and there were no significant changes of T scores following therapy. When comparing the change in slopes of BMD from month 12 through 36 (Table 3), CIN patients had significantly more positive slope at AP spine and most significant at the hip. CON patients' slopes were not significantly different from time 0 at all sites. Thus, cinacalcet therapy was associated with stabilization of BMD in treated patients compared to CON recipients. Cinacalcet was well tolerated. While cinacalcet therapy was associated with decrease in serum calcium levels in all patients, no patient developed symptomatic hypocalcemia. Three patients required dose reduction due to hypocalcemia of <8 mg/dL. One CIN patient developed a toe fracture and a CON patient had a knee fracture related to a fall. Another CON patient developed avascular necrosis of the hip. There was no obvious effect of cinacalcet on the tacrolimus level or the renal graft function.

DISCUSSION

Our study represents the first attempt to evaluate the effect of cinacalcet on bone density by comparing to age-, sex-, and race-matched controls in renal transplant recipients. Cinacalcet therapy was associated with reduction in serum calcium and PTH in our kidney transplant patients. Our study suggests that cinacalcet therapy is associated with increased bone density at hip in post kidney transplant patients with persistent hyperparathyroidism. Although the absolute change is too small to impact the T scores and the clinical status, the consistent trend for greater BMD gain in CIN is intriguing, particularly given that we have compared to a control group with significantly more favorable clinical attributes for bone health. CON patients had a shorter duration of dialysis, lower PTH and calcium levels, and lower overall steroid burden, all the factors associated with better preservation of BMD following kidney transplantation. Yet, CIN patients exhibited better preservation of BMD at the hip during the study period. Compared to CON patients whose slope of BMD change remained unchanged, CIN patients exhibited significant BMD gain between 12-36 months post kidney transplant at the hip and AP spine. Our finding is consistent with the previously published data to suggest that cinacalcet may improve BMD in post kidney transplant patients.

Our study has several important limitations. Foremost, this was a retrospective analysis of prospective data with a small sample size, with inherent biases in CIN and CON groups. We lacked randomization in our study design and thus did not have the ideal control group. We tried to address this issue by selecting controls with more favorable baseline attributes for bone health, such as shorter dialysis duration, to make it more difficult to observe positive effects of cinacalcet. In addition, because of its retrospective nature, all subjects in the study were started on cinacalcet at different points post transplant and were continued on the medication for variable durations, making direct comparison of outcome variables more challenging. Although we report the data analysis that includes up to three years of

observation, there were progressively fewer patients at each succeeding time point and thus the analysis had sequentially decreased power. We addressed this limitation by using Mixed Model to address the interaction between group assignment and duration of therapy. Nonetheless, none of these measures can fully adjust for the inherent problems of a retrospective design or a small sample size. Moreover, the absolute changes of BMD seen in our study were small, as shown in Table 2 and were not sufficient enough to significantly increase T scores.

In conclusion, cinacalcet may have a favorable effect on preserving BMD in kidney transplant patients and is well tolerated. Randomized controlled trials are needed to adequately evaluate long-term safety and efficacy of cinacalcet in kidney transplant population and to evaluate if cinacalcet can reduce clinically relevant endpoints, such as fracture and cardiovascular events.

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Figure 1.

Laboratory value changes over the study period. P values for interaction between group assignment (CIN vs. CON) and time by Mixed Model. Changes from baseline values are expressed by least square means and standard error. P values <0.05 denotes that the changes in laboratory measurements over time were significantly different between CIN and CON. Sample sizes for CIN at month 0, 12, 24, 36 are 8, 8, 8, 7 (PTH are available in 5 patients). Sample sizes for CON at month 0, 12, 24, 36 are 15, 15, 15, 11.

Figure 2.

Bone mass density changes from baseline. P values for interaction between group assignment (CIN vs. CON) and time by Mixed Model. Changes from baseline values are expressed by least square means and standard error. P values <0.05 denotes that BMD changes over time is significantly different between CIN and CON. Sample sizes for CIN at month 12, 24, 36 are 7, 7, 5. The CIN sample size is not 8 at months 12 and 24 because of missing values by two different patients. Sample sizes for CON at month 12, 24, 36 are 8, 14, 9.

Table 1

Baseline characteristics.

		CIN (n=8)	CON (n=15)	p [*]
Gender	Women	2 (25%)	3 (20%)	1.000
	Men	6 (75%)	12 (80%)	
Race	White	5 (63%)	12 (80%)	0.639
	Black	1 (13%)	1 (7%)	
	Other	2 (25%)	2 (13%)	
Age		44.9±15.0	44.3±13.5	1.000
BMI		26.3±4.9	28.2±4.8	0.458
Years on dialysis		6.4±5.2	1.4±1.9	0.002
Creatinine	Month 0	1.2±0.2	2.0±2.4	0.120
	Month 4	1.3±0.2	1.4±0.4	0.699
Phosphorus	Month 0	2.5±0.9	3.1±1.0	0.107
	Month 4	2.2±0.7	2.6±0.7	0.107
Calcium	Month 0	2.6±0.2	2.3±0.2	0.042
	Month 4	2.6±0.1	2.3±0.2	0.017
PTH	Month 0	405.4±366.2	171.7±134.0	0.015
	Month 4	145.6±39.5	77.7±39.2	0.032
Alkaline phosphatase	Month 0	113.1±49.2	85.3±41.7	0.079
	Month 4	159.9±64.8	128.1±48.3	0.403

* Fisher's exact test for categorical data, Wilcoxon test for continuous variables. Values expressed as mean±SD.

Table 2

Baseline bone density and T score mean values.

	CIN			CON		
	N	BMD (SD)	T score (SD)	N	BMD (SD)	T score (SD)
AP spine	8	1.05 (0.2)	-0.43 (1.6)	15	0.97 (0.1)	-1.01 (0.9)
Lateral Spine	8	0.81 (0.2)	-1.30 (0.9)	14	0.70 (0.1)	-1.61 (0.6)
Femoral Neck	7	0.81 (0.1)	-0.94 (0.7)	15	0.78 (0.1)	-1.12 (0.8)
Trochanter	7	0.75 (0.1)	-0.21 (0.5)	15	0.71 (0.1)	-0.51 (0.6)
Intertrochanter	7	1.18 (0.2)	-0.16 (0.9)	15	1.10 (0.1)	-0.49 (0.5)
Total Hip	7	0.98 (0.1)	-0.37 (0.7)	15	0.93 (0.1)	-0.66 (0.5)
Forearm	8	0.65 (0.1)	-1.87 (2.2)	15	0.74 (0.1)	-0.92 (1.2)

CIN, Cinacalcet group; CON, Control group; BMD, bone mass density expressed as Gm/cm^2 ; SD, standard deviation. At all sites of BMD measurement, there was no statistical difference between CIN and CON means (both BMD and T scores) at baseline by t test.

Table 3

The slope of BMD changes between 12 and 36 months post kidney transplantation.

	Cinacalcet			Control			CIN vs CON		
	Slope/yr	SE	p *	Slope/yr	SE	p *	p *	p **	p **
AP Spine	0.049	0.017	0.007	0.020	0.014	0.17	0.17	0.21	0.21
Lateral Spine	0.022	0.025	0.39	0.007	0.021	0.75	0.75	0.65	0.65
Forearm	0.005	0.008	0.54	0.0004	0.0058	0.95	0.95	0.64	0.64
Femoral Neck	0.025	0.009	0.03	-0.004	0.007	0.6	0.6	0.04	0.04
Trochanter	0.036	0.011	0.01	0.009	0.008	0.34	0.34	0.09	0.09
Total Hip	0.047	0.014	0.01	0.011	0.011	0.35	0.35	0.07	0.07

* p value for test of slope = 0

** p value for comparison of Cinacalcet and Control slopes