Efficacy of early treatment with calcimimetics in combination with reduced doses of vitamin D sterols in dialysis patients

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Abstract
Vitamin D is an important physiologic regulator of bone and mineral metabolism. In chronic kidney disease, reduced renal production of calcitriol contributes to secondary hyperparathyroidism (SHPT). Consequently, supplementation with vitamin D sterols is an important treatment for SHPT and its associated mineral and bone disorders. However, doses of vitamin D sterols required to suppress parathyroid hormone (PTH) secretion often promote hypercalcaemia and hyperphosphataemia. Therefore, there is a trade-off between reduced serum PTH and increased levels of serum calcium, phosphorus and calcium–phosphorus product. It has been suggested that treatment of SHPT with cinacalcet, a type II calcimimetic, with reduced doses of vitamin D sterols could enhance achievement of calcium and phosphorus treatment targets while maintaining goals for PTH. Recent clinical trials have evaluated this hypothesis and demonstrated that treatment with cinacalcet in combination with reduced doses of vitamin D sterols is an effective treatment for the management of SHPT.

Keywords: calcimimetics; calcium; parathyroid hormone; phosphorus; secondary hyperparathyroidism; vitamin D

Biologic role of calcitriol

Physiologic effects

The chief physiologic role of calcitriol (the active form of vitamin D) is the maintenance of bone mineralization and turnover through increased absorption of calcium and phosphorus and suppression of parathyroid hormone (PTH) synthesis. Calcitriol increases calcium and phosphorus absorption from the gut; in excess, it mobilizes calcium from bone; and, in the parathyroid gland, suppresses PTH synthesis [1]. These effects of calcitriol are mediated through the vitamin D receptor (VDR), a ligand-activated nuclear receptor that modulates gene transcription in vitamin D-sensitive tissues through interaction with vitamin D-response elements (VDREs) [2–4]. The VDR is localized not only in target organs involved in mineral homeostasis but also in many other tissues. Nonclassic vitamin D systems and tissues include the immune system [5,6], myeloid tissue [7–9], the heart [10], skeletal muscle [11], the brain, and nerve tissue [12–14]. This wide distribution of the VDR suggests that calcitriol has physiologic roles other than mineral homeostasis. These physiologic roles have been extensively reviewed and, consistent with the nonclassic vitamin D tissues described above, include effects on the haematopoietic system, immune system, skin, muscle and nervous system [1,2,15,16]. Evidence also suggests that calcitriol can mediate nongenomic actions through a cell surface receptor distinct from the nuclear VDR [1].

The synthesis of calcitriol (the most potent endogenously produced vitamin D metabolite) occurs primarily in the kidney but also in a variety of other tissues [17,18]. The renal production of calcitriol is tightly regulated and is thought to account primarily for the level of calcitriol in serum under normal physiologic circumstances [1]. Control of calcitriol is achieved through the coordinated action of the kidneys, intestine, bone and parathyroid glands in response to physiologic calcium and phosphorus requirements [1]. Serum calcium, phosphorus and PTH regulate vitamin D through activation or suppression of the enzymes involved in its synthesis, bioactivation and catabolism [17].

Role of calcitriol in the development of SHPT in chronic kidney disease

A common complication of chronic kidney disease (CKD) is the development of secondary hyperparathyroidism (SHPT) [19]. SHPT begins to develop when reduced renal function results in dysregulation of the complex interactions involved in calcium and phosphorus homeostasis. Reduced renal excretion of phosphorus and synthesis of calcitriol both contribute to the development of hypocalcaemia that, in turn, leads to increased serum PTH [19]. Both the parathyroid gland calcium-sensing receptor (CaR) and VDR are down-regulated in the hyperplastic parathyroid gland, resulting in reduced sensitivity to calcium and vitamin D, respectively [19–22]. This abnormal calcium sensing leads to elevated serum PTH and abnormalities...
increased calcium–phosphorus product (Ca \times P) is associated with vascular calcification [24,25].

In addition to the effects of reduced calcitriol on serum calcium that contribute to SHPT, a decrease in calcitriol has a number of direct effects that influence the development of SHPT. Calcitriol reduces parathyroid gland synthesis of PTH through the actions of the VDR on two VDREs located in the 5' promoter region of the PTH gene [1,4]. In animal studies, calcitriol was shown to regulate the CaR in the parathyroid gland. Compared with controls, rats fed a vitamin D-deficient diet had reduced parathyroid gland CaR mRNA content [26]. Administration of calcitriol increased CaR mRNA. Interestingly, rat CaR mRNA was unaffected by diet-induced changes in serum ionized calcium [26].

**Vitamin D sterol therapy in patients with CKD**

Treatment with vitamin D sterols in CKD patients on dialysis has two principle goals. First, it corrects the vitamin D deficiency that commonly develops as renal function declines [27], and second, treatment with higher doses of vitamin D sterols has been demonstrated to decrease serum PTH [28,29]. Therefore, therapy with vitamin D sterols has become a primary treatment for SHPT [30]. Because vitamin D sterols also act to promote intestinal absorption of calcium and phosphorus and, in excess, mobilize calcium from bone [1], this effect on PTH comes at the expense of increased serum calcium, phosphorus and Ca \times P. Indeed, clinical studies have shown that treatment with vitamin D sterols can increase serum calcium [31–34]. In some instances, increases in serum phosphorus [34] and Ca \times P have been reported [33,34]. Thus, as with other traditional therapies for SHPT in CKD (such as phosphate binders), there is a trade-off between reduced serum PTH and increased Ca \times P [35,36]. Potentially, hypercalcaemia and hyperphosphataemia associated with vitamin D sterol use could result in elevations of calcium and phosphorus and their product, leading to an increased risk of cardiovascular calcification and subsequent mortality [24,37]. Moreover, oversuppression of serum PTH from excessive vitamin D sterol treatment can result in reduced bone turnover (dynamic bone) [38].

The recognition of the hyperphosphataemic and hypercalcaemic effects of vitamin D sterols has led to the development of novel vitamin D sterols, such as paricalcitol, that retain the ability to suppress PTH secretion with reduced calcaemic effects [39]. This benefit was demonstrated in a study comparing paricalcitol with calcitriol in rats [40], yet only a small benefit was observed in a clinical trial [41]. These findings may be attributed to the fact that, although the calcaemic effects of paricalcitol may be reduced in comparison with calcitriol, they are not absent [36]. In patients on haemodialysis, paricalcitol treatment was shown to significantly increase serum calcium and serum phosphorus compared with placebo [28].

Observational studies have investigated the effects of vitamin D sterols, such as paricalcitol, calcitriol and alfacalcidol (1α-hydroxyvitamin D3) on survival in haemodialysis patients. In a retrospective epidemiologic analysis of a large database of haemodialysis patients [42], those treated with injectable vitamin D sterols (≥95% receiving paricalcitol or calcitriol) were shown to have a 2-year survival advantage of 20% compared with those not receiving vitamin D sterol treatment (hazard ratio, 0.80; 95% confidence interval, 0.76–0.83). Cardiovascular mortality was also lower in the vitamin D sterol-treated group (7.6/100 person-years) compared with the control group (14.6/100 person-years; P < 0.001). Similarly, in an observational study of 242 haemodialysis patients with stage 5 kidney disease, patients receiving alfacalcidol had a significantly lower risk of cardiovascular death compared with nonusers (hazard ratio, 0.287; P = 0.003) [43]. However, not all studies have demonstrated a survival benefit associated with vitamin D sterol treatment. In the observational Dialysis Outcomes and Practice Patterns Study, no association between vitamin D sterol use and mortality was observed [44]. The results of a retrospective study investigating the relative effects of paricalcitol and calcitriol on survival are also controversial. Patients treated with paricalcitol had a 16% lower mortality rate than patients treated with calcitriol [45]. It should be noted that all of these studies are observational, not randomized, and thus there was a fundamental difference in patients selected/not selected to receive vitamin D. In addition, the two groups were not matched with respect to a number of baseline characteristics, including comorbidities and demographics and, pre-study treatment data were not collected. Thus, that a difference in outcome was found is not unexpected. Prospective, randomized trials will be necessary to conclusively demonstrate if there is a survival benefit associated with vitamin D sterol treatment and whether the potential reduced calcaemic effects of paricalcitol compared with calcitriol translate into lower mortality rates.

**Combining cinacalcet and vitamin D sterols to maximize control of SHPT**

Because the therapeutic window for treatment with vitamin D sterols is narrow, it is difficult to determine an optimal dose that will sufficiently suppress PTH secretion without also increasing calcium and phosphorus absorption. Cinacalcet has a novel mechanism of action, acting on the CaR to simultaneously reduce serum PTH, calcium, phosphorus and Ca \times P [46]. A new treatment paradigm has been proposed in which cinacalcet is used in combination with conventional therapies, such as vitamin D sterols and phosphate binders, for the treatment of SHPT. Phase 2 and phase 3 registrational studies were designed to compare cinacalcet in combination with traditional therapies with placebo and traditional therapies. In these studies, strict protocol-defined rules were followed to maintain the dose of vitamin D sterols at a constant level throughout the study period. These trials demonstrated that cinacalcet enabled significantly more haemodialysis patients with SHPT to achieve individual and combined National Kidney Foundation Kidney Disease Outcomes Quality Initiative
(KDOQITM) targets and that cinacalcet induced simultaneous reductions in PTH and Ca × P [47–50].

It has been postulated that treatment with cinacalcet in combination with doses of vitamin D sterols sufficient for replenishment might limit the hypercalcaemia and hyperphosphataemia associated with vitamin D sterol therapy while maintaining control of SHPT. The following section of this review describes the results of two trials that investigated the effects of reduced-dose vitamin D combined with cinacalcet therapy on the achievement of KDOQITM goals: Cinacalcet Open-Label Study to Reach KDOQITM Levels (CONTROL) [51] and An Open-Label, Randomized Study Using Cinacalcet to Improve Achievement of KDOQITM Targets in Patients With End-Stage Renal Disease (OPTIMA) [52–55].

The CONTROL study

The CONTROL study was a 16-week open-label trial in 72 adult haemodialysis patients in the United States with controlled biointact PTH (biPTH) levels (80–160 pg/mL) and uncontrolled Ca × P (>55 mg²/dL²) (Table 1) [51]. At study entry, all patients were receiving moderate to high doses of intravenous vitamin D sterols (paricalcitol, doxercalciﬁerol or calcitriol; mean ± standard deviation paricalcitol equivalent dose, 14.1 ± 7.8 µg/week) and phosphate binders. Doses of vitamin D sterols were reduced on day 1 of the dose-titration phase (to 2 µg paricalcitol equivalent dose per dialysis session) but could be increased during the 8-week titration phase if serum calcium was <8.4 mg/dL or if biPTH was >270 pg/mL and Ca × P was <70 mg²/dL² and cinacalcet could not be titrated further. The vitamin D sterol dose could be decreased after reaching two consecutive biPTH values of <80 pg/mL. During the 8-week titration phase, cinacalcet doses were titrated in stepwise increments from 30 to 180 mg/d (when biPTH was >160 pg/mL or when biPTH was 80–160 pg/mL and Ca × P was >55 mg²/dL²) to reach treatment targets. Cinacalcet dose adjustments were allowed during the assessment phase, and dose reductions were allowed at any time during the study. The primary efficacy measures were the achievement of biPTH ≤160 pg/mL and Ca × P ≤55 mg²/dL².

Although the dose of vitamin D sterols was reduced, the introduction of cinacalcet enabled PTH control to be maintained (85% achieved their biPTH target versus 91% of patients at baseline, P = not significant), and Ca × P control was markedly improved (72% versus 21% at baseline; P < 0.0001). Serum calcium and phosphorus levels were simultaneously reduced by 9.7% and 11.1% from baseline, respectively. More patients treated with cinacalcet achieved both biPTH and Ca × P goals at assessment compared with baseline (47% versus 17%; P < 0.01) (Figure 1A). At the assessment phase, vitamin D sterol use was discontinued in 21% of patients, and in the other patients, the dose was reduced by 49% (to 6.9 µg/week) compared with baseline (Figure 1B). Taken together, these results demonstrate that cinacalcet and reduced-dose vitamin D sterols can simultaneously address all four KDOQITM targets.

The OPTIMA study

The OPTIMA study was a 23-week, randomized, standard care-controlled, multicentre, open-label study in 552 dialysis patients in Europe (Table 1) [52–55]. This study used a predefined algorithm designed to optimize the combination

Table 1. Early-use cinacalcet/vitamin D sterol combination trials: study design

| Study design | CONTROL | OPTIMA |
|--------------|---------|--------|
| Titration phase: Weeks 1–8; Assessment phase: Weeks 8–16 (n = 53); PTH controlled (biPTH: 80–160 pg/mL), elevated Ca × P at baseline | Dose optimization phase: Weeks 1–16; Assessment phase: Weeks 16–23 (n = 552); Baseline PTH elevated (iPTH: 300–800 pg/mL) | Algorithm to optimize combination of cinacalcet, vitamin D sterols and phosphate binder or use best conventional methods; vitamin D sterol dose adjusted according to algorithm to a minimum 2 µg paricalcitol equivalent |

Fig. 1. CONTROL trial: comparison of standard care with cinacalcet; (A) percentage of patients achieving KDOQITM targets and (B) dose of paricalcitol at baseline and endpoint. Note that the biPTH target in this study was ≤160 pg/mL. The KDOQITM target range is approximately 80–160 pg/mL. *P < 0.01, **P < 0.001. Adapted with permission from Chertow et al. [51].
of cinacalcet and existing treatments of vitamin D sterols and phosphate binders to control intact PTH (iPTH) and reduce serum calcium and phosphorus (Figure 2). Patients were assigned to cinacalcet or conventional therapy in a 2:1 ratio. Conventional therapy gave investigators full freedom to administer vitamin D sterols and phosphate binders as appropriate to maximize target achievement. Cinacalcet was titrated from a starting dose of 30 mg/d until an iPTH of 150–300 pg/mL was achieved. Dose reductions related to patient safety were allowed at any time during the 23-week study. Vitamin D sterol dose was reduced in patients with calcium $\geq 9.5$ mg/dL or phosphorus $\geq 5.5$ mg/dL. The dose of vitamin D sterols was reduced by 50% in sequential steps until a minimum dose (calcitriol, 0.5 $\mu$g three times per week [TIW] intravenous or 0.25 $\mu$g TIW oral; alfacalcidol, 1 $\mu$g TIW intravenous or 0.25 $\mu$g daily oral; paricalcitol, 2 $\mu$g TIW intravenous) was prescribed. Efficacy as measured by achievement of KDOQITM targets was evaluated during Weeks 17–23.

More patients achieved the primary endpoint of iPTH control ($\leq 300$ pg/mL) with cinacalcet compared with standard care (71% versus 22%; $P < 0.001$). Cinacalcet reduced iPTH levels irrespective of the baseline PTH level (Table 2). When patients were stratified into a less severe SHPT group (baseline iPTH, 300–500 pg/mL) and more severe SHPT group (baseline iPTH, 500–800 pg/mL), the greatest reduction in serum iPTH was achieved in patients with more severe SHPT (Table 2). However, the proportion of patients in the cinacalcet group reaching the primary endpoint of iPTH $\leq 300$ pg/mL was greater in the less severe SHPT group (Figure 3). Additionally, the median dose of cinacalcet was lower in the less severe SHPT group (30 mg/d) than in the more severe SHPT group (60 mg/d).

Compared with the best standard care, the cinacalcet-based algorithm used in the OPTIMA study provided superior control of SHPT. Attempts by physicians to maximize therapy with standard care to attain the recommended targets were generally unsuccessful, with just 30% of patients in the less severe SHPT group achieving the primary endpoint (iPTH $\leq 300$ pg/mL) and 20% of patients reaching the composite endpoint (iPTH $\leq 300$ pg/mL and $Ca \times P < 55$ mg$^2$/dL$^2$). In contrast, 80% of cinacalcet-treated patients in the less severe SHPT group reached the primary endpoint, and 64% reached the composite endpoint (Figure 3).

As previously discussed, treatment with vitamin D sterols is often associated with hypercalcemia and hyperphosphatemia, with consequent risk of increased mortality [24,37,45]. Importantly, in this study, treatment with cinacalcet in combination with vitamin D sterols enabled.
approximately a 24% reduction in the dose of vitamin D sterols compared with baseline.

Summary and conclusions

Overall, evidence from the CONTROL and OPTIMA trials demonstrates the clinical utility of treatment with cinacalcet in combination with reduced doses of vitamin D sterols. These treatment regimens allowed for both rephosphatation of vitamin D and improved control of SHPT. Compared with conventional therapy, an increased proportion of CKD patients were able to achieve their individual KDOQI™ targets, as well as combined targets of reduced iPTH, calcium, phosphorus and Ca × P. Furthermore, in the OPTIMA trial, this treatment regimen improved control of both PTH and Ca × P in patients with moderate (300–500 pg/mL PTH) and severe (500–800 pg/mL PTH) SHPT. Given the potential risks involved in therapy with vitamin D sterols, including vascular calcification and abnormal bone, the ability to lower vitamin D sterol doses while maintaining, and indeed improving, KDOQI™ target achievement is an exciting development. Prospective, long-term clinical trials will be necessary to definitively evaluate the effects of this treatment on mortality, cardiovascular calcification and other outcomes.

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Early use of calcimimetics and reduced-dose vitamin D sterols

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