

Short Communication

Effect of cinacalcet cessation in renal transplant recipients with persistent hyperparathyroidism

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Abstract

Background. Persistent hyperparathyroidism after renal transplantation affects bone and allografts. Cinacalcet, a calcimimetic, reduces serum calcium and PTH in renal transplant recipients with persistent hyperparathyroidism. Here, we address the question whether this effect of cinacalcet persists after withdrawal.

Methods. Therefore, cinacalcet was stopped after 12 months treatment in 10 stable renal transplant patients. Serum calcium, phosphate, PTH, creatinine and cystatin C were monitored for 3 months.

Results. Serum calcium, normalized in nine patients before cessation of cinacalcet (2.32 ± 0.05 mmol/l, mean \pm SEM), increased after 3 months of discontinuation by 0.17 ± 0.04 mmol/l, $P < 0.05$, but remained within the normal range in eight patients. Compared with the time point of cessation, PTH remained unchanged or decreased further after 3 months without therapy in six patients. Measurements of cystatin C suggested an improvement of the glomerular filtration rate after cessation in 9 out of 10 patients (1.55 ± 0.09 vs 1.33 ± 0.12 mg/l, $P < 0.01$).

Conclusion. First, a beneficial effect of cinacalcet beyond the duration of a 12-month therapy appears to be present in some patients and second, the previously suspected influence of cinacalcet therapy on renal function is reversible. Thus, it is reasonable to consider a trial of cinacalcet cessation to identify these patients. The optimal time point for such a discontinuation is unknown. The present observations are preliminary. They clearly require a prospective randomized trial for definitive confirmation.

Keywords: calcimimetic; cinacalcet; hypercalcaemia; kidney transplantation; parathormone; persistent hyperparathyroidism

Introduction

Secondary hyperparathyroidism is a common complication of renal failure and end-stage renal disease. Despite normalization of renal function and normal concentrations of 1,25-dihydroxyvitamin D after renal transplantation, elevated parathormone (PTH) concentrations often persist, leading to markedly increased serum calcium levels, decreased bone mass and possibly perpetuating allograft nephropathy [1]. In about one-third of the patients, hyperparathyroidism does not completely resolve after transplantation. In some of these patients, a surgical intervention is hazardous and therefore medical treatment of interest. In addition, parathyroidectomy is associated with a decline in the glomerular filtration rate in some patients [2,3].

Cinacalcet, a calcimimetic, has been reported to reduce serum calcium and PTH concentrations in renal transplant patients. So far, this has been shown in about 40 patients, including our own 10 subjects [4–7]. Whether the beneficial effect of cinacalcet persists in these patients after withdrawal cannot be predicted on the basis of the various mechanisms of action of calcimimetics. The initial mechanisms considered for the calcimimetics were decreased PTH secretion [8] and reduced parathyroid gland hyperplasia [9]. More recently, Levi and co-workers [10] presented evidence that calcimimetics decrease PTH concentration because its transcript levels are post-transcriptionally modified by a post-translational regulation of the mRNA binding protein AUF1.

In order to analyse whether a beneficial effect on PTH and calcium concentrations persists after prolonged therapy with a calcimimetic without affecting renal function, the calcimimetic cinacalcet was withdrawn after 1 year of treatment in 10 renal transplant recipients with persistent hyperparathyroidism. This approach is of interest, because contrary to patients on haemodialysis the main stimuli for hyperparathyroidism, hyperphosphataemia and hypocalcaemia in the presence of low concentrations of

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1.25-dihydroxyvitamin D are absent with stable renal transplant function.

Subjects and methods

Fifteen renal transplant patients who were followed in our unit received 30 mg of cinacalcet once daily in the evening for at least 1 year due to persistent hyperparathyroidism with hypercalcaemia. Thirteen were previously evaluated and reported after beginning of therapy [4]. Because of unstable conditions due to neoplasia, gastrointestinal bleeding, recurrent infections and rejection, five were not electable to be included in the present study. In 10 stable renal transplant patients (seven males, three females, aged 28–66 years) cinacalcet therapy was discontinued and the patients were followed for an additional 3 months without therapy. Hyperparathyroidism was defined by increased serum calcium concentrations, in the presence of elevated PTH levels on dialysis not normalized 12 months after renal transplantation, despite normal or increased 1.25-dihydroxyvitamin D levels. Cinacalcet treatment was started 16–162 months (median 35 months) after renal transplantation. All patients received prednisone at doses up to 10 mg/day and in addition nine were on cyclosporine A and one on tacrolimus. Four patients were given mycophenolate mofetil and two azathioprine. Five patients were treated with 1.25-dihydroxyvitamin D orally and two with cholecalciferol. This treatment remained unchanged after stopping cinacalcet. One patient received intravenous pamidronate every third month until 1 month before cinacalcet treatment was begun, but not thereafter. Eight patients were on β -blockers, seven on ACE-inhibitors, six on calcium channel blockers, four on angiotensin II antagonists and four on loop diuretics as antihypertensive therapy. Five patients had ongoing hypertension with blood pressure $\geq 135/85$ mmHg. In three patients the dosage of ACE-inhibitor or angiotensin II antagonist respectively was increased during follow-up. In one patient, the loop diuretic torasemide was slightly increased from 10 to 12.5 mg daily. Two patients were treated for diabetes, one with metformin, one with insulin. Outpatient visits were scheduled the day before cinacalcet withdrawal and 2 weeks, 2 months and 3 months after cinacalcet treatment was stopped. Thereafter, the study was completed and the transplant nephrologists followed the patients routinely. At month nine after cessation of cinacalcet, the files from all 10 patients were reviewed again at a routinely scheduled visit in our clinic.

The following parameters were assessed: PTH (intact), 1.25-dihydroxyvitamin D, calcium, phosphate, creatinine and cystatin C in serum, calcium, phosphate and creatinine in the urine; Cyclosporine A whole blood through levels as well as office blood pressure. Concomitant medication and medical events were recorded.

Statistical analyses were performed using SAS Inc. 9.1. The ANOVA with Student–Newman–Keuls-test was applied. Data are given as means \pm SEM or as otherwise indicated.

The study was approved by the local Ethical Review Board. Informed consent was given by all patients.

Results

Effect of cinacalcet withdrawal on calcium, PTH, 1.25-dihydroxyvitamin D and phosphate

Serum calcium was well controlled in nine out of 10 patients before cessation of therapy (2.32 ± 0.05 mmol/l, normal range: 2.10–2.55 mmol/l) (Figure 1; month 0). After cinacalcet withdrawal at 3 months, mean serum calcium concentrations increased by 0.17 ± 0.04 mmol/l ($P < 0.05$), but remained within the normal range in eight out of 10 patients whereas reaching 2.6 mmol/l in the remaining two (Figure 1; month 3). Interestingly serum calcium concentrations increased immediately after cessation of cinacalcet as shown in Figure 1 (month 0.5) in all of the 10 patients, an effect followed by a decline at month 2 in seven patients out of 10 and at month 3 in nine out of 10 when compared with month 0.5. Calciuria calculated as the calcium/creatinine ratio tended to increase 2 weeks after stopping cinacalcet when compared with values obtained during treatment (0.30 ± 0.07 vs 0.25 ± 0.06 mmol calcium/mmol creatinine), but did not change significantly at any time point.

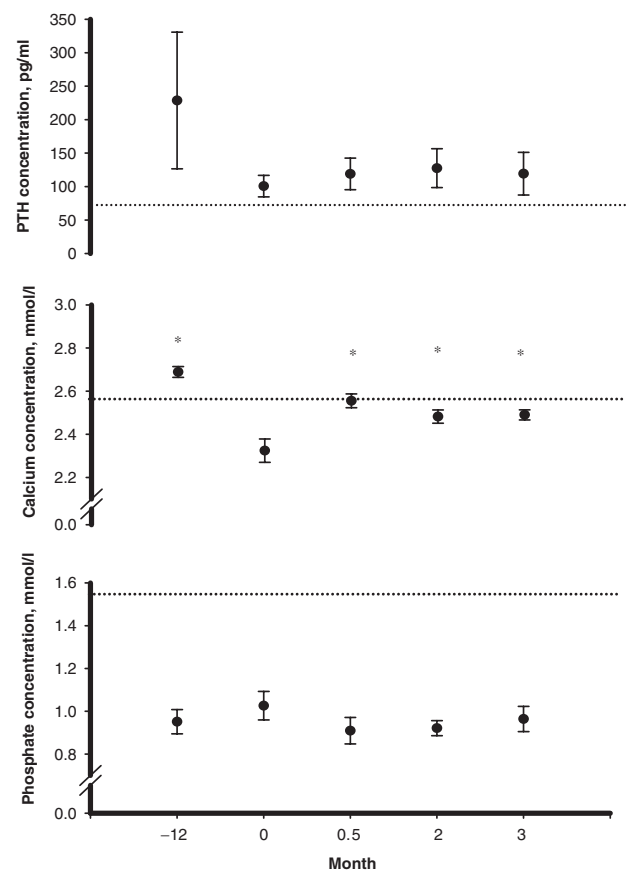


Fig. 1. Mean (\pm SEM) serum concentrations of PTH, calcium and phosphate before initiation (–12), after 1 year of cinacalcet (0) and 2 weeks (0.5), 2 months (2) and 3 months (3) after cessation of cinacalcet. * $P < 0.05$ vs month 0. Upper limits of normal ranges are depicted by dotted lines.

Serum concentrations of PTH tended to rise during the initial 2 weeks after cessation of cinacalcet in eight out of 10 patients (Figure 1; month 0 and 0.5). Compared with the time point of cessation, PTH levels remained unchanged or decreased further after 3 months without therapy in six patients. In two patients, PTH remained below pre-treatment levels. In the remaining two patients, PTH concentrations rose to pre-treatment levels. Mean 1.25-dihydroxy-vitamin D concentrations were 69.8 ± 7.5 pmol/l during treatment with cinacalcet and lower ($P < 0.05$) than at week 2 (93.7 ± 10.1 pmol/l), month 2 (105.8 ± 13.5 pmol/l) and month 3 (101.3 ± 11.7 pmol/l) after cessation of cinacalcet. Serum phosphate concentrations (mean 1.03 ± 0.07 mmol/l at the end of the treatment phase *vs* 0.96 ± 0.06 mmol/l after 3 months without) and calcium-phosphate products (2.39 ± 0.17 *vs* 2.40 ± 0.16 mmol²/l²) did not change after withdrawal of cinacalcet. Fractional urinary phosphate excretion remained unaltered throughout the 3 months of cinacalcet withdrawal.

Beyond the 3 months prospective study protocol the patient files were reviewed for data at month 9 after cessation of cinacalcet. At this time point, two patients described as insufficiently controlled during the study period were again on cinacalcet. Of the remaining eight patients, five still maintained their PTH concentration below the concentrations measured at the time point when cinacalcet was discontinued. Serum calcium concentrations were normal in four of these eight patients and exceeded the upper limit of 2.6 mmol/l in the remaining four patients.

Effect of cinacalcet withdrawal on renal function

Serum creatinine concentrations ranged from 89 to 229 μ mol/l with a median of 113 μ mol/l (normal range 45–104 μ mol/l) before cinacalcet therapy. In seven of the 10 patients, serum creatinine concentrations increased during the 12 months on cinacalcet therapy (Figure 2; see month -12 and 0). Following cinacalcet withdrawal the concentrations declined again in seven out of 10 patients during the following 3 months. In three patients, serum creatinine slightly increased. Two of these patients were prescribed an increasing dose of an ACE inhibitor or angiotensin II receptor antagonist. Mean creatinine clearance calculated by the MDRD formula was 51.11 ± 4.22 ml/min/1.73m² when starting treatment with cinacalcet, 47.97 ± 4.26 ml/min/1.73m² after 1 year of therapy with cinacalcet and 52.42 ± 5.86 ml/min/1.73m², 3 months after cessation of the drug. The differences were not significant. In order to add an additional independent parameter of the glomerular filtration rate, cystatin C concentrations were determined at the end of cinacalcet therapy and thereafter (Figure 2). Cystatin C decreased after cessation of cinacalcet in 9 out of 10 patients within 3 months (month 0 *vs* month 3: 1.55 ± 0.09 *vs* 1.33 ± 0.12 mg/l, $P < 0.01$, normal range 0.63–1.44 mg/l), suggesting an improvement of the glomerular filtration rate. Cystatin C levels before

treatment were not measured routinely and are therefore not available.

At month 9 after cessation of cinacalcet two patients were taking cinacalcet again. In six of the remaining eight patients serum creatinine concentrations were lower and in two, higher than at the end of cinacalcet therapy. Cyclosporine A through levels as well as blood pressure remained stable throughout the observation period. No side effects attributable to cinacalcet withdrawal were encountered.

Discussion

In the present study, we report the effect of an extended treatment with cinacalcet and its withdrawal in renal transplant patients with persistent hyperparathyroidism. Three months after cessation of a 1 year lasting calcimimetic therapy serum calcium concentrations remained normal in eight patients and only slightly increased to 2.6 mmol/l in two out of 10 patients. Similarly, PTH levels remained below the concentrations encountered before cinacalcet therapy was initiated in eight out of 10 patients. Based on the present investigation, we cannot unambiguously establish whether the persistent improvement of the hyperparathyroidism in our patients was due to the calcimimetic or to the natural history because of the absence of a control group. Frequently, secondary hyperparathyroidism spontaneously disappears during the first year after renal transplantation. Thereafter, the prevalence of persistent hyperparathyroidism was reported to remain stable [11]. Our patients were transplanted for 1.3–13 years before

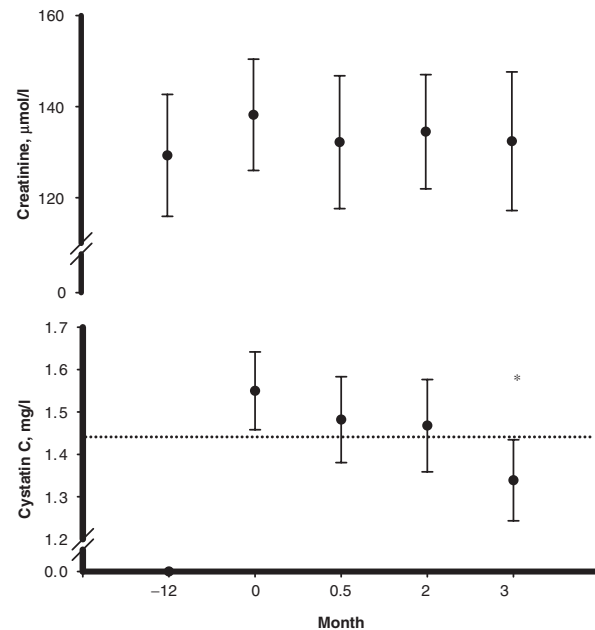


Fig. 2. Mean (\pm SEM) serum concentrations of creatinine and cystatin C before initiation (-12), after 1 year of cinacalcet (0) and 2 weeks (0.5), 2 months (2) and 3 months (3) after cessation of cinacalcet. * $P < 0.05$ *vs* month 0. Upper limit of normal cystatin C range is depicted by dotted line.

cinacalcet was prescribed. Therefore, it is reasonable to conclude that treatment with this drug appears to have some efficacy, which is present beyond the duration of the prescription.

The mechanism by which cinacalcet appears to exhibit a PTH suppressive effect beyond the duration of therapy remains to be clarified. Calcimimetics were shown to attenuate the progression of parathyroid hyperplasia in rats [9]. Whether the inhibition of proliferation causes a reduction of the size of the parathyroid glands in renal transplant patients with persistent hyperparathyroidism awaits confirmation. Recently, Rodriguez *et al.* [12] observed an increase of the VDR expression in parathyroid cells of rats given the calcimimetic R-568. It is unknown whether such an effect of a calcimimetic, if present in humans, persists beyond the time the drug was prescribed. Since the principle ligand of VDR, 1,25-dihydroxyvitamin D increased after cessation of cinacalcet in our patients, a persistent VDR-mediated inhibition of PTH-synthesis is an attractive hypothesis for the reduced PTH-release after withdrawal of cinacalcet.

The effect of cinacalcet on renal function is of special interest and difficult to dissect from other factors modulating the glomerular filtration rate in renal transplant patients. In our previous investigation, we showed that the mean serum creatinine concentration rose significantly from $140 \pm 15 \mu\text{mol/l}$ at baseline to $153 \pm 17 \mu\text{mol/l}$ at two and $148 \pm 46 \mu\text{mol/l}$ at 3 months of treatment with cinacalcet [4]. Similarly, serum creatinine concentrations tended to increase, albeit not significantly, from $116.1 \pm 8.7 \mu\text{mol/l}$ at baseline to $127.6 \pm 11.1 \mu\text{mol/l}$ during a 26-week course of cinacalcet in ten renal transplant patients reported by Serra *et al.* [13]. On the other hand, Srinivas *et al.* [7] treated ten patients for 3–18 months and observed a reduction of mean serum creatinine concentration from 152 ± 14 to $144 \pm 12 \mu\text{mol/l}$ during treatment. Given the small number of patients observed and the controversial results with respect to cinacalcet on renal function, the present results derived from patients after discontinuation of cinacalcet deserve special attention. In seven out of 10 patients both, serum creatinine concentrations and cystatin C declined and in two additional patients cystatin C diminished while serum creatinine concentrations increased slightly. The reversibility of the impairment of renal function as assessed by cystatin C after cinacalcet withdrawal suggests that the impairment might be due to some haemodynamic calcium or PTH mediated effects rather than structural changes in the transplanted kidney. This is supported by the observation of deterioration of renal function and the influence of serum calcium and PTH after surgical parathyroidectomy [14].

In conclusion, the preliminary results from the present observational study suggest a therapeutic effect of cinacalcet beyond the duration of therapy and how long this effect persists has to be established.

Nevertheless, it is reasonable to consider a trial of cinacalcet discontinuation in order to establish if stable renal transplant patients still need this drug, possibly at a higher dose or alternatively eventually require surgical parathyroidectomy. The optimal time point after starting cinacalcet therapy for such a trial of discontinuation is unknown and deserves a prospective controlled trial [13].

Conflict of interest statement. None declared.

References

- Schwarz A, Mengel M, Gwinner W *et al.* Risk factors for chronic allograft nephropathy after renal transplantation: a protocol biopsy study. *Kidney Int* 2005; 67: 341–348
- Lee PP, Schiffmann L, Offermann G, Beige J. Effects of parathyroidectomy on renal allograft survival. *Kidney Blood Press Res* 2004; 27: 191–196
- Rostaing L, Moreau-Gaudry X, Baron E, Cisterne JM, Monrozies-Bernadet P, Durand D. Changes in blood pressure and renal function following subtotal parathyroidectomy in renal transplant patients presenting with persistent hypercalcemic hyperparathyroidism. *Clin Nephrol* 1997; 47: 248–255
- Kruse AE, Eisenberger U, Frey FJ, Mohaupt MG. The calcimimetic cinacalcet normalizes serum calcium in renal transplant patients with persistent hyperparathyroidism. *Nephrol Dial Transplant* 2005; 20: 1311–1314
- Leca N, Laftavi M, Gundroo A *et al.* Early and Severe Hyperparathyroidism Associated with Hypercalcemia After Renal Transplant Treated with Cinacalcet. *Am J Transplant* 2006; 6: 2391–2395
- 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* 2005; 20: 1315–1319
- Srinivas T, Schold J, Kea W. Improvement in hypercalcemia with cinacalcet after kidney transplantation. *Clin J Amer Soc Nephrol* 2006; 1: 323–326
- Nemeth EF, Steffey ME, Hammerland LG *et al.* Calcimimetics with potent and selective activity on the parathyroid calcium receptor. *Proc Natl Acad Sci USA* 1998; 95: 4040–4045
- Wada M, Nagano N, Furuya Y, Chin J, Nemeth EF, Fox J. Calcimimetic NPS R-568 prevents parathyroid hyperplasia in rats with severe secondary hyperparathyroidism. *Kidney Int* 2000; 57: 50–58
- Levi R, Ben-Dov IZ, Lavi-Moshayoff V *et al.* Increased parathyroid hormone gene expression in secondary hyperparathyroidism of experimental uremia is reversed by calcimimetics: correlation with post-translational modification of the trans acting factor AUF1. *J Am Soc Nephrol* 2006; 17: 107–112
- Evenepoel P, Claes K, Kuypers D, Maes B, Bammens B, Vanrenterghem Y. Natural history of parathyroid function and calcium metabolism after kidney transplantation: a single-centre study. *Nephrol Dial Transplant* 2004; 19: 1281–1287
- Rodriguez M, Almaden Y, Canadillas S *et al.* The Calcimimetic R-568 Increases Vitamin D Receptor Expression in Rat Parathyroid Glands. *Am J Physiol Renal Physiol* 2007 (Epub ahead of print)
- Serra AL, Savoca R, Huber AR *et al.* Effective control of persistent hyperparathyroidism with cinacalcet in renal allograft recipients. *Nephrol Dial Transplant* 2007; 22: 577–583
- Schwarz A, Rustien G, Merkel S, Radermacher J, Haller H. Decreased renal transplant function after parathyroidectomy. *Nephrol Dial Transplant* 2007; 22: 584–591

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