Potential future uses of calcimimetics in patients with chronic kidney disease

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Abstract
Calcimimetics have proven effective in the treatment of secondary hyperparathyroidism (SHPT) in dialysis patients, and it may also have benefits in stage 3 and 4 chronic kidney disease (CKD). The efficacy of cinacalcet in the treatment of SHPT was investigated in a study of 54 patients with stage 3 and 4 CKD not receiving dialysis. A significant number of these patients achieved at least a 50% reduction in parathyroid hormone (PTH) from baseline with cinacalcet therapy compared with placebo (56% versus 19%; P = 0.006). Another potential use of cinacalcet is in the treatment of chronic kidney disease (CKD). The efficacy of the calcimimetic cinacalcet was recently explored in these two distinct patient populations. In this article, the manifestations of hyperparathyroidism in stage 3 and 4 CKD and in kidney transplant patients will be discussed, and data regarding the efficacy of cinacalcet in these two groups of patients will be presented.

Keywords: chronic kidney disease; persistent hyperparathyroidism; renal transplant

Introduction
Secondary hyperparathyroidism (SHPT) is often underdiagnosed or insufficiently treated in patients not yet receiving dialysis, when therapy would have greater short- and long-term benefits [1]. Hyperparathyroidism also frequently persists after successful renal transplantation [2,3] and is present in up to 50% of patients 1 year after renal transplant surgery [2,4]. Thus, early diagnosis and management of SHPT in chronic kidney disease (CKD) patients and recognition and treatment of persistent hyperparathyroidism in post-transplant patients is important and might reduce morbidity from cardiovascular and bone disease. The efficacy of the calcimimetic cinacalcet was recently explored in these two distinct patient populations. In this article, the manifestations of hyperparathyroidism in stage 3 and 4 CKD and in kidney transplant patients will be discussed, and data regarding the efficacy of cinacalcet in these two groups of patients will be presented.

Manifestations of stage 3 and 4 CKD
Patients with stage 3 and 4 CKD are more likely to die than to progress to end-stage renal disease [5]. Among patients with stage 3 CKD, 24.3% of patients died within 5 years versus 1.3% who progressed to renal replacement therapy. Among patients with stage 4 CKD, 45.7% died within 5 years, compared with 19.9% who progressed to dialysis or transplantation (Figure 1). SHPT is a well-recognized complication of stage 3 and 4 CKD. Accordingly, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommend treatment of SHPT in stage 3 and 4 CKD patients to reduce disease severity and associated morbidity [6]. The under-recognition and undertreatment of SHPT in these patients [1,7] has serious consequences, including vascular calcifications and bone disease [8,9]. Thus, in the context of SHPT, elevated serum phosphorus has been associated with increased mortality risk and with acute myocardial infarction in CKD patients not receiving dialysis [10].

The hypercalcaemia, hyperphosphataemia and increased calcium–phosphorus product (Ca × P) associated with SHPT contribute to the development of vascular calcifications that are commonly observed in chronic dialysis patients [11,12]. The process of vascular calcification begins early in the progression of CKD and continues as kidney function declines [9,13,14]. The incidence of vascular calcifications among CKD patients not receiving dialysis is 40% [9]; this value increases to 64% in patients who are starting dialysis [13] and to 83% in patients established on dialysis [14]. SHPT also contributes to renal bone disease, which may cause additional morbidity in haemodial-
Cinacalcet treatment in stage 3 and 4 CKD

Manipulation of the calcium-sensing receptor (CaR) impacts the synthesis and secretion of parathyroid hormone (PTH) and parathyroid gland hyperplasia. Calcimimetics, by modulating the CaR, can directly address the pathophysiology of SHPT early in CKD. Charytan et al. [16] reported the results of a double-blind, placebo-controlled trial to determine the safety and efficacy of cinacalcet in 54 patients with stage 3 and 4 CKD. All patients included in the study had a serum intact PTH (iPTH) concentration of >130 pg/mL and a serum calcium concentration of >9.0 mg/dL. Phosphate-binder and/or vitamin D therapy was permitted during the study. Doses of vitamin D could be adjusted appropriately: decreased if hypercalcaemia (calcium >11 mg/dL) or hyperphosphataemia (phosphorus >5.5 mg/dL) occurred, or increased if serum calcium was <8.4 mg/dL or iPTH concentrations were at least 50% greater than baseline on three consecutive visits. The study design consisted of a 12-week titration phase during which the cinacalcet dose was adjusted between 30 and 180 mg/day according to the iPTH and calcium concentrations. Efficacy was assessed during the following 6 weeks of treatment by measuring weekly iPTH concentrations.

More patients treated with cinacalcet achieved the primary endpoint of at least a 30% reduction in iPTH from baseline compared with placebo-treated patients (56% versus 19%, *P* = 0.006; Figure 2). After 2 weeks, mean iPTH decreased by approximately 33% in the cinacalcet group and remained approximately 30% to 40% below baseline for the duration of the study. In contrast, mean iPTH in the placebo group remained near baseline levels throughout the study (Figure 3).

Mean serum calcium concentrations were decreased by 7% in the cinacalcet treatment group but were unchanged (−0.1%) in the placebo group. Patients with CKD not on dialysis receiving cinacalcet were more likely to experience low serum calcium levels compared with those on dialysis [17–20]. In most instances, low serum calcium concentrations (<8.4 mg/dL) were successfully treated by increasing the dose of vitamin D sterols, phosphate binders and/or calcium supplements. Four patients discontinued treatment because of low serum calcium while receiving the lowest dose of cinacalcet, and serum calcium levels returned to normal after stopping therapy. The increased likelihood of hypocalcaemia appeared to be associated with lower calcium concentrations before the commencement of cinacalcet therapy in stage 3 and 4 CKD patients. Urinary calcium excretion was more elevated in the cinacalcet group compared with the placebo group (*P* < 0.05; Table 1) but
iPTH levels were measured over a 0.5- to 3 clinical trial.

The patient population requires further investigation in a phase determination of an appropriate dosing strategy for this strat. These findings need to be confirmed, and in particular the treatment of SHPT in stage 3 and 4 CKD patients.

In addition, cinacalcet was well tolerated in this population of stage 3 and stage 4 CKD patients. The most common adverse events were nausea, myalgia and diarrhoea (Table 2).

Table 2. Most common adverse events in stage 3 and 4 CKD patients treated with placebo or cinacalcet

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Placebo (n = 26)</th>
<th>Cinacalcet (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2 (7.7)</td>
<td>9 (33.3)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4 (15.4)</td>
<td>7 (25.9)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>4 (15.3)</td>
<td>6 (22.2)</td>
</tr>
</tbody>
</table>

Data from Charytan et al. [16].

remained below the upper limit of normal (300 mg/24 h) in both treatment groups.

Mean serum phosphorus concentrations were increased in the cinacalcet treatment group but were unchanged in the placebo group (P < 0.05, cinacalcet versus placebo). This effect of cinacalcet was most likely due to reduced PTH secretion, resulting in reduced urinary excretion of phosphorus. Consistent with this hypothesis, 24-h urine phosphorus excretion was decreased by 13.3% in the cinacalcet group and was unchanged in the placebo group (−1.5%; P = 0.19). In the cinacalcet group, Ca × P increased 6.7% from baseline, whereas in the placebo group, Ca × P increased 3.2% from baseline. Importantly, in both the cinacalcet- and placebo-treated groups, the mean values of serum calcium and phosphorus remained within normal limits at each visit.

The glomerular filtration rate was not significantly changed from baseline in either treatment group (Table 1). In addition, cinacalcet was well tolerated in this population of stage 3 and stage 4 CKD patients. The most common adverse events were nausea, myalgia and diarrhoea (Table 2). These side effects were of mild to moderate severity and of short duration. In summary, the results of this study demonstrate, for the first time, the efficacy and safety of cinacalcet in the treatment of SHPT in stage 3 and 4 CKD patients. These findings need to be confirmed, and in particular the determination of an appropriate dosing strategy for this patient population requires further investigation in a phase 3 clinical trial.

Kidney transplant patients

Hyperparathyroidism frequently persists after successful renal transplantation [2,3]. In a study by Lobo et al. [4], iPTH levels were measured over a 0.5- to >4-year period in 52 patients with intact graft function after renal transplantation. One year after transplantation, iPTH remained elevated (≥65 pg/mL) in more than 50% of patients. In a similar study, iPTH values were measured in the month preceding kidney transplant and over a mean 69-month follow-up period after transplant in 62 patients with stable graft function [21]. After >2.5 years following transplantation, only 23% of transplant patients with good renal function had normal iPTH levels, and 27% of patients had iPTH values more than twice the upper normal limit (>130 pg/mL) [21].

Persistent hyperparathyroidism causes hypercalcaemia, which is commonly observed following renal transplantation. In a study of 129 transplant patients, Reinhardt et al. [22] found that 52% were hypercalcemic (>10 mg/dL) 3 months after kidney transplantation, and 15% were still hypercalcemic at 24 months [22]. Post-transplant hypercalcaemia may pose a significant risk for renal and vascular calcifications following transplantation and a subsequent increased risk of cardiovascular death [relative risk (RR) = 2.6; P = 0.033] and overall mortality (RR = 1.8; P = 0.015) [23]. In the study by Gwinn et al., calcifications in the kidneys were present in 26% of renal transplant patients, and those patients with calcifications had both elevated iPTH and calcium [24]. Interestingly, even though there was no association between serum phosphorus and vascular calcification, post-transplant phosphorus supplementation occurred more frequently in those with vascular calcification [24]. Persistent hyperparathyroidism is also associated with high bone turnover and may contribute to bone disease following transplantation [25].

Of interest, there is a strong relationship between pretransplant and post-transplant hyperparathyroidism. Pretransplant iPTH level was significantly correlated (r = 0.58; P = 0.0001) with post-transplant iPTH level in patients with normal transplant function >2.5 years after transplantation [21]. A similar relationship between pre- and post-transplant iPTH levels was reported by Messa et al. [26]. Correlations between pretransplant and posttransplant iPTH levels have been shown to persist for up to 4 years after transplantation [2]. These studies suggest that treatment of hyperparathyroidism and hypercalcaemia before transplant surgery might help reduce the severity of hyperparathyroidism after transplantation.

The current treatment strategies for hyperparathyroidism after renal transplantation are limited and have important
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Table 3. Baseline demographics in renal transplant patients with persistent hyperparathyroidism

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference(s)</th>
<th>Study duration</th>
<th>Cinacalcet patients (n)</th>
<th>PTH</th>
<th>Ca</th>
<th>P</th>
<th>Ca × P</th>
<th>Immuno-suppressants</th>
<th>Graft function (creatinine clearance or serum creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serra et al.</td>
<td>[33,38]</td>
<td>6 months</td>
<td>12</td>
<td>↓</td>
<td></td>
<td></td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Kruse et al.</td>
<td>[36]</td>
<td>3 months</td>
<td>14</td>
<td>↓ns</td>
<td></td>
<td></td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Szwarc et al.</td>
<td>[35]</td>
<td>6 months</td>
<td>9</td>
<td>↓</td>
<td></td>
<td></td>
<td>↑ns</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Leca et al.</td>
<td>[37]</td>
<td>6 months</td>
<td>10</td>
<td>↓</td>
<td></td>
<td></td>
<td>↑ns</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Srinivas et al.</td>
<td>[40]</td>
<td>18 months</td>
<td>11</td>
<td>↓ns</td>
<td></td>
<td></td>
<td>↑</td>
<td>NR</td>
<td>↔</td>
</tr>
<tr>
<td>Apostolou et al.</td>
<td>[39]</td>
<td>18 months</td>
<td>7</td>
<td>↓</td>
<td></td>
<td></td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Apostolou et al.</td>
<td>[41]</td>
<td>14 months</td>
<td>2</td>
<td>↓ns</td>
<td></td>
<td></td>
<td>↑ns</td>
<td>NR</td>
<td>↔</td>
</tr>
<tr>
<td>El-Amm et al.</td>
<td>[41]</td>
<td>6 months</td>
<td>18</td>
<td>↓</td>
<td></td>
<td></td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
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<tr>
<td>Total</td>
<td></td>
<td></td>
<td>83</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

NR, not reported; ns, not significant. Arrows indicate increases, decreases or no change.

Table 4. Summary of results from cinacalcet studies in post-transplant patients

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side effects. As mentioned above, phosphorus supplementation has been associated with the occurrence of interstitial calcifications in the graft [24]. Vitamin D therapy may worsen hypercalcaemia [27]. Bisphosphonates generally do not reduce PTH levels significantly and may promote low turnover bone disease [28]. Parathyroidectomy is effective to lower PTH and to correct hypercalcaemia; however, several studies have suggested that renal allograft function may deteriorate, and cases of graft loss have been described after parathyroidectomy [29–32]. Based on these data, more suitable and safer therapies that correct persistent hyperparathyroidism and hypercalcaemia and the consequent morbidity would be beneficial to this group of patients.

Cinacalcet treatment in renal transplant patients

Given that hyperparathyroidism remains a problem for many patients after successful renal transplantation [2–4], and because there are few effective therapeutic options [33], there has been interest in novel treatments for the control of hyperparathyroidism in this group of patients. The effect of cinacalcet in patients with persistent hyperparathyroidism after renal transplant has been reported in a number of small prospective and retrospective open-label studies in transplant patients with stable allograft function [34–41]. In general, patients in these studies had stable renal function with mean creatinine clearances in the range of 30–75 mL/min. The primary objective of cinacalcet therapy was control of post-transplant hypercalcaemia, and cinacalcet was titrated to achieve this endpoint. Oral vitamin D therapy was not permitted in the studies by Szwarc et al. [35], Serra et al. [33,38] and Srinivas et al. [40] but was permitted in the study by Kruse et al. [36]. Leca et al. [37] avoided the use of vitamin D, whereas Apostolou et al. [34,39] allowed its use once calcium levels were normalized. The duration of treatment in these studies was up to 18 months. In general, the cinacalcet dosage needed to control hypercalcaemia was relatively low (average, 30–40 mg/day).

Baseline characteristics of the studies are summarized in Table 3. Overall, efficacy results across the studies were consistent (Table 4). Within 2 to 4 weeks of cinacalcet treatment, serum iPTH was significantly reduced and maintained over the treatment duration (10 weeks to 14 months) [34,35,37,38]. In the study by Kruse et al. [36], the sustained reduction in iPTH levels after cinacalcet treatment was not significant because of large iPTH differences among patients and the small sample size. Leca et al. reported that
cinacalcet reduced serum iPTH from baseline by an average of 40% during the first month of treatment; iPTH levels remained 40–50% lower than baseline for the duration of the 6-month follow-up [37]. Similarly, Serra et al. [33] observed a maximal reduction in iPTH following 8 weeks of cinacalcet treatment, with reduced iPTH being maintained for 26 weeks (Figure 4).

Cinacalcet significantly reduced calcium levels within days of treatment, and calcium levels overall were maintained in the normal range over the treatment periods [33–41]. Serra et al. [33] reported that serum calcium was maintained within normal limits in all patients for 6 months, with serum-ionized calcium being reduced by 17.7%. Kruse et al. [36] reported normalization of serum calcium in 12 of 14 patients. In the case report by Apostolou et al. [34], calcium levels declined rapidly after just 1 day of cinacalcet treatment. In general, serum phosphorus remained unchanged or was increased towards the normal range [34–41]. In one study, after 6 months of treatment with cinacalcet, 90% of patients had serum phosphorus levels within the normal range [33]. When it was measured, serum Ca × P remained unchanged (Table 4) [33,35,36,38,41].

Graft function was measured in seven studies of renal transplant patients treated with cinacalcet, and renal function remained stable in five of the studies (Table 4) [33–36,38–41]. In one study, the glomerular filtration rate, measured by serum creatinine prediction equations, declined over the observation period of cinacalcet treatment; however, the observation period was only 3 months, precluding conclusions regarding long-term graft function [36]. In another study [41], the decline in the glomerular filtration rate after cinacalcet therapy was consistent with the rate of decline before treatment, and therefore, this may not have been a result of cinacalcet therapy. There was no reported interference of cinacalcet with immunosuppressants, and no increase in rejection episodes was reported in these studies. In summary, the results of these small studies show that treatment with cinacalcet effectively normalized hypercalcaemia and significantly reduced iPTH levels in renal transplant recipients, without adversely affecting graft function. Larger studies are required to confirm these findings and to obtain long-term data regarding safety and efficacy.

Summary and conclusions

In patients undergoing chronic dialysis, cinacalcet has been demonstrated to substantially improve the control of SHPT compared with standard care [17–19,42,43]. The role of calcimimetics in the treatment of SHPT in stage 3 and 4 CKD patients and in the treatment of persistent hyperparathyroidism in post-transplant patients is less well characterized. Nonetheless, the CaR is a promising target for these two distinct patient populations.

In the early studies reported here, cinacalcet significantly reduced iPTH concentrations by more than 30% in most patients with stage 3 and 4 CKD. In kidney transplant patients, cinacalcet therapy significantly reduced calcium and iPTH levels and placed phosphorus into the normal range. These early clinical studies suggest that cinacalcet is effective in controlling mineral metabolism in patients with stage 3 and 4 CKD and post-renal transplantation. Because these studies were of short duration and included only small numbers of patients, long-term studies in larger groups of patients are needed to fully evaluate the efficacy and safety of cinacalcet in these populations.

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