

Improvement in Hypercalcemia with Cinacalcet after Kidney Transplantation

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Cinacalcet, a calcimimetic, was evaluated in persistent hyperparathyroidism after kidney transplantation (Tx). Ten kidney transplant recipients and one kidney-pancreas recipient with persistent post-Tx hypercalcemia (serum calcium [SCa] > 10.2 mg/dl), stable graft function, and intact parathyroid hormone (iPTH) ≥ 2 times normal received 30 mg/d cinacalcet between 2 mo and 5 yr after Tx. SCa, serum phosphorus (SP), and iPTH were measured before and after cinacalcet. Mean pre-cinacalcet SCa was 10.9 mg/dl (8.6 to 11.9 mg/dl). Average pre-cinacalcet SP was 2.9 mg/dl (1.8 to 4.0 mg/dl). Mean pre-cinacalcet iPTH was 267.0 pg/ml (99 to 723 pg/ml). After cinacalcet, SCa decreased on average by 1.6 mg/dl (95% confidence interval 1.2 to 2.1; $P < 0.0001$). Post-cinacalcet SP increased on average 0.45 mg/dl ($P = 0.046$). Post-cinacalcet iPTH averaged 156.9 mg/dl ($P = 0.10$). Graft function remained stable. Cinacalcet lowers SCa and raises SP in the short term in patients with persistent post-Tx hyperparathyroidism; long-term bone effects and persistent hyperparathyroidism merit further study.

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Hypercalcemia is a frequent complication that ensues after successful kidney transplantation (KTx) (1). Persistent hyperparathyroidism (HPT) is the most frequent cause of post-KTx hypercalcemia (1). The usual management of hypercalcemia after KTx involves a period of conservative management followed by parathyroidectomy in cases with unremitting hypercalcemia >6 to 12 mo after KTx (1). In recent years, intravenous vitamin D₃ and other vitamin D analogs have been used in dialysis patients to suppress parathyroid hormone (PTH) levels (2). After successful KTx, these agents are discontinued abruptly, followed by an increase in PTH levels, a change in the known natural history of HPT attendant to renal failure. Recently, the calcimimetic agent cinacalcet was approved to treat the HPT that accompanies renal failure (3,4). We hypothesized that cinacalcet may be effective in lowering serum calcium (SCa) and PTH levels in some patients with persistent post-KTx hypercalcemia. We report herein our experience with cinacalcet in the management of persistent HPT and hypercalcemia after KTx. We also compare and contrast our experience with the recently published experience of two other groups that have used cinacalcet in a similar manner (5,6).

Materials and Methods

This study is a retrospective review of the clinical experience with cinacalcet at the University of Florida Kidney Transplant Program. Ten KTx patients (nine deceased donor, two living donor; six male, five female) and one simultaneous kidney-pancreas Tx patient with stable renal allograft function and persistent hypercalcemia after KTx (SCa >10.2 mg/dl), intact PTH (iPTH) greater than twice the upper limit of normal and stable graft function were started on a single daily oral dose of 30 mg cinacalcet. Cinacalcet was started between 2 mo and 5 yr (median 3 yr) after KTx. We measured SCa, phosphorus (P), and iPTH before and after cinacalcet. After cinacalcet, SCa and P were obtained monthly. We did not allow concomitant treatment with bisphosphonates or vitamin D. Only one patient received a small dose of neutral potassium phosphate at a dose of 250 mg twice daily. All of these measurements were made at the clinical laboratory of our institution in the context of usual clinical care. All patients had their blood drawn for measurement of biochemical parameters early in the morning before taking any of their medications, in accordance with usual instructions provided by our transplant clinic. All patients were instructed to take cinacalcet with their morning dose of medications after breakfast. Immunosuppression consisted of cyclosporine or tacrolimus and mycophenolate mofetil or azathioprine with corticosteroids. Only one of the patients had received antithymocyte globulin induction. Cyclosporine (Neoral; Novartis Pharmaceuticals, Hanover, NJ) was dosed to achieve trough levels of 275 to 35 ng/ml in the first month after Tx, 225 to 250 ng/ml to month 3, and 125 to 175 ng/ml thereafter. Tacrolimus (Prograf; Astellas Pharmaceuticals, Chicago, IL) dose was titrated to trough levels of 10 to 12 ng/ml in the first month after Tx, 8 to 10 ng/ml thereafter to day 90 after Tx, and 5 to 7 ng/ml thereafter. Prednisone was tapered to a maintenance dose of 10 mg/d by 90 d after Tx. This retrospective review of the use of cinacalcet in persistent hypercalcemia after KTx was approved by the Institutional Review Board at the University of Florida.

General linear models were used to assess the change in parameters

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over time. Repeated measures at a given interval were treated as a blocking variable. Analyses were conducted using SPSS software Version 13.0 (SPSS, Chicago, IL) and SAS version 9.1 (SAS Institute, Cary, NC).

Results

The demographic characteristics of the study patients are summarized in Table 1. The mean pre-cinacalcet SCa was 10.9 mg/dl (8.6 to 11.9 mg/dl), and the average pre-cinacalcet serum P(PTH) was 2.9 mg/dl (1.8 to 4.0 mg/dl). Mean pre-cinacalcet iPTH was 267.0 pg/ml (99 to 723 pg/ml).

After treatment with cinacalcet, the mean SCa was 9.3 mg/dl (7.5 to 10.7 mg/dl). With cinacalcet treatment, SCa decreased on average by 1.6 mg/dl, a statistically significant reduction (95% confidence interval [CI] 1.2 to 2.1; one-tailed $P < 0.0001$). This change in SCa was evident within 1 wk to 4 mo of starting cinacalcet (data shown in Table 2) and was sustained during the follow-up period ranging between 3 and 18 mo. The post-cinacalcet SP was 3.3 mg/dl, and SP increased on average 0.45 mg/dl (one-tailed $P = 0.046$). The raw values of pre- and post-cinacalcet iPTH, SCa, SP, and serum creatinine measurements are shown in Table 2. Five of eight patients with paired measurements of iPTH exhibited reductions in iPTH. The average post-cinacalcet iPTH was 156.9 mg/dl, a 41.5% reduction (one-tailed $P = 0.10$). These results are summarized in Table 3 and depicted in Figure 1. Pre-cinacalcet serum creatinine averaged 1.52 mg/dl, and the mean serum creatinine after cinacalcet was 1.44 mg/dl ($P = 0.23$; Table 3).

One patient was frankly noncompliant and was not taking her cinacalcet as directed, leading to stoppage of the cinacalcet. No significant changes in the renal function, BP, or hematocrit were noted in the follow-up period (data not shown). In one other patient, who had a simultaneous kidney-pancreas Tx, cinacalcet was stopped during a hospitalization for urosepsis

and never restarted. No episodes of acute rejection or other side effects that were ascribable to cinacalcet have been noted to date. We also did not observe any unexpected need for dose modification of calcineurin inhibitors as a result of possible interactions with cinacalcet during the study (data not shown).

Discussion

Persistence of HPT after renal Tx may reflect secondary HPT in the face of suboptimal renal allograft function or autonomous secretion of PTH by functioning adenomas (1,7,8). The effects of such unregulated PTH hypersecretion are bone resorption principally manifest as progressive osteopenia or osteoporosis of the femoral neck, vascular calcification, and frank hypercalcemia with attendant complications (1). Traditional management in these circumstances dictates parathyroidectomy in an effort to prevent ongoing bone resorption or symptomatic hypercalcemia (1). Calcimimetics, phenylalkylamine agonists of the calcium sensing receptor, mimic the effect of extracellular calcium on this receptor and suppress the secretion of PTH by the parathyroid gland (9–11). In effect, these agents trick the parathyroid gland into a response that is appropriate for hypercalcemia despite a relatively normal ambient serum calcium concentration (12,13). Cinacalcet, the prototype of this class of compounds, has been used effectively in treating the secondary HPT of renal failure (3,4,14,15) and in primary HPT (16,17). More recently, cinacalcet has been used in KTx recipients (5,6). Kruse *et al.* (5) reported successful reduction in SCa levels in 14 KTx recipients with persistent HPT after TX. They did not see, however, a statistically significant decrease in PTH levels (5). These findings are very similar to ours. In our case series, five of eight patients with paired PTH measurements exhibited reduction in PTH levels with cinacalcet. This reduction of PTH levels averaged approximately 40%, a clinically significant suppression of PTH, albeit just approaching statistical significance. Increases in SP concentrations were noted and were statistically significant, corroborating the findings of both Kruse *et al.* (5,13) and Serra *et al.* (6,13). These findings are in contrast to the findings with cinacalcet in dialysis patients who have a reduction in SP with cinacalcet, most likely a reflection of preserved renal function in the transplant recipient (5,6,14). Kruse *et al.* (5) additionally noted a trend toward increasing serum creatinine concentrations in their study. We have not noted any such increases in serum creatinine in our patients to date. The study reported by Serra *et al.* (6) evaluated 11 renal transplant recipients who received cinacalcet for persistent HPT and did note statistically significant decreases in iPTH in addition to the decrease in serum calcium as observed in our series and the study of Kruse *et al.* (5). It should be noted that in our study and also in the study reported by Kruse *et al.* (5), cinacalcet was used in a single daily oral dose of 30 mg. The rebound increase in serum PTH after initial suppression that occurs with single daily doses of cinacalcet could account in part for this finding and account for the discordance between suppression of PTH levels and decline in SCa (5). In contrast, in the study reported by Serra *et al.* (6), some patients did receive higher doses of cinacalcet.

There are many obvious limitations to our study. We used

Table 1. Patient demographics and baseline characteristics

Donor source	
deceased	9
live donor	2
Gender	
male	6
female	5
Age (yr; range, median)	22 to 64, 48.5
Race	
white	6
black	3
Hispanic	1
Asian	1
Immunosuppression	
cyclosporine	5
tacrolimus	6
mycophenolate mofetil	8
azathioprine	3
prednisone	11

Table 2. Biochemical parameters before and after treatment with cinacalcet^a

Patient	Pre-CIN SCa (mg/dl)	Pre-CIN SP (mg/dl)	Post-CIN SCa (mg/dl)	Post-CIN SP (mg/dl)	Pre-CIN iPTH (ng/ml)	Post-CIN iPTH (ng/ml)	Time to Decline of SCa ^b (d)	Total Time on CIN (d)	Pre-CIN SCr (mg/dl)	Post-CIN SCr (mg/dl)
1	11	3.4	9.5	3.8	104	110	124	240	1.4	1.2
2	10.7	2.6	10.2	^c	339	467	92	334	2.2	1.9
3	11.3	3	11.4	2.7	274	173	210	210	0.9	1.0
4	10.4	3.4	9.5	4.2	173	^{c,d}	14 ^{c,d}	^d	1.0	1.0
5	11	2.2	9.8	3.5	99	81	7	209	1.2	1.2
6	11.6	2.6	10.7	1.9	247	72	150	504	1.7	1.8
7	11.7	3.3	10.8	2.4	723	^c	60	184	2	1.6
8	11.3	2.3	9.3	3.1	261	171	72	238	0.6	0.8
9	11.1	2.6	9.6	3.2	150	102	38	230	1.9	1.8
10	10.8	2.5	9.6	4.5	435	79	129	363	3.0	2.6
11	8.6	3.9	9.0	2.8	132	^{c,e}	^e	^e	1.0	0.9

^aCIN, cinacalcet; iPTH, intact PTH; SCa, serum calcium; SCr, serum creatinine; SP, serum phosphorus.

^bBy 10% or more below pre-CIN value.

^cMissing value.

^dNoncompliance; stopped drug.

^eStopped drug; intercurrent hospitalization.

Table 3. Change in SCa, SP, and PTH levels with CIN treatment

Variable	Pre-CIN (Mean ± SEM)	Post-CIN (Mean ± SEM)	One-Tailed P Value ^a
SCa (mg/dl)	10.9 ± 0.14	9.3 ± 0.19	<0.001
SP (mg/dl)	2.9 ± 0.13	3.3 ± 0.18	0.042
iPTH (pg/ml)	267.0 ± 49.5	156.9 ± 58.0	0.10
SCr (mg/dl)	1.52 ± 0.14	1.44 ± 0.12	0.23

^aFrom linear model assessing change in variable blocked for repeated trials at given time point.

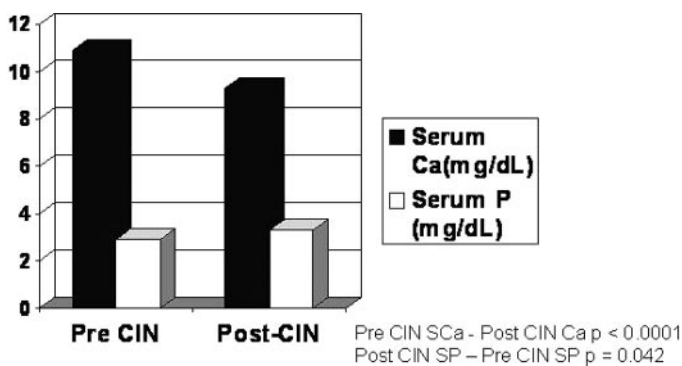


Figure 1. Change in serum calcium and phosphorus with cinacalcet. SCa, serum calcium; SP, serum phosphorus; CIN, cinacalcet.

cinacalcet in the relatively uncontrolled setting of clinical practice and did not take into account pre-Tx levels of PTH and pre-Tx therapy with vitamin D or its analogs. Furthermore, spontaneous resolution of HPT after successful Tx is expected in the majority of cases. However, as alluded to earlier, abrupt discontinuation of pre-Tx calcitriol or vitamin D analog treatment after Tx may manifest as HPT after Tx. That resolution of

this increase in PTH levels after vitamin D (or analog) withdrawal may represent in entirety the falling levels of PTH seen in our patient cohort seems unlikely as most patients had persistence of HPT beyond 1 yr after Tx, at the time when cinacalcet was started (7,18,19). The lack of a control group in a pilot study such as ours is another obvious limitation.

Past efforts to prevent post-Tx bone disease with calcitriol has been limited by hypercalcemia, and enthusiasm for bisphosphonates is often dampened by concerns of adynamic bone disease (20–22). In this regard, calcimimetics offer a direct means of suppressing PTH secretion and possibly mitigating the systemic and skeletal complications of HPT (5,12,13,16).

Our study and the published studies of Kruse *et al.* (5) and Serra *et al.* (6) thus far have not assessed the effects of calcimimetics on markers of bone formation or resorption, bone mineral density, and bone histology in the renal transplant population. These will need to be necessary parameters to evaluate in future studies that assess the effects of cinacalcet in the kidney transplant population. In our study and the studies reported by Kruse *et al.* (5) and Serra *et al.* (6), the effects of cinacalcet on SCa, SP, and PTH were observed in the context of excellent graft function at >1 yr after Tx. These findings thus support a possible role for cinacalcet in the management of

tertiary HPT (7,8). In our study, no significant interactions observed between cinacalcet and the calcineurin inhibitors or other drugs were noted. These findings mirror those reported both by Kruse *et al.* (5) and Serra *et al.* (6).

Conclusion

Cinacalcet seems to offer an alternative to parathyroidectomy in the management of persistent post-KTx HPT. Cinacalcet's long-term efficacy, safety, long-term effects on bone biology, and resolution of the systemic burden of HPT after KTx merit further study.

References

- Torres A, Lorenzo V, Salido E: Calcium metabolism and skeletal problems after transplantation. *J Am Soc Nephrol* 13: 551–558, 2002
- Wu-Wong JR, Tian J, Goltzman D: Vitamin D analogs as therapeutic agents: A clinical study update. *Curr Opin Investig Drugs* 5: 320–326, 2004
- Block GA, Martin KJ, de Francisco AL, Turner SA, Avram MM, Suranyi MG, Hercz G, Cunningham J, Abu-Alfa AK, Messa P, Coyne DW, Locatelli F, Cohen RM, Evenepoel P, Moe SM, Fournier A, Braun J, McCary LC, Zani VJ, Olson KA, Drueke TB, Goodman WG: Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med* 350: 1516–1525, 2004
- Lindberg JS, Culleton B, Wong G, Borah MF, Clark RV, Shapiro WB, Roger SD, Husserl FE, Klassen PS, Guo MD, Albizem MB, Coburn JW: Cinacalcet HCl, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: A randomized, double-blind, multicenter study. *J Am Soc Nephrol* 16: 800–807, 2005
- Kruse AE, Eisenberger U, Frey FJ, Mohaupt MG: The calcimimetic cinacalcet normalizes serum calcium in renal transplant patients with persistent hyperparathyroidism. *Nephrol Dial Transplant* 20: 1311–1314, 2005
- Serra AL, Schwarz AA, Wick FH, Marti HP, Wuthrich RP: Successful treatment of hypercalcemia with cinacalcet in renal transplant recipients with persistent hyperparathyroidism. *Nephrol Dial Transplant* 20: 1315–1319, 2005
- Lewin E: Involution of the parathyroid glands after renal transplantation. *Curr Opin Nephrol Hypertens* 12: 363–371, 2003
- Arnold A, Brown MF, Urena P, Gaz RD, Sarfati E, Drueke TB: Monoclonality of parathyroid tumors in chronic renal failure and in primary parathyroid hyperplasia. *J Clin Invest* 95: 2047–2053, 1995
- Drueke TB: Modulation and action of the calcium-sensing receptor. *Nephrol Dial Transplant* 19[Suppl 5]: V20–V26, 2004
- Hammerland LG, Garrett JE, Hung BC, Levinthal C, Nemeth EF: Allosteric activation of the Ca²⁺ receptor expressed in *Xenopus laevis* oocytes by NPS 467 or NPS 568. *Mol Pharmacol* 53: 1083–1088, 1998
- Nemeth EF, Steffey ME, Hammerland LG, Hung BC, Van Wagenen BC, DelMar EG, Balandrin MF: Calcimimetics with potent and selective activity on the parathyroid calcium receptor. *Proc Natl Acad Sci U S A* 95: 4040–4045, 1998
- Olgaard K, Lewin E: Prevention of uremic bone disease using calcimimetic compounds. *Annu Rev Med* 52: 203–220, 2001
- Nemeth EF, Bennett SA: Tricking the parathyroid gland with novel calcimimetic agents. *Nephrol Dial Transplant* 13: 1923–1925, 1998
- Goodman WG, Hladik GA, Turner SA, Blaisdell PW, Goodkin DA, Liu W, Barri YM, Cohen RM, Coburn JW: The calcimimetic agent AMG 073 lowers plasma parathyroid hormone levels in hemodialysis patients with secondary hyperparathyroidism. *J Am Soc Nephrol* 13: 1017–1024, 2002
- Quarles LD, Sherrard DJ, Adler S, Rosansky SJ, McCary LC, Liu W, Turner SA, Bushinsky DA: The calcimimetic AMG 073 as a potential treatment for secondary hyperparathyroidism of end-stage renal disease. *J Am Soc Nephrol* 14: 575–583, 2003
- Peacock M, Bilezikian JP, Klassen PS, Guo MD, Turner SA, Shoback D: Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 90: 135–141, 2005
- Shoback DM, Bilezikian JP, Turner SA, McCary LC, Guo MD, Peacock M: The calcimimetic cinacalcet normalizes serum calcium in subjects with primary hyperparathyroidism. *J Clin Endocrinol Metab* 88: 5644–5649, 2003
- Cundy T, Kanis JA, Heynen G, Morris PJ, Oliver DO: Calcium metabolism and hyperparathyroidism after renal transplantation. *Q J Med* 52: 67–78, 1983
- Koch Nogueira PC, David L, Cochat P: Evolution of secondary hyperparathyroidism after renal transplantation. *Pediatr Nephrol* 14: 342–346, 2000
- Moe SM: The treatment of steroid-induced bone loss in transplantation. *Curr Opin Nephrol Hypertens* 6: 544–549, 1997
- Fan SL, Kumar S, Cunningham J: Long-term effects on bone mineral density of pamidronate given at the time of renal transplantation. *Kidney Int* 63: 2275–2279, 2003
- Dissanayake IR, Epstein S: The fate of bone after renal transplantation. *Curr Opin Nephrol Hypertens* 7: 389–395, 1998

See related editorial, "Calcium, Calcimimetics and Clinical Outcomes," on pages 170–171.

Clinical use of the calcimimetic cinacalcet in hemodialysis (Chertow *et al.*) and transplant patients (Srinivas *et al.*) with the corresponding editorial by Block are featured in this month's *CJASN*. A study in experimental animals on another congener by Lopez *et al.* in this month's *JASN* (pages 795–804) shows a decrease in extrasosseous calcifications, even in calcitriol-treated animals.