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Short Communication

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The effects of discontinuing cinacalcet at the time of kidney transplantation

Michel Jadoul[1], Ana Baños[2], Valter J. Zani[3] and Gavril Hercz[4]

[1]Cliniques Universitaires St Luc, Université Catholique de Louvain, Brussels, Belgium, [2]Amgen Ltd, Uxbridge, UK, [3]Amgen GmbH, Zug, Switzerland and [4]Humber River Regional Hospital, Toronto, Canada

Correspondence and offprint requests to: Michel Jadoul; E-mail: michel.jadoul@uclouvain.be

Abstract

Background. The calcimimetic, cinacalcet, is approved for treating secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD) on dialysis. Biochemical profiles and clinical outcomes in patients discontinuing cinacalcet at kidney transplantation have not been previously described.

Methods. We performed a retrospective observational study evaluating post-transplant biochemical profiles and clinical outcomes in patients who had enrolled in phase 2 or 3 randomized, placebo-controlled studies of cinacalcet before receiving a kidney transplant.

Results. The study included 28 former cinacalcet and 10 former placebo patients. Post-kidney transplant, there were no obvious differences between the two groups in levels of serum intact parathyroid hormone, calcium or phosphorus. One patient in each group underwent post-transplant parathyroidectomy. Kidney transplant failure was apparent in one former cinacalcet-treated patient (4%) and three former placebo patients (30%). The duration of hospitalization (mean ± standard error) immediately post-transplant in these two groups was 2.3 ± 0.3 and 3.4 ± 0.8 weeks, respectively.

Conclusions. Using cinacalcet to treat SHPT in patients with CKD awaiting kidney transplantation does not appear to modify SHPT-related post-transplant biochemical profiles, or clinical outcomes, compared with placebo.

Keywords: cinacalcet; end-stage renal disease; kidney transplantation; secondary hyperparathyroidism

Introduction

Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney disease (CKD). The calcimimetic, cinacalcet, is approved for treating SHPT in CKD patients receiving dialysis. Randomized, double-blind, placebo-controlled clinical trials in dialyzed patients with SHPT have shown cinacalcet to lower serum parathyroid hormone (PTH), phosphorus, calcium and the calcium–phosphorus product (Ca × P) [1–4]. Cinacalcet facilitates achievement of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI™) recommended targets for serum PTH, phosphorus, calcium and Ca × P [4,5].

Patients undergoing kidney transplantation may have received cinacalcet before the procedure. However, the biochemical profile of patients who discontinue cinacalcet at the time of their transplant has not been previously described. We report a retrospective, observational study evaluating post-transplant biochemical profiles and clinical outcomes in such patients.

Subjects and methods

Patients

Patients were included in this study if they had withdrawn from a qualifying phase 2 or 3 Amgen-sponsored cinacalcet study to receive a kidney transplant. All patients signed an informed consent form.

Study design

This was an observational, retrospective study. No interventional procedures were undertaken. Patients did not receive cinacalcet after kidney transplantation; if they had been treated with cinacalcet during the qualifying study, the drug was withdrawn when patients left the qualifying study.

Data collection

Local laboratory data relating to serum PTH, calcium and phosphorus levels were collected when patients left the qualifying study, before kidney transplantation and up to 12 months afterwards. Only serum intact (i)PTH measurements were included in this analysis. Information related to the incidences of parathyroidectomy and kidney

Table 1. Demographic characteristics of the patients followed up in this study (recorded when patients entered the qualifying study from which they subsequently withdrew)

	Former placebo patients ($n = 10$)	Former cinacalcet patients ($n = 28$)
Age (years)		
Mean ± SE	43.7 ± 3.7	53.3 ± 2.0
Sex, *n* (%)		
Male	10 (100)	20 (71)
Race, *n* (%)		
White or Caucasian	8 (80)	18 (64)
Black or African American	1 (10)	9 (32)
Other	1 (10)	1 (4)
Duration of exposure to treatment[a] (days)		
Mean ± SE	213 ± 82	290 ± 30
Duration of dialysis (months)		
Mean ± SE	52 ± 14	57 ± 12
Time from last dose in previous study to kidney transplantation (days)		
Mean ± SE	1.4 ± 0.6	3.6 ± 2.3

SE = standard error.
[a]Duration of exposure does not include gaps between studies for patients participating in more than one qualifying study.

transplant failure, duration of post-transplant hospitalization and post-transplant creatinine clearance was also recorded.

Statistical methods

The sample size was determined by the number of patients participating in a qualifying study, withdrawing before kidney transplantation and consenting to follow-up. Data were analysed using descriptive statistics. Between-group comparisons were performed using the chi-square test (categorical variables) and Student's *t*-test or the Mann–Whitney test (continuous variables). $P < 0.05$ was considered statistically significant.

Results

Patients

Of 107 eligible patients (68 cinacalcet and 39 placebo), 38 (36%) (28 former cinacalcet, 10 former placebo) consented to follow-up, the demographic characteristics of whom were broadly representative of the overall eligible patient population (data not shown). The demographic and baseline biochemical characteristics of the study population are shown in Tables 1 and 2. The mean values for iPTH, phosphorus and calcium levels on entry to the qualifying study among patients consenting to the follow-up were similar to those of the overall eligible patient population (data not shown).

Evaluation of post-transplant biochemical parameters and clinical outcomes

Consistently measured iPTH data were available for only 7/28 former cinacalcet patients; The mean ± standard error (SE) serum iPTH values at the qualifying-study baseline, kidney transplant and 1, 6 and 12 months after transplantation were 881 ± 160 ($n = 7$), 568 ± 325 ($n = 7$), 557 ± 243 ($n = 7$), 481 ± 205 ($n = 7$) and 880 ± 588 ($n = 5$) pg/ml, respectively (93 ± 17, 60 ± 34, 59 ± 26, 51 ± 22 93 ± 62 pmol/l, respectively). The corresponding median ($Q1$, $Q3$) values were 970 (399, 1249), 226 (136, 712), 229 (173, 1175), 322 (156, 528) and 393 (191, 471) pg/ml, respectively. No regular iPTH measurements were available for former placebo patients. Twelve months post-transplant, based on all patients who had available data at this time point, the mean ± SE iPTH values for the former cinacalcet ($n = 7$) and former placebo ($n = 5$) groups were 769 ± 415 pg/ml (82 ± 44 pmol/l) and 674 ± 301 pg/ml (72 ± 32 pmol/l), respectively. The mean value in former cinacalcet patients was heavily influenced by one patient with a very high iPTH concentration (3219 pg/ml); this patient had very high iPTH levels throughout the study (712 pg/ml, 1750 pg/ml, 1663 pg/ml at the qualifying-study baseline and 1 and 6 months after transplantation). The transplant failed in this patient; creatinine clearance was only recorded at Week 1. Excluding this patient, the mean ± SE iPTH value was 361 ± 86 pg/ml (38 ± 9.2 pmol/l) at Month 12. The median ($Q1$, $Q3$) values at Month 12 for the former cinacalcet and placebo patients were 393 (191, 706) and 245 (159, 1302) pg/ml, respectively (Table 2). Median iPTH values at other time points, for both former cinacalcet and former placebo patients for whom data were available, are presented in Table 2. Despite the small number of patients evaluated and the variability of the data, there did not appear to be any obvious difference between the two patient groups. One former cinacalcet patient (4%) and one former placebo patient (10%) underwent post-transplant parathyroidectomy.

In both groups, mean total calcium levels remained similar and relatively unchanged (Table 2) and mean plasma phosphorus concentrations decreased during the first month post-transplant, but remained relatively unchanged thereafter (Table 2).

Kidney transplant failure was apparent in one former cinacalcet-treated patient (4%) and three former placebo patients (30%); the mean ± SE duration of hospitalization immediately post-transplant in these two groups was

Table 2. Biochemical parameters before and after kidney transplantation in patients who had received either cinacalcet or placebo prior to the transplant and consented to follow-up[a]

	On entry to the qualifying study		At the end of the qualifying study and before kidney transplant		1 month post-transplant		6 months post-transplant		12 months post-transplant	
	Former placebo patients	Former cinacalcet patients	Former placebo patients	Former cinacalcet patients	Former placebo patients	Former cinacalcet patients	Former placebo patients	Former cinacalcet patients	Former placebo patients	Former cinacalcet patients
iPTH (pg/ml)[b]	552 [413, 960][e] (*n* = 10)	607 [484, 925][e] (*n* = 28)	542 [424, 785][e] (*n* = 9)	225 [131, 611][e] (*n* = 24)	221 [221, 221][e] (*n* = 1)	229 [173, 1175][e] (*n* = 7)	741 [68, 851][e] (*n* = 3)	322 [156, 491][e] (*n* = 11)	245 [159, 1302][e] (*n* = 5)	393 [191, 706][e] (*n* = 7)
	676 ± 114 (*n* = 10)	701 ± 57 (*n* = 28)	876 ± 241 (*n* = 9)	415 ± 105 (*n* = 24)	221 (*n* = 1)	557 ± 243 (*n* = 7)	553 ± 245 (*n* = 3)	409 ± 134 (*n* = 11)	674 ± 301 (*n* = 5)	769 ± 415 (*n* = 7)
Calcium (mg/dl)[c]	9.6 ± 0.2 (*n* = 10)	9.8 ± 0.1 (*n* = 28)	9.6 ± 0.3 (*n* = 8)	9.5 ± 0.2 (*n* = 23)	9.9 ± 0.3 (*n* = 9)	10.1 ± 0.2 (*n* = 27)	10.1 ± 0.3 (*n* = 9)	10.3 ± 0.2 (*n* = 27)	10.4 ± 0.3 (*n* = 9)	10.9 ± 0.5 (*n* = 19)
Phosphorus (mg/dl)[d]	6.2 ± 0.6 (*n* = 10)	6.4 ± 0.3 (*n* = 28)	6.9 ± 0.8 (*n* = 10)	5.2 ± 0.3 (*n* = 27)	2.4 ± 0.3 (*n* = 10)	2.2 ± 0.1 (*n* = 28)	2.9 ± 0.2 (*n* = 8)	2.7 ± 0.1 (*n* = 27)	3.8 ± 0.7 (*n* = 8)	3.0 ± 0.2 (*n* = 18)

iPTH = intact parathyroid hormone.
[a]Data are missing for some patients.
[b]iPTH: 1 pmol/l = 1 pg/ml × 0.10611.
[c]Calcium: 1 mmol/l = 1 mg/dl × 0.25.
[d]Phosphorus: 1 mmol/l = 1 mg/dl × 0.323
[e]Median [*Q*1, *Q*3] values
For iPTH, median [Q1, Q3], mean ± standard error values, and the number of patients on whom data are based, are shown. For calcium and phosphorus, mean ± standard error values are shown, together with the number of patients on whom the data are based.

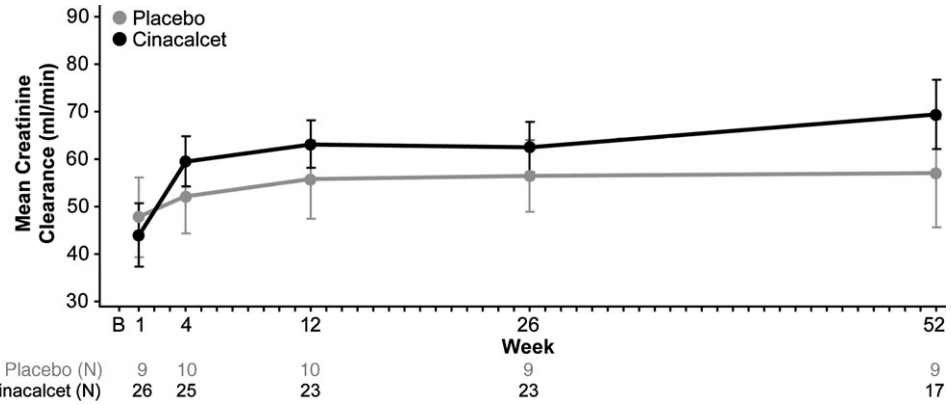

Fig. 1. Mean rates of creatinine clearance following kidney transplantation in patients who had received either cinacalcet or placebo prior to the transplant. Estimated glomerular filtration rate was calculated based on the Cockcroft and Gault formula [6]. Error bars represent standard errors.

2.3 ± 0.3 and 3.4 ± 0.8 weeks, respectively; mean values for creatinine clearance appeared consistently higher in former cinacalcet patients than former placebo (Figure 1). These differences were not statistically significant.

Discussion

The results from this study suggest that using cinacalcet to treat SHPT in patients with CKD awaiting kidney transplantation does not appear to modify SHPT-related post-transplant biochemical profiles compared with placebo. Limited data also suggest that cinacalcet does not appear to modify post-transplant clinical outcomes. In addition, former cinacalcet-treated patients did not appear to show large post-transplant changes in iPTH in our study—it is important that cinacalcet does not adversely impact on the post-transplant outcome of resistant hyperparathyroidism. However, our findings should be interpreted with caution because of the small sample size, within-group variability of the biochemical parameters we described and the possibility of bias. Its retrospective design made this study susceptible to population bias, but patients recruited were broadly representative of the overall eligible patient population from which they had been drawn. There was no patient selection bias within participating centres—all eligible patients were invited to enrol. However, measurement bias was a possibility—patients for whom no iPTH measurements were obtained may have had less severe SHPT, in which case an effect of cinacalcet may have been missed. Finally, the iPTH assays were measured at local laboratories and consequently there may have been some differences between assays that were not taken into account.

Although kidney transplantation can correct some abnormalities that result in SHPT and studies of early post-transplant changes [7,8] show that PTH levels may decrease, PTH may not completely normalize and data obtained 12 months post-transplant show that hyperparathyroidism may not have resolved [7]. Indeed, observational research examining post-transplant parameters has shown persistent hyperparathyroidism in ∼17% of patients [9]. Patients with moderate-to-severe SHPT before kidney transplant had a higher rate of persistent hyperparathyroidism (∼30%) and an incidence of hypercalcaemia of ∼50% during the first year post-transplant [9]. In several small studies of up to 6-month duration, cinacalcet controlled persistent hyperparathyroidism in kidney transplant recipients, significantly reducing serum calcium and PTH levels [10–18]. These studies indicate that cinacalcet is a promising therapeutic option for kidney transplant patients with persistent hyperparathyroidism, and a potential alternative to parathyroidectomy. Additional research is warranted to determine whether cinacalcet treatment should be withdrawn or continued in the peri- and post-transplant periods in patients with severe SHPT during dialysis.

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