Secondary hyperparathyroidism disease stabilization following calcimimetic therapy

João Frazão¹ and Mariano Rodriguez²

¹Nephrology Research and Development Unit and School of Medicine, University of Porto, Porto, Portugal and ²Unidad de Investigacion, Servicio de Nefrologia, Hospital Universitario, Reina Sofia, Cordoba, Spain

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 (Ca × 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 Ca × 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
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; aP < 0.05 versus calcimimetic; bP < 0.05 versus control. Data are mean ± 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 upregulate 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. Preclinical 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 (Ca × 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 Ca × 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 Ca × 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless 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 Ca × P levels regardless of disease severity (300 to >1000 pg/mL). Findings from this analysis indicate...
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 concentration of ≤300 pg/mL after 1 year of cinacalcet treatment. Of this group who achieved an iPTH concentration of ≤300 pg/mL, with 53% of this group continuing to maintain an iPTH of ≤300 pg/mL after 1 year (Figure 3B). Cinacalcet also improved maintenance of the combined iPTH and Ca × 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 concentration of ≤300 pg/mL at each study visit. Serum Ca × 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 × 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.
João M. Frazão has been a scientific consultant for Amgen and Genzyme. He has also participated in advisory boards for Amgen and Shire. Mariano Rodriguez has received honoraria and grants from Amgen and Shire. He has also participated in advisory boards for Amgen and Shire.

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