Control of Secondary Hyperparathyroidism by Vitamin D Receptor Agonists in Chronic Kidney Disease

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Effective treatment options for managing secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD) have advanced steadily since the early 1980s, from surgical removal of the parathyroid gland to pharmacologic intervention focused on reestablishing hormonal and mineral balances. In addition, earlier recognition of CKD via estimated GFR and educational efforts have led to advancements in diagnosis and treatment of elevated parathyroid hormone (PTH) and vitamin D deficiency. Clinical studies support the efficacy and safety of vitamin D receptor (VDR) agonists as effective treatments for SHPT. A number of considerations to ensure optimal SHPT control in CKD patients are apparent. VDR agonists effectively treat SHPT and vitamin D deficiency, but dosing needs to be optimized for each patient because the patient responds in an individualized manner to treatment to suppress and stabilize PTH levels. VDR agonist therapy should be continuous to ensure continued PTH suppression, coupled with strict monitoring of calcium and phosphorus to ensure compliance within target ranges. Awareness of the complex and beneficial effects of VDR agonists contributes to improved benefits in bone mineral disease and lower mortality risks.

T
reatment of secondary hyperparathyroidism (SHPT) in chronic kidney disease (CKD) has evolved over the last few decades, with a better understanding of the underlying pathophysiology and the development of advanced and safer medications. Management of SHPT remains a challenge because of the complex interrelationship of hormones, bone health, diet, and mineral balances within the body. Bone and mineral guidelines were recently updated by the Kidney Disease: Improving Global Outcomes (KDIGO) working group from the 2003 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI), with the goal of providing guidance in managing CKD patients (1,2). At the time of the release of the 2003 guidelines, clinical studies in patients with moderate to severe CKD and SHPT showed that treatment with vitamin D receptor (VDR) agonists lowered elevated parathyroid hormone (PTH) levels but caused variable increases in serum calcium (Ca) and phosphorus (P) (3,4). Although the target ranges for PTH per each CKD stage have been updated in the new KDIGO guidelines to be more reflective of current trends, changes in Ca and P outside of normal levels are still viewed as potentially harmful by experts (2).

Observational data have shown a more complex and even contradictory relationship of Ca and P to mortality, challenging theories that any increase in these mineral ions increases risk to the patient (5,6). Observational studies have shown that low vitamin D (25-hydroxyvitamin D (25-D) and 1,25-dihydroxyvitamin D (1,25-D)) levels are associated with CKD progression (7) as well as increased risk of mortality beginning at stage 3 CKD (7,8). Administration of oral or injectable vitamin D and/or VDR agonists (e.g., calcitriol) in patients on dialysis or with stages 3 and 4 CKD has been correlated with improved survival in observational studies (8–11). Additional observational analyses have shown that treatment with paricalcitol, an analog of calcitriol with fewer calcemic and phosphatemic effects, is associated with enhanced survival in patients undergoing long-term hemodialysis compared with those who did not receive vitamin D analogs (12). Another study showed enhanced survival benefit of paricalcitol compared with calcitriol (13). Although use of these and other VDR agonists (Table 1) to treat low endogenous 1,25-D hormonal levels is hypothesized to account for clinical benefits that include improved survival, prospective randomized, controlled trials are necessary to validate these findings. On the basis of results from clinical studies and through the practical use of therapies to control elevated PTH, replete vitamin D levels, and treat bone mineral disease, a number of considerations when using VDR agonists have arisen that should be taken into account for providing optimal SHPT control in patients with CKD (Table 2).

CKD, SHPT, and Vitamin D Deficiency
An estimated 16 million people in the United States have stage 3 or 4 CKD (eGFR 15–59 ml/min per 1.73 m²), with diabetes mellitus and hypertension as major underlying causes (14). Despite the high prevalence of CKD in the adult population, less than 20% of patients who have moderately decreased
kidney function are aware of this impairment (15). A prospective, observational study of 1814 CKD patients with a recent historic eGFR of \(60 \text{ ml/min per 1.73 m}^2\) confirmed that 78% of patients had stage 3, 4, or 5 CKD with elevated PTH and significantly reduced 1,25-D levels (16). Rising PTH levels were inversely correlated with declining 1,25-D and 25-D levels; 1,25-D levels were approaching very low levels (\(<25 \text{ pg/ml}\)) as eGFR measurements signified stage 3 CKD. eGFR continued to decline thereafter. These and other study findings substantiate a high incidence of SHPT and low endogenous vitamin D (25-D and/or 1,25-D) levels, and the nomenclature for endogenous and exogenous vitamin D is very similar (Table 1). Because 1,25-D functions as a native hormone, providing complex, tissue-specific signaling throughout the body, it is a challenge to accurately measure the relative contribution of exogenously administered vitamin D with signaling that is occurring through autocrine/paracrine feedback loops (20). The interrelated effects between native and supplemented vitamin D are reiterated in a study examining the effects of exogenously administered 1,25D (i.e., calcitriol) in healthy volunteers and uremic patients. Gallieni et al. (21) showed that although dialysis patients have impaired uptake and metabolism of 25-D, treatment with calcitriol not only repleted serum 1,25-D levels but also increased the uptake of 25-D (as examined in monocytes). Thus, with exogenous 1,25-D administration, there are potential complementary benefits to both 1,25-D and 25-D in an effort to rebalance the hormonal system.

**Table 1. Vitamin D nomenclature**

<table>
<thead>
<tr>
<th>Vitamin D Term</th>
<th>Sterol</th>
<th>Type of Vitamin D</th>
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<tbody>
<tr>
<td>Vitamin D</td>
<td>Cholecalciferol</td>
<td>D$_3$</td>
</tr>
<tr>
<td></td>
<td>Ergocalciferol</td>
<td>D$_2$</td>
</tr>
<tr>
<td>25-Hydroxyvitamin D</td>
<td>Calcidiol (25(OH)D$_3$)</td>
<td>D$_3$</td>
</tr>
<tr>
<td></td>
<td>Eracalcidiol (25(OH)D$_2$)</td>
<td>D$_2$</td>
</tr>
<tr>
<td>Vitamin D receptor agonist prohormone$^a$</td>
<td>Alfacalcidol (1(OH)D$_3$)</td>
<td>D$_3$; Synthetic prohormone</td>
</tr>
<tr>
<td></td>
<td>Doxercalciferol (1(OH)D$_2$)</td>
<td>D$_2$; Synthetic prohormone</td>
</tr>
<tr>
<td>Vitamin D receptor agonist</td>
<td>Calcitriol (1,25(OH)$_2$D$_3$)</td>
<td>D$_3$; Natural analog</td>
</tr>
<tr>
<td></td>
<td>Paricalcitol (19nor,1,25(OH)$_2$D$_2$)</td>
<td>D$_2$; Synthetic analog</td>
</tr>
<tr>
<td></td>
<td>Maxacalcitol (22oxa,1,25(OH)$_2$D$_3$)</td>
<td>D$_3$; Synthetic analog</td>
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</table>

$^a$Requires 25-hydroxylation by the liver to become an active analog.

**Table 2. VDR agonists and SHPT control**

<table>
<thead>
<tr>
<th>Considerations for Use of VDR Agonists for SHPT Control</th>
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<tbody>
<tr>
<td>- CKD patients should be identified on the basis of eGFR, and PTH and vitamin D levels should be evaluated early (e.g., stage 3 CKD).</td>
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<tr>
<td>- VDR agonists effectively suppress SHPT in a dose-dependent manner.</td>
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<tr>
<td>- When administering a VDR agonist to lower and maintain steady PTH levels and avoid hypercalcemia, dosing should be determined on the basis of individual patient response.</td>
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<tr>
<td>- VDR agonist therapy should be continuous, rather than intermittent, to ensure continued PTH suppression and replacement of low endogenous 1,25-D.</td>
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<td>- Dietary phosphate restriction, phosphate binders, and repletion of nutritional vitamin D stores are effective complementary treatments.</td>
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Vitamin D Deficiency and Treatment to Modulate SHPT in CKD Patients

There is ongoing debate regarding a clear definition for what is considered vitamin D (25-D and/or 1,25-D) deficiency. Vitamin D deficiency is usually defined as concentrations <10 ng/ml (25 nmol/L), whereas vitamin D insufficiency is defined as levels between 10 and 32 ng/mL (80 nmol/L). Vitamin D concentrations between 32 and 80 ng/mL (200 nmol/L) are generally considered sufficient (2). Vitamin D (25-D and/or 1,25-D) sufficiency is less well defined because numerous factors contribute to achieving adequate endogenous vitamin D levels, and the nomenclature for endogenous and exogenous vitamin D is very similar (Table 1). Because 1,25-D functions as a native hormone, providing complex, tissue-specific signaling throughout the body, it is a challenge to accurately measure the relative contribution of exogenously administered vitamin D with signaling that is occurring through autocrine/paracrine feedback loops (20). The interrelated effects between native and supplemented vitamin D are reiterated in a study examining the effects of exogenously administered 1,25D (i.e., calcitriol) in healthy volunteers and uremic patients. Gallieni et al. (21) showed that although dialysis patients have impaired uptake and metabolism of 25-D, treatment with calcitriol not only repleted serum 1,25-D levels but also increased the uptake of 25-D (as examined in monocytes). Thus, with exogenous 1,25-D administration, there are potential complementary benefits to both 1,25-D and 25-D in an effort to rebalance the hormonal system.

**Treatment of Vitamin D Deficiency and SHPT in Patients with Stages 3 and 4 CKD**

Deficiencies in 25-D and/or 1,25-D have been associated with an elevated risk of cardiovascular disease and mortality in the general population (22,23). Suboptimal levels of vitamin D contribute to the development of SHPT through reduced intestinal Ca absorption, increased PTH production, and parathyroid hormone (PTH) levels, and the nomenclature for endogenous and exogenous vitamin D is very similar (Table 1). Because 1,25-D functions as a native hormone, providing complex, tissue-specific signaling throughout the body, it is a challenge to accurately measure the relative contribution of exogenously administered vitamin D with signaling that is occurring through autocrine/paracrine feedback loops (20). The interrelated effects between native and supplemented vitamin D are reiterated in a study examining the effects of exogenously administered 1,25D (i.e., calcitriol) in healthy volunteers and uremic patients. Gallieni et al. (21) showed that although dialysis patients have impaired uptake and metabolism of 25-D, treatment with calcitriol not only repleted serum 1,25-D levels but also increased the uptake of 25-D (as examined in monocytes). Thus, with exogenous 1,25-D administration, there are potential complementary benefits to both 1,25-D and 25-D in an effort to rebalance the hormonal system.
roid cell proliferation (24). Elevated PTH may also initiate increased Ca and P resorption from bone and promote vascular calcification (24,25). Despite elevation in PTH and reductions in endogenous vitamin D (i.e., 25-D and 1,25-D), serum Ca and P usually remain within normal physiologic range in stages 3 and 4 CKD (16,17).

Inactive forms of supplementary vitamin D, ergocalciferol (vitamin D$_2$), and cholecalciferol (vitamin D$_3$), significantly increase 25-D and 1,25-D levels in patients with stages 3 and 4 CKD and suppress, but do not normalize, PTH concentrations (26–28). Beginning with stage 4 CKD, the ability of vitamin D supplements to correct elevated PTH concentrations is significantly reduced compared with earlier stages of CKD (26,28). These supplements are generally considered ineffective for PTH suppression in usual doses in patients with stage 5 CKD (before or in those receiving dialysis), although they may prevent osteomalacia due to vitamin D deficiency and possibly have other benefits.

The biologically active VDR agonists calcitriol and paricalci-
tol, and the prohormone doxercalciferol, suppress PTH in a dose-related fashion independent of the stage of CKD. Placebo-controlled trials of these exogenously administered agents in patients with stages 3 and 4 CKD demonstrated that calcitriol and doxercalciferol elevated serum Ca, although doxercalciferol may have been less calcemic than calcitriol (3,29,30). Trials of paricalcitol showed significant and sustained control of PTH, with minimal alterations in Ca and P compared with placebo (30). Although the changes observed in Ca and P in these studies are consistent with animal data showing differences in the calcemic and phosphatemic effects of these agents (31,32), definitive claims of differences between compounds await randomized trials comparing these agents in patients with CKD stages 3 and 4. Markers of bone formation, such as bone-specific alkaline phosphatase, were also significantly reduced by VDR agonist treatment (3,29,30). Current KDIGO guidelines do not recommend bone mineral density measurements for CKD but do suggest that stages 3 to 5 CKD patients be measured for serum PTH or bone-specific alkaline phosphatase to predict for low or high bone turnover (2).

**Treatment of SHPT in Dialysis Patients**

In the late 1980s, intravenous (IV) calcitriol was recom-
manded as an alternative therapy to either oral calcitriol or parathyroidectomy in dialysis patients with SHPT. Long-term intermittent infusions of IV calcitriol 1 to 2.5 µg thrice weekly for an average of 11.5 months in dialysis patients with concomi-
tant osteitis fibrosa achieved significant reductions in PTH and alkaline phosphatase, and resulted in fewer episodes of hyper-
calcemia than experienced with prior therapy (33). In the late 1990s, investigators demonstrated that by lowering the level of PTH in hemodialysis patients, IV calcitriol 2 µg twice weekly not only attenuated the SHPT effects but also displayed cardio-
protective effects (34). Interestingly, the increased use of calcitriol as a therapeutic intervention has been associated with a reduction in parathyroidectomy rates in the late 1990s to <1% and a shift in the treatment paradigm from a surgical interven-
tion to pharmacologic management of SHPT (35).

Doxercalciferol (a prohormone that can be hepatically acti-

ated into a VDR agonist) was originally investigated as a treatment for osteoporosis (36) and later demonstrated its efficacy by reducing PTH in hemodialysis patients, albeit with elevations in serum Ca and P (37,38). Unfortunately, there have been no studies directly comparing doxercalciferol with other VDR agonists. Alphacalcidol (not approved for use in the United States) is 1α-hydroxyvitamin D$_3$, which is rapidly converted in the liver to 1,25-dihydroxy vitamin D$_3$ (39). Vitamin-resistant disorders, such as renal bone disease, hypoparathy-
roidism, and pseudodeficiency rickets, which usually require large amounts of vitamin D, respond to physiologic doses of alphacalcidol. Alphacalcidol may cause hypercalcemia. In a randomized prospective phase III study, IV paricalcitol 0.04 to 0.24 µg (given for up to 32 weeks) showed similar or improved PTH suppression and fewer hypercalcemic episodes compared with IV calcitriol 0.01 to 0.06 µg (40).

Optimal PTH Suppression through Individualized Dosing and Continuous VDR Agonist Therapy

In 2003, KDOQI experts offered CKD stage-specific PTH target ranges; these targets lacked rigorous trial evidence and are no longer considered adequate for management of the individual patient (1). Bone biopsy series in dialysis patients indicate a high prevalence of adynamic bone (low bone turn-
over) despite PTH levels in or above the KDOQI recommended range, and this is thought to be due to overly aggressive treat-
ment of SHPT in many patients (41). Black dialysis patients in particular may require maintenance of a higher PTH level to avoid adynamic bone (42). Although a patient may not reach PTH levels within KDOQI ranges, continued use of VDR ago-

nists usually leads to significantly reduced PTH that remains stable over time and is accompanied by normalization of other markers of high bone turnover, such as bone-specific alkaline phosphatase and osteocalcin (30,43,44). In the clinical setting, the optimal level of PTH suppression by VDR agonists has been a matter of discussion because PTH levels are lowered and steady themselves at varying levels on the basis of individual patient response to therapy. Hypercalcemia after VDR agonist therapy may be an indication of ensuing adynamic bone and also suggests that the dose of VDR agonist should be reduced (45). In the recently released KDIGO guidelines, target ranges for PTH are set in context with the upper limit of normal per the PTH assay used (2). However, the guidelines do not make formal recommendations for PTH levels in CKD patients. Ide-
ally, an optimal PTH level would result in a nearly normal bone formation rate (BFR). Unfortunately, PTH has only a weak correlation with BFR; therefore, despite achieving otherwise “normal” PTH levels, individuals may have low, normal, or high BFR. In general, patients with CKD stages 3 to 5 who are not on dialysis should achieve stable PTH levels near the upper limit of normal that are maintained with VDR agonist therapy while avoiding hypercalcemia and hyperphosphatemia. In dialysis patients, PTH levels should, in general, be stable and maintained at two or more times the upper limit of normal with VDR agonist therapy while avoiding hypercalcemia. The KDIGO guidelines suggest a PTH goal of two to nine times the
upper limit for the assay being used in patients with CKD stage 5D (2). An elevated alkaline phosphatase level is suggestive of inadequately suppressed PTH, and therapy should be intensified to further suppress PTH.

Similar to treating other hormone-deficient diseases (e.g., hypothyroidism) (46), it is the authors’ opinion that VDR agonist treatment should in general be continuous in dialysis patients so that patients can maintain normal to nearly normal levels of vitamin D hormone rather than being treated for episodic vitamin D deficiencies and/or rising PTH levels. These patients show moderate to severe 1,25-D deficiency (8) in addition to commonly having hyperphosphatemia and relative or absolute hypocalemia. The hormonal and mineral imbalances (i.e., 1,25-D, Ca, and P) are potent inducers for PTH secretion and parathyroid proliferation. Uninterrupted use of VDR agonists can therefore remove the PTH stimulatory effect of 1,25-D deficiency and help maintain normal serum Ca, although greater use of phosphate binders may be necessary. This rationale is also consistent with the hypothesis that treatment of the 1,25-D hormonal deficiency plays a role in maintaining health via activation of the VDR in multiple organ systems, such as kidney, immunologic, and cardiovascular systems (reviewed by Andress (47)).

**Effects of Vitamin D Receptor Agonist Treatment on Survival in Dialysis Patients.** Numerous observational studies in dialysis patients have shown improved survival after VDR agonist therapy (8,10,12,48,49). Increased risks of all-cause mortality were observed in patients with elevated mineral levels outside of KDOQI-based normal ranges (12). Hypercalcemia, hyperphosphatemia, and increased Ca × P were significantly associated with an increased risk of death. The reverse also appeared to be true; abnormally low mineral levels elevated a patient’s risk of death, rounding out a U-shaped effect on mortality. In addition, the Kalantar-Zadeh et al. study (12) took into account patients who received VDR agonist therapy and demonstrated that treatment, compared with no treatment, was associated with a trend toward improved survival.

Injectable VDR agonists have been associated with a survival advantage that appears to be independent of Ca, P, and PTH levels (48). The benefit with paricalcitol was evident at essentially all baseline strata of Ca, P, and PTH. In a historic cohort study evaluating patients who changed VDR agonist therapy, those crossing over from calcitriol to paricalcitol also demonstrated a survival advantage at 2 years compared with the inverse crossover regimen (13). Cardiovascular-related mortality rates (at all basal levels of Ca, P, or PTH) were also significantly different for patients receiving paricalcitol versus patients who did not (13). Patients with advancing stages of CKD are at correlative increasing risk for cardiovascular-related events (50). Low vitamin D and 1,25-D levels correlate with increased cardiovascular disease and deaths, whereas use of VDR agonist therapy may be cardioprotective (23,48). Cardiac myocytes express the VDR (51), and vitamin D-deficient animals have significantly higher left ventricular systolic pressures compared with vitamin D-sufficient animals (52). Animals lacking signaling through the VDR, because of either knockout of the VDR (53) or 1α-vitamin D hydroxylase (54), develop left ventricular hypertrophy (LVH), whereas treatment of the latter knockout model with 1,25-D prevents LVH (54). The Dahl salt-sensitive rat develops severe hypertension, LVH, and vitamin D deficiency when maintained on a high-salt diet. Cotreatment of the Dahl salt-sensitive rats with paricalcitol has been shown to prevent LVH while not altering hypertension (55). More importantly, use of 1,25-D in dialysis patients has been shown to reduce LVH (34). Prospective cohort studies of peritoneal dialysis and hemodialysis patients with deficient or insufficient 25-D (i.e., ≤30 ng/ml) have demonstrated significantly elevated risk of cardiovascular-related mortality (8,56). This increased risk was significantly diminished in patients receiving VDR agonists (8). Collectively, these preclinical and clinical data provide a plausible mechanism by which use of VDR agonist therapy may attenuate cardiovascular-related mortality.

**Conclusions**

Optimal SHPT control is important in managing the course of CKD, as well as reestablishing PTH, mineral, and vitamin D balances in the CKD patient. It is clear that vitamin D deficiency contributes to the development of SHPT in CKD patients. Depending on the stage of kidney dysfunction, repletion of both inactive (25-D) and active (1,25-D) vitamin D may be needed to adequately replace and balance physiologic levels, because signaling pathways are disrupted owing to a reduction in VDR activity. Characteristics and some of the challenges associated with vitamin D therapies for SHPT in CKD patients are presented in Table 3. Guidelines for the treatment of CKD patients with SHPT were recently updated by the KDIGO working group to include a more recent perspective on SHPT treatment in CKD patients since the prior 2003 guidelines; comprehensive study details are presented by the KDIGO group (1,2). Taking the KDIGO guidance into account, as well as practical patient management experiences, several considerations are proposed to ensure optimal SHPT control in CKD patients, including early recognition of reduced eGFR, evaluation of PTH, 25-D, and/or 1,25-D starting at stage 3 CKD; optimizing VDR agonist dosing per PTH response in the individual patient; maintenance of continuous VDR agonist therapy to ensure continued PTH suppression; and vigilant monitoring of Ca and P to conform with target ranges (Table 2). The authors believe that it is a rational approach to maintain continuous VDR agonist therapy; however, there are no data to support the effectiveness of inter-
ruptured use. In addition to management of SHPT, the overall goals of these proposals are to treat what is actually a chronic hormonal deficiency and increase patient survival. Numerous observational analyses have shown beneficial effects of VDR agonists on both cardiovascular and all-cause mortality rates (8,11,22,56). These potential vitamin D-reliant cardiovascular effects and survival benefits remain to be confirmed in prospectively planned, randomized, controlled trials.

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Disclosures
D.C. is a consultant to Abbott, INEOS, and Shire; is a speaker for Abbott; and participates in multicenter studies or receives research support from Abbott, Amgen, and INEOS. S.M.S. is a consultant to Abbott, Amgen, INEOS, and Shire; is a speaker for Abbott and Shire; and participates in multicenter studies or receives research support from Abbott, Amgen, INEOS, Mitsubishi, and Shire. D.C. and S.M.S. are principal investigators of a trial of comparing calcitriol to paricalcitol treatment of SHPT in stages 3 and 4 CKD.

References

Table 3. Effects and challenges with vitamin D to treat SHPT in CKD patients

<table>
<thead>
<tr>
<th>Vitamin D Term</th>
<th>Biologic and Clinical Effect</th>
<th>Challenges of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphacalcidol</td>
<td>• Effective in repleting 25-D and 1,25-D in patients with early-stage CKD and adequate kidney function</td>
<td>• Requires activation in kidney to generate active 1,25-D</td>
</tr>
<tr>
<td>Ergocalciferol, cholecalciferol</td>
<td>• Effective in repleting 25-D and 1,25-D in patients with early-stage CKD and adequate kidney function</td>
<td>• Requires activation in kidney to generate active 1,25-D</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>• Biologically active VDR agonist • Effectively suppresses SHPT • Reduces abnormal high bone turnover</td>
<td>• Requires activation in liver to generate active 1,25-D • Induces significant elevation of serum P, elevating need for phosphate binder use</td>
</tr>
<tr>
<td>Doxercalciferol</td>
<td>• Suppresses SHPT similar to or better than calcitriol • Noted reduction in serum bone-specific alkaline phosphatase and osteocalcin</td>
<td>• Requires activation in kidney to generate active 1,25-D</td>
</tr>
<tr>
<td>Paricalcitol</td>
<td>• Biologically active VDR agonist • Effectively suppresses SHPT • Noted reduction in serum bone-specific alkaline phosphatase and osteocalcin</td>
<td>• Minimal elevation in Ca, P, and Ca × P product, requiring Ca and P monitoring</td>
</tr>
</tbody>
</table>


