CONCISE REVIEW

Efficacy and Safety of Cinacalcet in Chronic Kidney Disease Stage III and IV

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Abstract: Treatment of secondary hyperparathyroidism in patients with chronic kidney disease (CKD) stage III and IV with vitamin D sterols is useful to maintain optimal parathyroid hormone (PTH) levels and thereby, reduces the severity of bone abnormalities caused by high PTH levels. However, it should be borne in mind that serum calcium (Ca) levels may easily increase as bone turnover is easily suppressed due to diffuse or early nodular parathyroid tissue in these patients. Furthermore, an elevated risk of cardiovascular disease due to advanced atherosclerosis associated with both secondary hyperparathyroidism and the administration of vitamin D sterols has been reported in patients with moderate to severe CKD, resulting in a high mortality in these patients. In order to control serum Ca levels, therefore, additional use of cinacalcet hydrochloride may be useful. However, acute reduction of serum Ca levels and chronic hyperphosphatemia should be avoided; therefore, the doses of phosphorus (P) binders should be increased or the initiation of low doses of vitamin D sterols may be favorable in patients with stage III and IV CKD receiving cinacalcet hydrochloride. The phosphaturic effect of FGF-23 after treatment with cinacalcet is estimated to be small as compared with that of vitamin D in moderate to severe CKD patients, therefore, evaluation of osteocytes should be performed in patients with secondary hyperparathyroidism treated with cinacalcet hydrochloride.

Keywords: chronic kidney disease, secondary hyperparathyroidism, cinacalcet, hypocalcemia, hyperphosphatemia

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Introduction

Cinacalcet hydrochloride (HCl) is an oral calcimimetic agent which is used for the treat of secondary hyperparathyroidism. Secondary hyperparathyroidism is the consequence of persistently elevated serum phosphorus (P), low serum calcium (Ca) and low 1,25-(OH)2D3 levels in patients with chronic kidney disease (CKD). Cinacalcet exerts its action by binding to the parathyroid Ca sensing receptor (CaSR). This leads to a decrease of circulating parathyroid hormone (PTH) levels in CKD stage V patients,1–3 and thereby allows to achieve the goals set up by the NKF-K/DOQI guidelines.4 As a consequence of cinacalcet use, a decrease of serum alkaline phosphatase levels,5 and an improvement of hyperparathyroid bone disease6,7 has been documented (Fig. 1). In particular, woven bone volume was decreased after 52 weeks treatment with cinacalcet although it was not changed at 1 week after parathyroidectomy. Both these effects have been associated with decreased mortality in observational cohort study.5,8 An increase of the minimodelling volume7,9,10 and a direct and favorable effect of cinacalcet HCl on bone adipocyte volume were also shown in CKD stage V patients.11

CKD and Bone Health

The severity of CKD was classified into the 5 categories (stages I–V) according to glomerular filtration rate (GFR) of the patients; GFR values of stage I, II, III, IV and V were ≥90, 60–89, 30–59, 15–29 and <15 ml/min/1.73 m2, respectively.12 During the progression of renal failure from CKD stage II through V, serum vitamin D levels gradually decline,13,14 leading to a gradual rise of serum PTH levels. These elevated serum PTH levels lead to an increased recruitment of P and Ca from the bone and thereby to a decrease of bone mineral content. Therefore, to vitamin D sterols are also administered in the early stages CKD. Serum intact PTH levels above 70 pg/ml, but not serum Ca and P levels, have been reported to be associated with cardiovascular disease (CVD) in CKD stage III and IV patients.15 While 40%–87% of incident dialysis patients suffer from secondary hyperparathyroidism,16,17 the corresponding number have not yet been clarified.

Figure 1. Woven bone volume was decreased and lamellar bone volume was increased after treatment with cinacalcet hydrochloride in maintenance dialysis patients with secondary hyperparathyroidism. High bone turnover was suppressed, resulting in the disappearance of tunneling resorption spaces and an increase of new bone formation after the treatment.
in predialysis patients. It is clear, however, that osteitis fibrosa and mixed osteodystrophy can already be found in this patient population. Histologically, high PTH levels lead to an increase of woven bone volume and to a decrease of cortical bone volume. These effects are due to enhanced bone resorption both at endocortical surface and intracortical resorption spaces con- jointly leading to increased bone fragility. Additional devastating effects are periosteal bone loss and the woven texture of the bone around the periosteal surface and those cannot be reversed even by total parathyroidectomy. Anemia, extraosseous ossification and muscle weakness with consecutive poor bone health are already present at the initiation of dialysis therapy and are believed to contribute to the increased mortality of these patients. Oral administration of calcitriol (1α, 25-dihydroxyvitamin D₃) or alfalcacidol (1α-hydroxyvitamin D₃) at doses of 0.25–0.5 μg/day early in the course of renal insufficiency (creatinine clearance above 25 ml/min) halts the development of secondary hyperparathyroidism and maintains a well mineralized bone matrix. Once secondary hyperparathyroidism has developed, administration of vitamin D sterols can effectively suppress elevated PTH levels. The abnormalities of bone and mineral metabolism go in parallel with the increased cardiovascular morbidity and mortality encountered in these patients.

In patients with CKD stage V, the biological effects of PTH are attenuated. This resistance towards PTH is due to a reduced number of PTH receptors on osteoblasts and to the accumulation of the 7–84 PTH fragment which exerts effects opposite to those of the full length 1–84 PTH protein. Therefore, the optimal range of PTH to maintain normal bone turnover are higher in CKD stage V than in CKD stage II–IV patients. To conclude, secondary hyperparathyroidism should be corrected, but over-suppression of PTH avoided to maintain bone health in CKD stage II to IV. Importantly, physical activity helps to maintain both, osteocyte number and function, and thereby contributes to the preservation of bone quality and mass.

Whether cinacalcet HCl should be used for the management of secondary hyperparathyroidism in patients with CKD stage III and IV patients is controversial. Currently, FDA and health Canada do not approve the use of the calcimimetic cinacalcet in predialysis CKD patients with secondary hyperparathyroidism. To date, a small study has reported the efficacy of cinacalcet to lower PTH level in predialysis patients and its safety with regard to serum Ca and P levels. The other two studies concluded that special attention should be paid to the frequent occurrence of hypocalcemia and long-term hyperphosphatemia in CKD stage III and IV patients receiving cinacalcet. Most notably, pronounced hyperphosphatemia represents a serious complication which may occur during treatment with cinacalcet in these patients. As possible causes for these elevated P levels, changes of two substances promoting urinary P excretion (phosphatonin) have to be taken into consideration: fibroblast growth factor 23 (FGF-23) and PTH. FGF-23 levels have been shown to be increased in the early stages of CKD and they are also increased after treatment with vitamin D sterols. FGF-23 is mainly secreted from the osteocytes and osteoblasts where its release is mediated via PTH receptors. PTH receptors are known to be expressed on osteoblasts and have also been found on osteocytes. Therefore, if the osteocyte number is reduced as is the case following surgical treatment for secondary hyperpara-thyroidism, FGF-23 production will be reduced. Accordingly, it is currently speculated that while vitamin D sterols increase serum FGF-23 levels, cinacalcet probably has little effect on FGF-23 levels. Therefore, the phosphaturic effect of FGF-23 after treatment with cinacalcet is probably small when compared to that of vitamin D in predialysis CKD patients. If parathyroidectomy is performed in CKD stage III and IV, the reduction of FGF-23 levels after surgery may be followed by a decline of urinary P excretion. In addition, FGF-23 levels have been shown to be increased in the early stage of CKD and it is also increased after treatment with vitamin D sterols. However, the osteocyte number may not be significantly decreased by the use of cinacalcet. Therefore, cinacalcet may exert a beneficial effect on bone metabolism in CKD patients by allowing the osteocyte number to be well maintained although admittedly cases of adynamic bone disease have been reported after treatment with cinacalcet.

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of bone fragility by allowing the osteocyte number to be well maintained because osteocytes play the important role in maintaining bone volume and bone quality.\(^{38-43}\) This notion was supported by the personal communication between Dr. Kamyar Kalantar-Zadeh and Dr. Eduard Slatopolsky. Dr. Eduard Slatopolsky commented that cinacalcet probably has no effect on FGF-23 (as compared to vitamin D sterols\(^?\)),\(^{46}\) while vitamin D sterols increase the serum FGF-23 levels. Therefore, the phosphaturic effect of FGF-23 after treatment with cinacalcet is estimated to be small as compared with that of vitamin D in moderate to severe CKD patients, which could lead to hyperphosphatemia. If parathyroidectomy is performed in CKD stage III and IV, the reduction of FGF-23 levels after surgery may be followed by a decline of urinary P excretion.\(^{34}\) However, the accumulation of serum P in these patients will be at least partially offset by the reduction of osteoclast number and continued mineralization after parathyroidectomy.\(^{55}\) Consequently, no serious changes of serum P levels do occur after parathyroidectomy in stage III and IV CKD. This difference between parathyroidectomy and cinacalcet may be caused by quantitative difference in serum PTH after each treatment. And the additional effect of cinacalcet on osteocytes may be another cause of serum P level.

Three clinical studies have indicated significant cinacalcet-induced increases of serum P levels.\(^{46-48}\) Charytan et al reported a phase II, randomized, double-blind, placebo-controlled, 18-week study of cinacalcet administered to predialysis patients. The doses of cinacalcet administered ranged from 30 to 180 mg/day and the mean serum intact PTH levels decreased by 32% in these patients, while they increased by 6% in the placebo group. However, the mean serum P level increased significantly (\(p < 0.005\)) during the 18-week administration period in patients receiving cinacalcet, while they remained unchanged in the placebo group.\(^{45}\) Chonchol et al reported from a phase III trial that while the serum intact PTH levels decreased by 43%, serum P levels increased by 21.4% (to a mean of 4.5 \(\pm\) 1.0 mg/dl) after 32 weeks of treatment. In the placebo group, the serum P levels increased by only 6.8%.\(^{46}\) Forslund et al also reported that although the serum intact PTH decreased and remained at 40%–50% as compared to baseline level, the serum P levels increased after 12 months of treatment.\(^{47}\)

From these reports, it would seem that the administration of phosphorus binders should be initiated or their dosages increased in stage III and IV CKD patients receiving cinacalcet. One of the most serious problems of treatment with cinacalcet HCl is acute hypocalcemia. Charytan et al reported that the serum Ca level decreased during the study period and the mean 24-hour urine Ca excretion was 74.0 \(\pm\) 21.0 mg/24 h in the cinacalcet group compared to 53.9 \(\pm\) 13.7 mg/24 h in the placebo group, and that the urinary Ca excretion did not exceed 300 mg/24 h in either group.\(^{46}\) Chonchol et al also reported that the mean serum Ca level decreased: it was 8.9 \(\pm\) 0.8 mg/dl in the cinacalcet group after 32 weeks of treatment, while it was 9.9 \(\pm\) 0.6 mg/dl in the control group.\(^{47}\) Therefore, Dr. Kamyar Kalantar-Zadeh estimated that cinacalcet may aggravate the deficiency of activated vitamin D\(_3\) by suppressing 1\(\alpha\)-hydroxylation of 25-hydroxyvitamin D. Enlarged parathyroid glands may contain PTH-responsive diffuse hyperplastic parathyroid tissue or early nodule formation in predialysis patients.\(^{56}\) Therefore, serum PTH levels are being readily when peak serum concentration of cinacalcet occur. In sight of decreasing serum cinacalcet concentrations, serum PTH may then rise again. Parathyroidectomy in stage V CKD patients with secondary hyperparathyroidism leads to an immediate cessation or reduction of osteoclastic bone resorption. This results in a decline of serum Ca levels post surgery, so called “hungry bone syndrome”. Serum Ca levels may be easily reduced immediately after cinacalcet administration in predialysis patients because it appears that the function of diffuse or early nodular hyperplastic parathyroid tissue can be easily suppressed. The acute reduction of the serum Ca levels may be associated with an increased mortality\(^{57,58}\) and sustained long-term hypocalcemia may decrease bone mineralization and cause low-turnover osteomalacia.\(^{59}\) Therefore, vitamin D sterols and Ca-containing phosphate binders are needed to maintain the serum Ca levels, bone mass and bone health, and decrease the mortality in these patients.\(^{60}\) However, caution should also be exerted to prevent hypercalcemia which might lead to extrasosseous ossifications and mental disturbance.\(^{61}\) Therefore, in this setting high doses of vitamin D sterols or Ca-containing phosphate binders should be avoided. It has been reported that the renal function during treatment
with cinacalcet remained unchanged and also, calcification of the aorta and heart was suppressed in the rats. Thus, the use of cinacalcet may be safe if attention is paid to balance both hyperphosphatemia and hypocalcemia with the use of vitamin D sterols and/or Ca-containing phosphate binders. In addition, the use of cinacalcet may be effective and safe when ultrasound evaluation of the parathyroid glands reveals diffuse or early nodular hyperplasia.

Conclusion
To conclude, cinacalcet may be an effective and relatively safe treatment for stage III and IV CKD patients with secondary hyperparathyroidism when used in conjunction with low doses of vitamin D sterols along with phosphate binders. When cinacalcet is applied to CKD stage III and IV patients, serum Ca and P levels have to be closely monitored.

Disclosures
The authors report no conflicts of interest.

References


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