Long-term treatment of secondary hyperparathyroidism with the calcimimetic cinacalcet HCl

Sharon M. Moe1, John Cunningham2, Ju¨rgen Bommer3, Stephen Adler4, Steven J. Rosansky5, Pablo Urena-Torres6, Moetaz B. Albizem7, Matthew D. Guo7, Valter J. Zani7, William G. Goodman8 and Stuart M. Sprague9

1Indiana University School of Medicine and Roudebush VAMC, Indianapolis, IN, USA, 2The Middlesex Hospital, London, UK, 3Klinikum der Universität Heidelberg, Heidelberg, Germany, 4Westchester Medical Center, NY Med College, Valhalla, NY, USA, 5WJB Dorn Veterans Hospital, Columbia, SC, USA, 6Clinique de l’Orangerie, Aubervillers, France, 7Amgen Inc, Thousand Oaks, CA, USA, 8UCLA School of Medicine, Los Angeles, CA, USA and 9Evanston Northwestern Healthcare and Northwestern University Feinberg School of Medicine, Evanston, IL, USA

Abstract

Background. Patients with secondary hyperparathyroidism often require therapy that provides long-term control of parathyroid hormone concentrations without increasing calcium and phosphorus concentrations. Cinacalcet modulates the calcium-sensing receptor on the parathyroid gland to reduce secretion of parathyroid hormone and lower serum calcium, phosphorus and calcium–phosphorus product in haemodialysis patients.

Methods. Dialysis patients with secondary hyperparathyroidism [parathyroid hormone (PTH) level ≥300 pg/ml] who were enrolled in one of four phase 2 placebo-controlled studies were eligible to enrol in an open-label extension study in which all patients received cinacalcet. For this extension study, cinacalcet was initiated at 30 mg in all patients and the dose was escalated to a maximum of 180 mg once daily if PTH concentrations were >250 pg/ml. Use of concomitant vitamin D sterols and phosphate binder therapy remained stable. Cinacalcet was safe and generally well tolerated at doses up to 180 mg/day.

Conclusions. In this long-term study, cinacalcet effectively sustained reductions in PTH for up to 3 years without increasing concentrations of serum calcium, phosphorus or calcium–phosphorus product.

Keywords: calcium-sensing receptor; chronic kidney disease; end-stage renal disease; haemodialysis; parathyroid hormone

Introduction

Secondary hyperparathyroidism, a common complication of chronic kidney disease, is characterized by increased parathyroid hormone (PTH); the most widely recognized complication of secondary hyperparathyroidism is renal osteodystrophy [1,2]. The accompanying abnormalities in bone metabolism, together with the abnormal mineral metabolism that result from secondary hyperparathyroidism, are associated with poor quality of life, fractures, and increased mortality [3–7]. Current treatment addresses the prevention and reduction of secondary hyperparathyroidism through dietary phosphate restriction, administration of calcium or non-calcium-containing phosphate binders, phosphate removal by dialysis, maintenance of adequate serum calcium concentrations, and the administration of calcitriol or other vitamin D sterols to suppress PTH. Surgical parathyroidectomy may be required in cases of uncontrolled, severe secondary hyperparathyroidism. In patients undergoing maintenance dialysis therapy, increased serum phosphorus concentrations and calcium–phosphorus product are...
Control of Secondary HPT with Cinacalcet HCl

associated with an increased risk of cardiac, visceral and vascular calcifications [8,9], and an increased risk of cardiovascular death [10–14]. Unfortunately, these complications also frequently arise in response to therapy with vitamin D and/or calcium-based phosphate binders, requiring withholding treatment for safety considerations. Repeated interruptions in therapy lead to inadequate PTH control and disease progression [6,15]. Recognition of the complications of abnormally bone and mineral metabolism has led to the proposal of new National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQITM) targets for PTH (150–300 pg/ml), serum calcium (8.4–9.5 mg/dl), phosphorus (3.5–5.5 mg/dl) and calcium–phosphorus product (<55 mg²/dl²) [16]. These targets are difficult to achieve in most patients receiving dialysis, with an estimated 50% of dialysis patients not achieving guideline targets for PTH concentrations [1,17]. Thus, new therapies are needed to treat this serious disorder.

Cinacalcet HCl is a calcimimetic agent that acts as an allosteric modulator of the calcium-sensing receptor present on the surface of parathyroid cells. By targeting the calcium-sensing receptor, cinacalcet provides a new means of regulating PTH secretion by amplifying the receptor’s sensitivity to extracellular calcium and reducing PTH concentrations. Results from clinical trials examining single and multiple doses up to 180 mg once daily suggest that treatment with cinacalcet not only reduces plasma PTH concentrations but also leads to a concomitant decrease of serum calcium and phosphorus in patients with secondary hyperparathyroidism receiving haemodialysis [9,18–20]. This study was designed to investigate the long-term use of cinacalcet to treat secondary hyperparathyroidism in patients receiving maintenance dialysis.

Subjects and methods

Research patients

The institutional review boards of the participating medical centres approved the protocol, and all patients gave written informed consent before any study-related procedures were conducted. For patients to be eligible for this open-label extension study, they must have participated in one of four randomized, placebo-controlled qualifying phase 2 trials. The inclusion criteria for these qualifying studies were age ≥18 years, receiving maintenance haemodialysis, plasma PTH concentration ≥300 pg/ml, serum calcium concentration ≥8.8 mg/dl but <11.0 mg/dl, calcium–phosphorus product <70.0 mg²/dl², haemoglobin concentration >9.0 g/dl or a haematocrit >27%, and liver transaminases and bilirubin concentrations no more than twice the upper limit of normal. Additionally, patients were required to be medically stable with no evidence of an active infectious or malignant process and no evidence of diseases known to cause hypercalcaemia. Patients were to be receiving a constant dose of vitamin D and phosphate binders (if prescribed) for at least 21 days and receiving a stable dialysate calcium concentration for at least 7 days before the first day of study drug administration.

Study design

All patients who completed a qualifying phase 2 study were offered enrolment into the extension study (Figure 1). Every patient who enrolled in the open-label extension study received cinacalcet and the dose was titrated from an initial dose of 30 mg, without a washout period. Eligible patients began the open-label extension study the day of their end-of-study assessment for the qualifying phase 2 study.

During the initial 12-week dose-titration phase of the extension study, patients received escalating doses of cinacalcet every 3 weeks from 30 to 100 mg to achieve plasma PTH concentrations ≤250 pg/ml. During the study, the protocol was amended to allow higher doses of cinacalcet (up to 180 mg) for patients who did not achieve the PTH target. Patients were not eligible for cinacalcet dose increases if their corrected serum calcium concentration was <8.0 mg/dl or if an adverse event occurred that precluded a dose increase. The dose of cinacalcet was reduced if the PTH concentration was <100 pg/ml. To mimic clinical practice, no restrictions were imposed on the dose or type of phosphate-binding drug or vitamin D sterol used.

Laboratory data were collected weekly during the titration phase, every 8 weeks during the first year of the maintenance phase, and every 12 weeks thereafter. Investigators could request additional laboratory tests as needed throughout the study. All laboratory and PTH determinations were performed at a central laboratory (Covance Laboratory Services, Inc, Indianapolis, IN). Plasma PTH concentrations were determined by the central laboratory using a double-antibody immunoradiometric assay for the intact hormone (Nichols Institute Diagnostics, San Juan Capistrano, CA).

Study assessments

The primary assessments included evaluation of long-term treatment with cinacalcet on plasma PTH, serum calcium, phosphorus and calcium–phosphorus product, and concomitant therapy with vitamin D and phosphate binders in subjects who completed all 2 years (100 weeks) of the extension study. In addition, the same assessments were analysed for patients who completed 3 years of study that included 1 year as the cinacalcet treatment group of a phase 2 controlled study plus the 2 years of the open-label extension study. For all analyses, results at weeks 52 and 100 were compared to the phase 2 qualifying study baseline, before any patient was treated with cinacalcet. Safety was evaluated by reports of adverse events.
Statistical analysis

All patients who received at least one dose of cinacalcet were evaluated for efficacy and safety. To evaluate the effects of long-term treatment with cinacalcet on the concentration of plasma PTH, three types of analyses were performed including the number of patients who achieved plasma PTH/C20 ≤250 pg/ml (reflecting the primary endpoints of the phase 2 studies), the number of patients who achieved plasma PTH/C20 ≥300 pg/ml (reflecting the recent NKF-K/DOQI guidelines [16]), and the percentage of patients with a ≥30% reduction in plasma PTH at each measurement time point of the extension study. The proportion of patients who achieved each of these PTH targets at weeks 52 and 100 was compared to the proportion at baseline of the qualifying studies using a McNemar’s Test. Baseline laboratory values and patient characteristics represent data collected during the 30 days before patients entered each of the four qualifying phase 2 studies. Results were expressed as means ± standard error of the mean (SEM) and categorical variables were expressed as a percentage of all patients in the dataset. Percentage change in PTH was compared to the PTH level before enrolment into the qualifying studies using a paired t-test. The incidence of all adverse events within this extension study was summarized by body system and preferred terms.

Results

Patients

A total of 170 patients were enrolled into the open-label extension study and 59 completed at least 2 years of the extension study. Patients discontinued the study due to adverse events (17 patients), noncompliance/administrative decision (16 patients), kidney transplant (14 patients), withdrawal of consent (13 patients), death (8 patients), and other causes (12 patients) including 2 patients who underwent a parathyroidectomy. The remaining 31 patients were not included because they had not yet reached 100 weeks of treatment. Nausea was the most common adverse event that led to discontinuation, which occurred in 7 patients. All other adverse events that led to discontinuation occurred in no more than one patient. Baseline demographics, disease characteristics and laboratory values for the 59 patients are given in Table 1. The patients enrolled in this study were characteristic of the dialysis population treated for secondary hyperparathyroidism in the community setting.

Study assessments (PTH, serum calcium, serum phosphorus, and Ca × P)

PTH values. The mean (SEM) plasma PTH concentration at the beginning of the phase 2 qualifying studies, before treatment with either cinacalcet or placebo was 590 (39) pg/ml. Mean (SEM) plasma PTH concentrations at the beginning of the extension study were 445 (57) pg/ml in patients who received cinacalcet (n = 28) in the phase 2 qualifying studies and 730 (86) pg/ml in those who received placebo (n = 31) (Table 1). After these 59 patients had received

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Table 1. Patient demographics/characteristics and baseline laboratory values

<table>
<thead>
<tr>
<th>Baseline (n = 59)a</th>
<th>Values at start of extension study</th>
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<tbody>
<tr>
<td></td>
<td>Cinacalcet n = 28</td>
</tr>
<tr>
<td>Sex (n/%)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>26 (44)</td>
</tr>
<tr>
<td>Men</td>
<td>33 (56)</td>
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<tr>
<td>Race (n/%)</td>
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</tr>
<tr>
<td>White</td>
<td>28 (47)</td>
</tr>
<tr>
<td>Black</td>
<td>23 (39)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Age (years)</td>
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</tr>
<tr>
<td>Mean (SEM)</td>
<td>51 (1.7)</td>
</tr>
<tr>
<td>Range</td>
<td>29–76</td>
</tr>
<tr>
<td>Duration of dialysis (months)</td>
<td>77 (9)</td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>1–244</td>
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<tr>
<td>Baselineb (beginning of phase 2 qualifying study)</td>
<td></td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td></td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>590 (39)</td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td></td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>9.7 (0.1)</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
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</tr>
<tr>
<td>Mean (SEM)</td>
<td>5.8 (0.2)</td>
</tr>
<tr>
<td>Ca × P product (mg²/dl²)</td>
<td></td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>56.4 (1.6)</td>
</tr>
</tbody>
</table>

Note: All patients completed one of four separate, randomized, placebo-controlled phase 2 trials before enrolling in the extension study. aBaseline is entry at start of qualifying phase 2 studies. These 59 patients were then all restarted on 30 mg cinacalcet as part of the open-label extension study. bBaseline value of the extension study before receiving treatment with cinacalcet.
cinacalcet for 1 year in the extension study (week 52), PTH concentrations were 437 (56) pg/ml ($P = 0.019$). After 2 years of treatment in the extension study (week 100), PTH was 451 (65) pg/ml ($P = 0.025$). Forty-seven percent and 53% of patients had achieved a PTH concentration $\leq 250$ pg/ml after 1 and 2 years (52 and 100 weeks) of treatment in the extension study, respectively ($P < 0.001$ for both time points). A slightly higher proportion of patients had a plasma PTH concentration $\leq 300$ pg/ml at the 1 and 2 year time points (52 and 59%, respectively) ($P < 0.001$ for both time points) (Figure 2). After 1 year of cinacalcet treatment in the extension study, 57% of the 59 patients had a $\geq 30\%$ reduction from the qualifying study baseline plasma PTH value ($P < 0.001$). By the end of the 2 years of the extension study, 66% of patients had achieved a $\geq 30\%$ reduction in plasma PTH from the baseline value ($P < 0.001$).

![Figure 2: Number of patients who achieved an intact parathyroid hormone concentration $\leq 300$ pg/ml during the 2-year open-label extension study. For the baseline data (end of qualifying studies and entry into extension study): shaded box = patients who had received placebo in the double-blind qualifying study; open box = patients who received cinacalcet. Numbers on top of bar indicate the number of patients who achieved a PTH $\leq 300$ pg/ml over the number of patients with evaluable data. Numbers inside box are the percentages of patients who achieved this PTH level.](image)

In the patients who achieved PTH $\leq 250$ pg/ml at week 52 and 100, the mean (SE) baseline PTH was 457 (63) and 477 (58) pg/ml, respectively. In patients who did not achieve PTH $\leq 250$ pg/ml at week 52 and 100, the mean (SE) baseline PTH was higher: 693 (83) and 725 (92) pg/ml, respectively. However, 85% of all patients, regardless of baseline PTH value, achieved a PTH value $\leq 250$ pg/ml at some point during the study. There was no difference in the proportion of patients who experienced a serum calcium $< 8.4$ mg/dl between those patients who achieved and did not achieve the PTH target at weeks 52 and 100.

**PTH values in patients who received cinacalcet for 3 years.** Sixteen patients completed 3 years of treatment with cinacalcet, including 1 year in the cinacalcet treatment group of the phase 2 qualifying double-blind study and 2 years of the extension study. Mean (SEM) plasma PTH concentration in these patients was 547 (46) pg/ml at baseline in the qualifying study and this concentration decreased to a mean (SEM) of 446 (64) pg/ml after 1 year in the extension study ($P = 0.321$), and to a mean (SEM) of 390 (70) pg/ml after 2 years in the extension study ($P = 0.056$) (total of 3 years on study; Figure 3). Fifty-nine percent of these 16 patients completing 3 years of therapy achieved a PTH $\leq 300$ pg/ml after 2 years in the extension study and 70% of patients achieved a $\geq 30\%$ reduction in PTH concentration from baseline of the qualifying phase 2 studies.

**Serum calcium, phosphorus and Ca$\times$P values.** Serum calcium, phosphorus, and calcium–phosphorus product remained stable during the extension study (Table 2). The proportion of patients with serum calcium $> 10.2$ mg/dl, serum phosphorus $> 6.0$ mg/dl and Ca$\times$P $> 60$ mg$^2$/dL$^2$ was not significantly different from baseline at weeks 52 or 100. Approximately 30% of patients had serum calcium $> 10.2$ mg/dl and $\sim 35\%$ had serum phosphorus $> 6.0$ mg/dl or Ca$\times$P $> 60$ mg$^2$/dL$^2$ at these two time points. Serum calcium concentrations were $< 8.4$ mg/dl in four and three

![Figure 3: Mean (SEM) intact parathyroid hormone concentration at each scheduled visit for the subset of patients who completed 3 years of therapy. Open circles = placebo ($n = 17$); closed circles = cinacalcet ($n = 16$). The first year of therapy was 1 year as the treatment group in a 1 year phase 2 study. Years 2 and 3 are the extension study, when all patients received cinacalcet.](image)
Achievement of NKF-K/DOQI targets

Greater than 50% of all patients treated with cinacalcet achieved the NKF-K/DOQI target recommended by the National Kidney Foundation for PTH after 52 and 100 weeks of treatment (Table 3) ($P < 0.001$, compared with baseline). These results are consistent with the study by Moe et al. [21] in which patients were treated with cinacalcet or placebo for 26 weeks. In that study, 56, 49, 46 and 65% of patients given cinacalcet achieved the NKF-K/DOQI targets for PTH, serum calcium, phosphorus and Ca×P, compared with 10, 24, 33 and 36%, respectively, for those given placebo.

Dose of cinacalcet

The median dose for patients who achieved a PTH ≤300 pg/ml was 70 mg at weeks 52 and 100. The median dose for patients who achieved a PTH reduction from baseline of ≥30% was 90 and 70 mg at weeks 52 and 100, respectively.

Concomitant therapy

Neither the proportion of patients receiving vitamin D sterols or phosphate binders nor the average dose of vitamin D sterols or phosphate binders significantly changed throughout the extension study. At baseline of

<table>
<thead>
<tr>
<th>Recommended NKF-K/DOQI targets</th>
<th>Baseline of qualifying study n (%)</th>
<th>Week 52 n (%)</th>
<th>Week 100 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH ≤300 pg/ml</td>
<td>6 (10%)</td>
<td>30 (52%)</td>
<td>35 (59%)</td>
</tr>
<tr>
<td>Serum calcium ≥8.4 to ≤9.5 mg/dl</td>
<td>25 (42%)</td>
<td>23 (40%)</td>
<td>22 (37%)</td>
</tr>
<tr>
<td>Serum phosphorus ≥3.5 to ≤5.5 mg/dl</td>
<td>19 (32%)</td>
<td>21 (37%)</td>
<td>22 (37%)</td>
</tr>
<tr>
<td>Ca×P &lt;55 mg$^2$/dl$^2$</td>
<td>25 (42%)</td>
<td>32 (56%)</td>
<td>31 (53%)</td>
</tr>
</tbody>
</table>

*P < 0.001 using the McNemar’s test.

Safety analyses

Adverse events were mostly mild to moderate in severity. Nausea and vomiting were the most common adverse events (seen in 34 and 44%, respectively, of patients). Nausea and vomiting resolved in 16 of these patients without any intervention, the dose of cinacalcet was reduced in five patients, and anti-emetics were administered to 16 of these patients. No patients were hospitalized during the study because of nausea or vomiting.

Discussion

The results of this long-term study suggest that cinacalcet can effectively maintain reductions in PTH for up to 2 years without increasing concentrations of serum calcium or phosphorus, increasing Ca×P, and without any attenuation of effect. Furthermore, therapy in a subset of patients treated for 3 years showed sustained efficacy and safety. The continued control of PTH over 3 years with cinacalcet in a subgroup suggests that this agent can stabilize the disease process and prevent disease progression. Fifty-two percent and 59% of patients had a PTH concentration ≤300 pg/ml at weeks 52 and 100, respectively. This level of PTH is associated with relatively normal bone turnover [22–24], and is consistent with the NKF-K/DOQI guidelines [16]. However, definitive evidence of the positive effect of cinacalcet treatment on bone morphology and bone turnover in humans is not yet published, but positive effects have been presented in abstract form [25]. It should also be noted that the measurement of PTH in this study was 24 h after the administration of cinacalcet, whereas maximum PTH suppression occurs after 4–6 hours [26]. Thus, our data probably underestimate the number of patients who achieve PTH control. This oscillatory pattern of PTH suppression, which is not seen in patients treated with vitamin D, may have a stimulatory effect on osteoblast bone formation [27], forming the basis for the use of intermittent PTH as an anabolic
therapy for post-menopausal osteoporosis. Short-term data reported in an abstract demonstrated that rats treated with cinacalcet had improved bone strength by biomechanical testing, the best predictor of reduced fractures [28].

We attempted to identify characteristics of the patients who achieved and did not achieve the PTH target of ≤250 pg/ml at weeks 52 and 100. Baseline PTH concentrations were higher in patients who did not achieve the PTH target, compared with those who did achieve the target; therefore, disease severity at baseline may be a contributing factor in achieving the target PTH. Intuitively, if the baseline PTH value is higher, it is more difficult to lower PTH to an absolute target. PTH variability may be a contributing factor in the overall proportion of patients who achieve the PTH target. The proportion of patients who met the PTH target at any time point during the study was 85%, even if they did not achieve the target PTH at weeks 52 or 100. These results suggest that a greater proportion of patients may have responded to cinacalcet therapy if efficacy was assessed at more than two time points. A review of laboratory parameters, concomitant therapy and doses of cinacalcet provided no additional observations indicating characteristics that were common among patients who achieved and did not achieve the PTH target.

Cinacalcet is a type II calcimimetic, which are allosteric activators of the calcium-sensing receptor. Allosteric activators of the calcium-sensing receptor also include certain L-amino acids and phenylalkylamine derivatives. These type II calcimimetics interact with the membrane-spanning segments of the calcium-sensing receptor and enhance signal transduction, reducing the threshold for calcium-sensing receptor activation, thereby reducing PTH secretion in the absence of a change in concentration of extracellular calcium. Activation of the calcium-sensing receptor not only reduces hormone secretion but also decreases parathyroid cell proliferation [29]. Because cinacalcet is an allosteric activator, and not a receptor agonist, the receptor is constantly subjected to increases in serum calcium concentrations and responds by turning off the secretion of PTH; the receptor concentration and affinity remain unchanged. For these reasons, it is not surprising that cinacalcet has sustained efficacy.

The duration of clinical experience presented in our study is significantly longer than recently published reports of prospective clinical trials with vitamin D analogues [22,30–33]. In addition, patients enrolled in our study had received dialysis for a mean of 6.4 years and had elevated PTH levels despite traditional therapy, including vitamin D sterols in ~92% of patients and phosphate binders in ~90% of patients, suggesting a considerable attempt to treat hyperparathyroidism in these patients.

Conventional therapies of vitamin D may suppress PTH concentrations, but often with a concomitant increase in serum calcium and phosphorus concentrations. These limitations lead to undertreatment of the disease, interruptions in therapy, and further progression of secondary hyperparathyroidism [6]. Evidence for these limitations is demonstrated in a retrospective study comparing the efficacy of calcitriol and paricalcitol in clinical practice over a 3 year period [33]. After 3 months of treatment in the Teng et al. [33] study, both calcitriol and paricalcitol reduced mean concentration of PTH by 30 and 22%, respectively; however, after just 1 year of treatment, an attenuation of efficacy was observed (5 and 15% reduction in PTH with calcitriol and paricalcitol, respectively). In both treatment groups, concentrations of calcium and phosphorus increased throughout the study (by 14 and 7% at year 1, respectively, compared with baseline). In contrast, in the present study, cinacalcet lowered PTH concentrations 20% on average (~20% (median: 41%) by the end of the second year and ~21% (median: 46%) by the end of the third year), which was sustained over 3 years. Ca × P product remained unchanged despite stable, or even decreased amount of phosphate binder intake, demonstrating an ability to control PTH without increasing serum calcium and phosphorus concentrations in patients treated with cinacalcet. The latter findings are of particular interest since increases in serum phosphorus and Ca × P concentrations in patients with chronic kidney disease are associated with adverse cardiovascular outcomes and high mortality rates [7,10–14].

Changes in vitamin D sterol and phosphate-binder therapy were unrestricted in this study, and PTH was checked every 3 months, allowing for assessment of the long-term control of secondary hyperparathyroidism by cinacalcet in a setting reflective of clinical practice. Despite the flexibility permitted, overall the use of vitamin D sterols remained constant. Phosphate binder therapy also remained relatively constant, although there was a trend towards decreasing calcium-containing binder use, and increasing sevelamer use. Although individual dialysis patients frequently have changes in therapy for secondary hyperparathyroidism, which was also true in this study, the use of concomitant therapy in the overall population remained generally constant. This observation is notable, especially in light of the known effects of cinacalcet to reduce PTH, serum calcium, phosphorus, and Ca × P concentrations. The optimal management strategy has not been determined for patients who have uncontrolled secondary hyperparathyroidism, but the results from our study suggest that cinacalcet can be used either alone with phosphate binders or in combination with vitamin D sterols and phosphate binders to control hyperparathyroidism.

In conclusion, cinacalcet provides a specific therapeutic intervention that effectively lowers concentrations of plasma PTH, without increasing the incidence of hypercalcaemia or hyperphosphataemia, which currently complicate secondary hyperparathyroidism and its management. With the release of the NKF-K/DOQI guidelines for the management of bone and mineral disease in patients with chronic kidney disease [16], the advantages of improved control of mineral metabolism in patients treated with cinacalcet offers
hope that new management strategies using cinacalcet to treat secondary hyperparathyroidism could improve patient outcomes.

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