

Secondary hyperparathyroidism disease stabilization following calcimimetic therapy

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Abstract

Standard therapy for secondary hyperparathyroidism (SHPT) includes dietary calcium supplementation, active vitamin D, and phosphate binders; however, these are often insufficient to allow patients to achieve their serum parathyroid hormone (PTH), calcium and calcium–phosphorus product ($\text{Ca} \times \text{P}$) targets. Recent preclinical studies have demonstrated that treatment with type II calcimimetics that increase the sensitivity of the calcium-sensing receptor (CaR) to calcium can reverse the alterations in CaR and vitamin D receptor expression and parathyroid cell proliferation that are associated with SHPT. These data suggest that calcimimetic treatment could stabilize disease progression and improve maintenance of treatment goals. In clinical trials involving SHPT patients, the calcimimetic cinacalcet has been shown to decrease PTH, calcium, phosphorus and $\text{Ca} \times \text{P}$. Significant improvements were seen regardless of initial disease severity, and benefits were maintained over the course of long-term therapy (up to 4 years), indicating effective disease stabilization. In conclusion, preclinical and clinical data provide both theoretical and empirical support for the use of calcimimetics in moderate and advanced SHPT to effectively stabilize disease.

Keywords: calcimimetic; calcium-sensing receptor; cinacalcet; secondary hyperparathyroidism

Stabilization of secondary hyperparathyroidism with calcimimetics: preclinical evidence

Calcimimetics provide an alternative approach to the traditional therapy with active vitamin D and phosphate binders for the management of secondary hyperparathyroidism (SHPT). Type II calcimimetics are positive allosteric modulators of the parathyroid gland calcium-sensing receptor (CaR) that increase its sensitivity to serum calcium, so that lower concentrations of calcium are sufficient to mediate signalling through the CaR [1]. This suggests that, despite

the reduced CaR expression observed in hyperplastic parathyroid tissues [2,3], calcimimetics have the potential to control even advanced disease by enhancing the function of the remaining CaR [4–7]. In addition, calcimimetics have the potential to influence both CaR expression and CaR functions that have been implicated in the progression of disease, particularly effects on parathyroid hormone (PTH), cell proliferation and hyperplasia. These characteristics suggest that targeting the CaR presents a therapeutic option for the stabilization of early disease, as well as remaining a viable therapeutic target in the face of advancing disease. In addition to being effective in patients with mild to moderate disease [5], calcimimetics may be the most viable option for chronic kidney disease (CKD) patients with advanced hyperparathyroidism, who are often refractory to standard calcitriol therapy [8–10]. The data below summarize preclinical findings providing a rationale for the clinical use of calcimimetics.

CaR expression

Animal data indicate that calcimimetic therapy can have a direct impact on CaR expression. Administration of cinacalcet or the calcimimetic R-568 to 5/6 nephrectomized rats prevented hyperplasia or increased CaR expression [2,11]. These actions support a possible role for calcimimetics in modifying the course of SHPT. Interestingly, in an *in vitro* study, the calcimimetic cinacalcet suppressed PTH secretion in human parathyroid cells with advanced hyperparathyroidism, even though CaR expression was significantly diminished [12].

Vitamin D receptor expression

Expression of vitamin D receptor (VDR) mRNA is reduced in the parathyroid gland of hypocalcaemic rats compared with normocalcaemic rats [13]. Because the VDR is a transcriptional repressor of PTH [14], these data suggest that reduced signalling through this receptor might affect PTH secretion. Recent studies indicate that type II calcimimetics, in the presence of low concentrations of calcium, can up-regulate VDR mRNA [15]. Rats injected with a calcimimetic (R-568, 1 mg/kg intravenously 3 and 6 h before euthanasia) exhibited an increase in VDR mRNA

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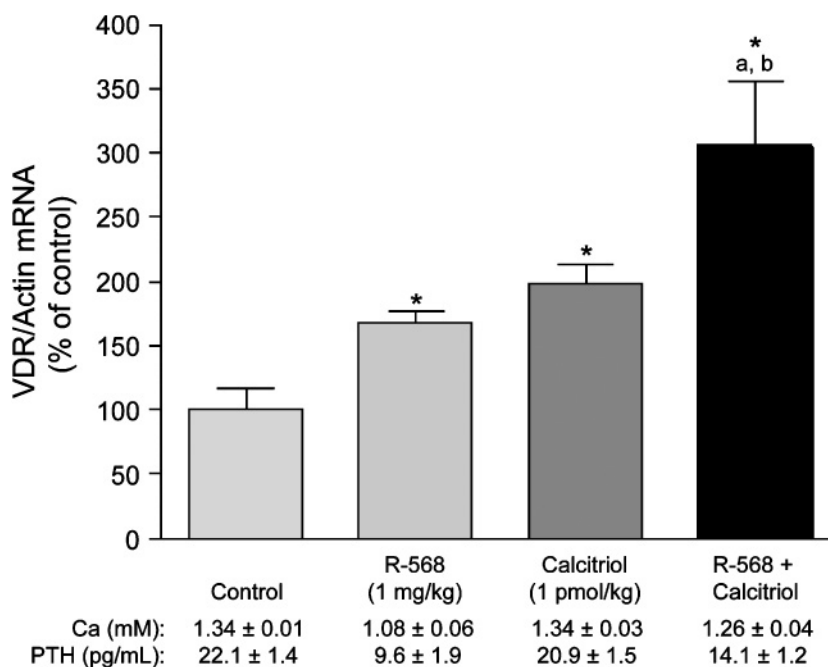


Fig. 1. The effect of the calcimimetic R-568 on rat parathyroid gland VDR mRNA *in vivo*. Rats were treated with R-568 (1 mg/kg intravenously 3 and 6 h before euthanasia; $n = 22$), calcitriol (10 pmol/kg intraperitoneally every 30 min for 5.5 h before euthanasia; $n = 22$), or a combination of R-568 and calcitriol ($n = 22$) before euthanasia and measurement of VDR mRNA by quantitative real-time polymerase chain reaction. A control group ($n = 20$) received no treatment. Mean serum concentrations of ionized calcium and PTH are also included. * $P < 0.01$ versus control; ^a $P < 0.05$ versus calcimimetic; ^b $P < 0.05$ versus control. Data are mean \pm standard error. Adapted with permission from Rodriguez *et al.* [15].

expression compared with controls ($P < 0.001$), with a marked increase observed when R-568 and calcitriol were coadministered (Figure 1).

These data indicate that, in addition to regulating PTH levels and restoring CaR density, calcimimetics can up-regulate VDR expression in parathyroid cells. This effect of calcimimetics on VDR expression is of clinical importance because it may result in an additive interaction between calcimimetic and vitamin D sterol therapy.

Parathyroid cell proliferation and parathyroid hyperplasia

Although parathyroid cells are relatively quiescent under normal conditions, the mineral and hormonal imbalances characteristic of SHPT, particularly low serum calcium and high serum phosphorus, drive cell proliferation leading to polyclonal and oligoclonal cell expansion [8]. The importance of maintaining calcium homeostasis is evidenced in weanling rats fed a low-calcium diet for 10 days, in which the number of proliferating cell nuclear antigen (PCNA)-positive parathyroid cells was increased sixfold compared with controls [16]. Calcimimetics, in the presence of low serum calcium, can hold proliferation in check, as evidenced by decreased parathyroid cell proliferation in uraemic rats following treatment [17] and their ability to cause regression of advanced hyperplasia in some experimental animal models [11,17]. Long-term administration of the calcimimetic cinacalcet significantly reduced the number of proliferating (PCNA-positive) cells and glandular hyperplasia, as measured by weight, in 5/6

nephrectomized rats. This effect was parathyroid tissue-specific and was due to a direct effect on cell growth, rather than to induction of apoptosis [11].

Taken together, the mechanistic data presented here, and reviewed in greater detail in another article in this supplement (Riccardi and Martin), suggest that calcimimetics have the potential to retard SHPT disease progression. Pre-clinical studies in uraemic rats indicate that calcimimetics can modify the defining parameters in SHPT by significantly lowering PTH and blood-ionized calcium in a dose-dependent manner without inducing significant changes in serum phosphate [11]. Clinical investigations supporting this therapeutic modality are evaluated in the remainder of this review.

Unmet medical need in SHPT management

One of the primary treatment goals of SHPT is to restore mineral and hormone balance. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQITM) has established recommendations regarding levels of serum calcium, phosphorus, calcium-phosphorus product ($\text{Ca} \times \text{P}$), and intact PTH (iPTH) for patients based on their degree of kidney function [18]. As kidney function decreases, mineral homeostasis is increasingly perturbed, resulting in increased PTH, serum phosphorus, and $\text{Ca} \times \text{P}$. As this dysregulation progresses, the response to standard therapy worsens [8]. Consequently, PTH can become high enough to increase mortality and impede adequate control

of phosphate [19–21]. These findings underscore the need for new or adjunct treatments with improved efficacy over current modalities that can stabilize disease progression during a long-term course when initiated early, but can also maintain effectiveness in patients with more severe disease.

Because of the ability of calcimimetics, demonstrated in animal studies, to modulate disease-related processes through multiple mechanisms of action implicated in the development of disease, this therapeutic modality appears to be well suited for use in combination with moderate doses of vitamin D as the primary mode of treatment in SHPT management. As described earlier, calcimimetics up-regulate CaR and VDR expression and inhibit parathyroid cell proliferation and hyperplasia. These multiple mechanisms of action may allow calcimimetics to (1) maintain effectiveness during long-term therapy; (2) maintain enhanced efficacy in patients with severe disease despite decreased CaR and VDR expression and (3) halt development of severe disease if initiated early in patients with mild or moderate SHPT. Each of these goals represents an unmet medical need in the management of SHPT.

Phase 3 clinical trials in SHPT patients with advanced disease have shown that cinacalcet decreased PTH, as well as serum calcium, phosphorus and $\text{Ca} \times \text{P}$ [5,7,22]. Analysis of the data from these trials has been performed to investigate the efficacy of cinacalcet in the treatment of both early- and later-stage SHPT and to investigate the potential of long-term cinacalcet therapy to stabilize disease progression. Results of these analyses, presented below, suggest that calcimimetics have the ability to address these unmet therapeutic needs.

Effect of cinacalcet on disease stabilization in clinical trials

A *post-hoc* analysis of the combined results of three 26-week, placebo-controlled, phase 3 studies evaluating the efficacy and safety of a once-daily dose of cinacalcet for the treatment of SHPT demonstrated the impact of therapy initiated in early or advanced disease [23]. These studies included adult patients on maintenance dialysis who had iPTH levels ≥ 300 pg/mL despite standard treatment with active vitamin D and phosphate binders. Patients received standard therapy in combination with cinacalcet ($n = 546$) or placebo ($n = 408$). Patients included in the analysis were divided into eight subgroups according to their baseline iPTH level, which was used as a marker of disease severity (300 to >1000 pg/mL). Findings from this analysis indicated that the use of cinacalcet (30 mg titrated up to 180 mg) significantly decreased both iPTH and $\text{Ca} \times \text{P}$ levels regardless of disease severity at baseline, compared with standard therapy (Figure 2). The progressive nature of SHPT, even when patients receive standard therapy, is evidenced by positive changes from baseline in iPTH seen in these patients (Figure 2A) [23]. Furthermore, the effect of cinacalcet on $\text{Ca} \times \text{P}$ (Figure 2B) and serum phosphorus levels was more pronounced in patients with more severe disease, suggesting a more significant impact of cinacalcet on bone turnover in these patients.

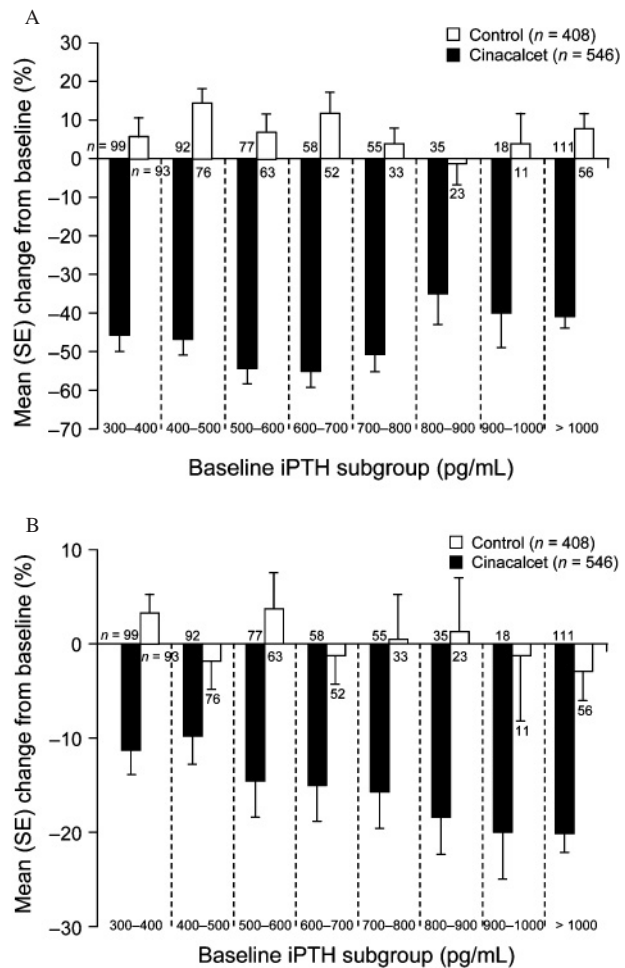


Fig. 2. Percentage change in (A) iPTH and (B) $\text{Ca} \times \text{P}$ by disease severity. Patients were treated with cinacalcet (beginning at 30 mg with possible titration up to 180 mg; $n = 546$) or placebo ($n = 408$) for 26 weeks. Patients were divided into groups according to baseline iPTH levels (pg/mL). Bars represent the mean (SE) percentage change from baseline for iPTH. SE, standard error. Adapted with permission from Frazão *et al.* [23].

However, although these data demonstrate that cinacalcet is effective in reducing serum iPTH and $\text{Ca} \times \text{P}$, even in patients with severe disease, these patients remain less likely to achieve their KDOQI™ targets than patients with less severe disease. After 6 months of treatment with cinacalcet, 76% of patients with a baseline iPTH of 300–500 pg/mL achieved a serum iPTH level of <300 pg/mL compared with 55% of patients with a baseline iPTH of 500–800 pg/mL and 16% of patients with a baseline iPTH of >800 pg/mL. Similarly, 54% of patients with a baseline iPTH of 300–500 pg/mL achieved an iPTH of <300 pg/mL and their $\text{Ca} \times \text{P}$ target ($<55 \text{ mg}^2/\text{dL}^2$), compared with 36% and 9% of patients in the 500–800 and >800 mg/mL groups, respectively [24]. These data suggest that early treatment of SHPT provides the best opportunity to maintain control of serum PTH, calcium, phosphorus and $\text{Ca} \times \text{P}$.

Treatment with cinacalcet for up to 1 year resulted in increased attainment of KDOQI™ targets compared with standard therapy [25]. After 12 months, 66% of patients

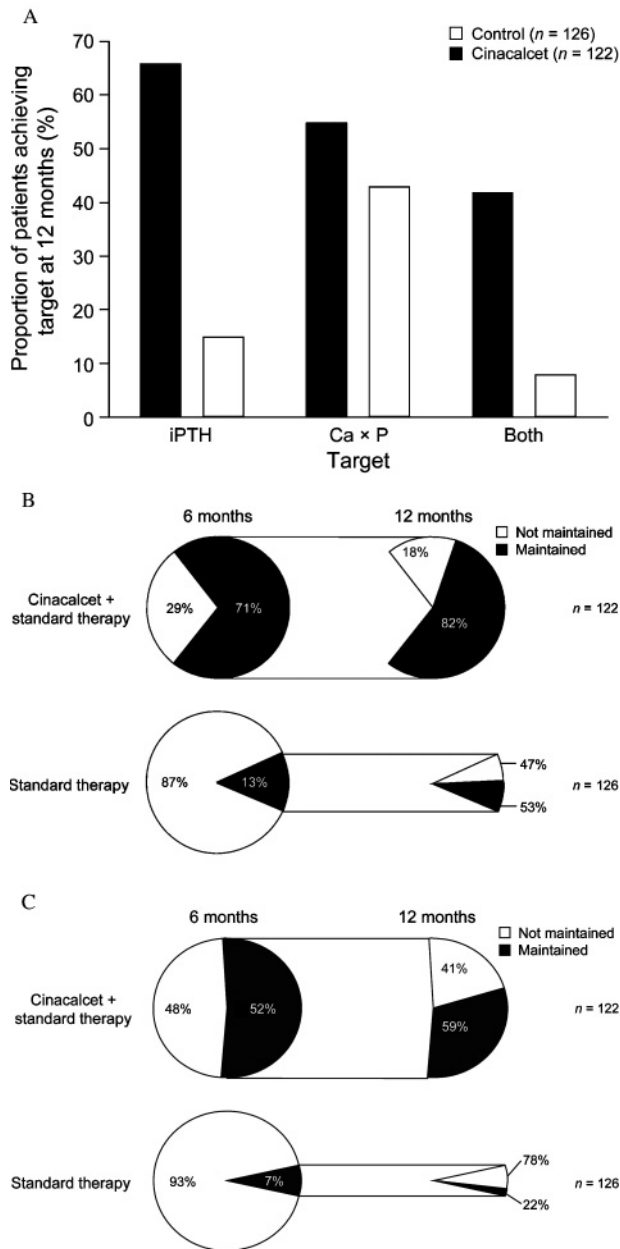


Fig. 3. Proportion of patients achieving serum iPTH ≤ 300 pg/mL and Ca \times P < 55 mg²/dL² during treatment with either cinacalcet ($n = 122$) or placebo ($n = 126$). (A) Achievement of serum iPTH ≤ 300 pg/mL and Ca \times P < 55 mg²/dL² after 1 year. (B) Maintenance of serum iPTH ≤ 300 pg/mL after 6 and 12 months of treatment. (C) Maintenance of combined serum iPTH and Ca \times P target after 6 and 12 months of treatment. Adapted with permission from Frazão *et al.* [25].

on dialysis receiving cinacalcet achieved an iPTH of ≤ 300 pg/mL compared with 15% in the placebo group. Similarly, 55% of patients receiving cinacalcet achieved their Ca \times P target (< 55 mg²/dL²) compared with 43% in the placebo group. Furthermore, the proportion of patients able to achieve both an iPTH of ≤ 300 pg/mL and their Ca \times P target was considerably higher in the cinacalcet group than in the placebo group; 42% of patients in the cinacalcet group achieved both targets simultaneously,

whereas only 8% of patients in the placebo group reached both targets (Figure 3A).

In this study, treatment with cinacalcet not only improved the ability of patients to achieve their KDOQITM targets, but also their ability to maintain these targets. Seventy-one percent of cinacalcet-treated patients were able to achieve an iPTH of ≤ 300 pg/mL after 6 months of cinacalcet treatment. Of the group who achieved an iPTH of ≤ 300 pg/mL at 6 months, 82% also maintained an iPTH of ≤ 300 pg/mL after 1 year. In contrast, in the standard care group, 13% of patients achieved an iPTH concentration of ≤ 300 pg/mL, with 53% of this group continuing to maintain an iPTH ≤ 300 pg/mL after 1 year (Figure 3B). Cinacalcet also improved maintenance of the combined iPTH and Ca \times P targets. In the cinacalcet group, 52% of patients reached the combined target after 6 months compared with 7% in the standard care group. Of these patients, 59% in the cinacalcet group maintained the combined target after 1 year compared with just 22% in the standard care group (Figure 3C). These data demonstrate that cinacalcet effectively reduces and maintains the four critical disease biomarkers associated with SHPT in CKD patients. Cinacalcet, therefore, reduces the shifting in and out of targets often observed in patients using standard therapy.

Open-label extension studies have evaluated the ability of cinacalcet to stabilize disease in SHPT patients for up to 4 years [26–28]. These analyses were based on a series of double-blind randomized clinical trials in which patients received standard care treatment in combination with either placebo or cinacalcet for 26 or 52 weeks, after which patients could receive open-label cinacalcet treatment. In one such open-label extension study, serum iPTH was found to progressively increase in patients treated with standard care for 52 weeks [26]. After open-label cinacalcet treatment was started, serum iPTH was rapidly reduced to a level matching that of cinacalcet-treated patients. After 2 years of open-label cinacalcet therapy, approximately 59% of all patients ($n = 59$) had achieved an iPTH of ≤ 300 pg/mL at each study visit. Serum Ca \times P did not increase during this period.

In a separate study, a limited number of patients ($n = 21$) taking cinacalcet were followed up for as long as 4 years [28]. A substantial upward trend in iPTH was noted in control patients who received standard therapy during the first year of treatment in this study, before switching to cinacalcet therapy, with levels increasing from approximately 600–850 pg/mL. In these patients, cinacalcet reduced and maintained iPTH levels throughout the follow-up period (Figure 4). After 4 years, the mean serum iPTH was 396 pg/mL, 65% of patients achieved a serum iPTH of ≤ 300 pg/mL, and the mean serum Ca \times P was 50.5 mg²/dL². These findings again highlight the progressive nature of SHPT in patients receiving standard therapy as first-line treatment [28], as well as the inability of traditional therapies to effectively control or stabilize disease in both the short and long term. These and other clinical observations discussed in this section are also consistent with preclinical evidence supporting the CaR as a therapeutic target to optimize the achievement of treatment goals and slow or prevent disease progression.

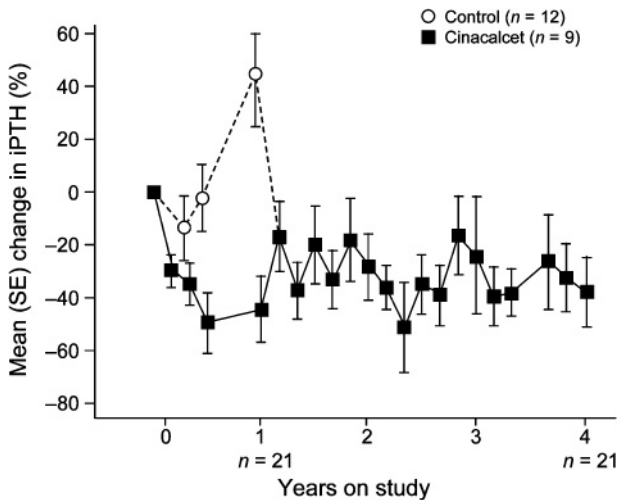


Fig. 4. Effect of long-term cinacalcet treatment on serum iPTH in dialysis patients. Patients received double-blind treatment with either cinacalcet ($n = 9$) or placebo ($n = 12$) for 1 year followed by a 3-year open-label extension treatment with cinacalcet. SE, standard error. Adapted with permission from Cunningham *et al.* [28].

Conclusions

Calcimimetics are highly specific therapeutic agents that effectively lower concentrations of plasma PTH and partially correct disturbances in mineral metabolism that are characteristic of SHPT. The mechanism of action involves allosteric modification of the CaR, rendering it more sensitive to calcium signalling, thereby helping counteract the decreased CaR expression and prevent and halt the progression of parathyroid hyperplasia. In addition to effects on CaR signalling, new experimental studies indicate that calcimimetics may act to increase VDR expression. These studies raise the possibility that treatment with calcimimetics might improve the sensitivity of the parathyroid glands to calcitriol and vitamin D analogues, allowing reduced doses to be used and thus minimizing the risk of hypercalcaemia and hyperphosphataemia.

Preclinical mechanistic studies with calcimimetics have suggested that this modality may arrest disease progression, even in patients with advanced disease at treatment onset, and stabilize SHPT, thereby allowing improved maintenance of KDOQITM targets. Thus far, clinical data support this scenario. In clinical use, cinacalcet was found to be effective for the reduction and long-term maintenance of iPTH, calcium and phosphorus levels in patients with SHPT. Cinacalcet has been shown to allow more patients to achieve and maintain KDOQITM targets compared with standard therapy, and extended use (up to 4 years) has been shown to be effective and well tolerated.

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