Treatment of Secondary Hyperparathyroidism in CKD Patients with Cinacalcet and/or Vitamin D Derivatives

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The discovery of the calcium-sensing receptor (CaR) 15 yr ago was rapidly followed by the development of drugs modulating its activity, the so-called calcimimetics (increasing the CaR signal) and calcilytics (decreasing the CaR signal). The indication for calcimimetics is treatment of primary and secondary hyperparathyroidism, whereas calcilytics have potential for treatment of osteoporosis. A large number of clinical studies has shown that cinacalcet, the only presently available calcimimetic, effectively reduces serum parathyroid hormone in dialysis patients with secondary hyperparathyroidism. In contrast to the effect of active vitamin D derivatives, it simultaneously decreases serum calcium and phosphorus. Experimental studies showed a concomitant decrease in parathyroid hyperplasia. In the treatment of secondary hyperparathyroidism of dialysis patients, important questions remain unresolved, for example, whether there are reasons to prefer calcimimetics to active vitamin D derivatives and whether combined administration offers advantages compared with calcimimetics or active vitamin D given in isolation. For lowering parathyroid hormone, available evidence from recent studies suggests that combination therapy should be preferred to single drug treatment because of less side-effects and greater efficacy in controlling parathyroid overfunction. Future randomized controlled trial must answer whether calcimimetics impact on cardiovascular events or survival and whether in this respect there are differences between vitamin D sterols and calcimimetics.

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Discovery and Function of Calcium-Sensing Receptor

Intracellular Ca\textsuperscript{2+} has long been known to play a major role as second messenger in signal transduction across the extracellular membrane, in response to a large number of activators and inhibitors outside the cell. Subsequently, it has become apparent that extracellular Ca\textsuperscript{2+} itself is one of these activators and inhibitors because a variety of tissues and cell types were capable of sensing and responding to changes in the concentration of extracellular Ca\textsuperscript{2+}. This is also true for endocrine cells. In most of them, extracellular Ca\textsuperscript{2+} stimulates hormone secretion, for instance, in the β-cells of the pancreas or the C-cells of the thyroid, where it increases insulin and calcitonin secretion, respectively. Not so in the principal cells of the parathyroid or the juxtaglomerular cells of the kidney, where extracellular Ca\textsuperscript{2+} inhibits parathyroid hormone (PTH) and renin secretion, respectively.

The observation that cells could sense the extracellular concentration of Ca\textsuperscript{2+} led Brown et al. to search for the existence of a calcium sensor located in the cell membrane. They were successful in cloning such a sensor 15 yr ago and called it “calcium-sensing receptor” (CaR) (1). The receptor is phylogenetically old. It has been detected in lower prevertebrate species such as the worm Caenorhabditis elegans and even plants such as Arabidopsis (2). A highly homologous CaR gene has also been identified in fishes, which use hormones distinct from PTH, such as stanniocalcin, to maintain extracellular Ca\textsuperscript{2+} homeostasis (3). The CaR, however, mediates olfactory sensitivity to changes in the environmental Ca\textsuperscript{2+} in the freshwater teleosts (4).

CaR activation occurs at surprisingly high extracellular Ca\textsuperscript{2+} concentrations, compared with activator concentrations needed for the majority of other extracellular receptors. Ca\textsuperscript{2+} is the main activator, although not the only one. It binds to specific sites on the extracellular domain of the CaR, with relatively high affinity. The receptor can be stimulated by many other cationic agents, including magnesium, aluminum, gadolinium, and organic compounds such as aminosides. The CaR is part of a large G-protein–coupled receptor family. Signal transduction occurs via several pathways (5). It interacts with Gα\textsubscript{q,11} subunits of heterotrimeric G proteins, resulting in the activation of phospholipases C and A2 and activation of protein kinase C. It activates phosphatidylinositol 4-kinase (PI4K), which catalyzes the first step of the inositol lipid biosynthesis, independently of the G proteins, by a p-dependent mechanism. In some cells, CaR interacts with protein Gα\textsubscript{q}, which results in inhibition of adenylyl cyclase-mediated cAMP production.

The expression of the CaR is practically ubiquitous. In addition to the classic organs involved in extracellular Ca\textsuperscript{2+} homeostasis, namely the kidney, the parathyroid gland, and the
C-cells of the thyroid gland, it also is present in tissues as different as the brain, the intestinal tract, vascular tissue including endothelium, smooth muscle cells, and perivascular neurons (6). Whether the same CaR also is expressed in bone remains a matter of debate. The observation that osteoblasts isolated from CaR-deficient mice retained responsiveness to extracellular Ca\(^{2+}\) led to the identification of another receptor, namely, GPRC6A. This is another member of the G-protein-coupled receptor family and mediates calcium sensing in osteoblasts and possibly other tissues even in CaR\(^{-/-}\) mice (7).

In humans, both inactivating and activating mutations of the CaR have been shown to lead to distinct clinical diseases with contrasting phenotypes. In heterozygotes, inactivating CaR mutations cause familial benign hypercalcemic hypercalciuria, and in homozygotes, severe neonatal primary hyperparathyroidism (8,9). In contrast, activating CaR mutations result in autosomal dominant hypocalcemia (10,11). The latter may be sometimes associated with hypercalcuria and a Bartter-like syndrome (12,13), explained by the fact that the CaR is also expressed by epithelial cells of Henle’s loop. Corresponding phenotypes have been reproduced in genetically modified animal models.

**Development of Calcimimetics and Calcilytics**

In addition to the activation of the CaR by extracellular Ca\(^{2+}\) and other cations, called “type I calcimimetics,” its sensitivity to these direct receptor agonists can be increased by CaR modulators, called “type II calcimimetics.” They act as positive allosteric activators. The prototype is cinacalcet. Alternatively, the sensitivity of the CaR to extracellular cations can be reduced by so-called calcilytics. The CaR modulators act through differing conformational changes of the tertiary structure of the receptor. The main clinical interest of the calcimimetics resides in the treatment of parathyroid overfunction, whereas that of the calcilytics is its potential for the treatment of osteoporosis (14).

Of note, the increase in the sensitivity of the parathyroid CaR to extracellular Ca\(^{2+}\) brought about by the calcimimetics is approximately 100 times higher than that of the C-cell of the thyroid gland (15). This probably explains why relatively low doses of cinacalcet generally allow control of secondary hyperparathyroidism in patients receiving dialysis therapy without inducing major side effects at other tissue sites, except initial hypocalcemia and gastrointestinal symptoms such as nausea and vomiting. These adverse effects can be avoided in the majority of patients by using cautious cinacalcet dose increments at treatment initiation. The administration of calcimetics to patients with chronic kidney disease (CKD) before the stage of dialysis, however, may lead to increased urinary calcium excretion and phosphate retention via direct effects on the kidney and indirect effects through inhibition of PTH. Recently, the group of the late Steve Hebert showed that modulation of intestinal CaR activity by calcimetics leads to a reduction of excessive fluid secretion into the gut lumen upon stimulation by cAMP- and cGMP-dependent secretagogues (16). Calcimetics could thus represent a new tool in the control of cholera toxin- and *Escherichia coli* endotoxin-induced diarrhea.

Several studies in experimental animals with chronic renal failure showed beneficial effects of calcimetics in terms of disturbed calcium and phosphate metabolism and beyond. Thus, the use of calcimetics led to a decrease in PTH synthesis and PTH release (17); modulated the regulation of genes involved in these processes, including upregulation of CaR (18) and VDR (19); reduced parathyroid cell proliferation (20); attenuated progression of parathyroid hyperplasia (21,22); and enhanced parathyroid cell apoptosis (23). In experimental animals, calcimetics attenuated or even halted the progression of osteitis fibrosa (24). They also have been shown to reduce the progression of arterial calcification or prevent their appearance in uremic rats (25,26) and mice (22).

Because CaR are expressed in many tissues unrelated to mineral metabolism, calcimetics have numerous, so-called pleiotropic effects. In experimental models, they have been reported to cause a short-term increase, but a long-term decrease, in BP and to reduce cardiac pathology at the microscopic level (27,28). They also caused reduction in serum LDL cholesterol concentration (28); slowing of CKD progression with less albuminuria and less morphologic abnormalities of the kidney (28), comparable to the effect of calcitriol (29); and improved survival (26). In this context, it is of interest that CaR polymorphisms in human subjects have been shown to be related to cardiovascular morbidity and mortality (30). The observation that cataracts and ectopic calcification develop in the Nuf mouse, caused by an activating CaR mutation (31), has been of some concern because this phenotypic feature was suggestive of similar complications in human patients treated with calcimetics. This finding probably reflects the consequences of profound hypocalcemia (cataract) and hyperphosphatemia (ectopic calcification) in the Nuf mouse model (32).

**Clinical Use of Cinacalcet**

The vast majority of experimental and clinical studies have been limited to the exploration of effects of calcimetics on serum biochemistry, that is, PTH, calcium, and phosphorus. Some of them also examined effects on vascular calcification and bone. Only a small number of reports dealt with pleiotropic effects, as alluded to above. Currently, there are no prospective randomized trials available to document the effect on patient outcome (see below).

It is noteworthy mentioning that the targets of the major biochemical parameters to which clinicians should be treating according to the guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) of 2003 (33) have recently become a matter of lively debate. This is particularly true for PTH. Studies from Brazil and Portugal have questioned the previously held assumption of a good correlation between serum intact PTH and bone turnover (34,35). Moreover, a variety of methodological problems with PTH assays have been identified (36–39), which make the recommendation of optimal targets even more difficult.

In patients with primary parathyroid adenomas and normal renal function (40) or in chronic hemodialysis patients with end-stage kidney disease (41), the acute effects of cinacalcet administration consist of a rapid decrease of serum PTH within
2 to 4 h, closely followed by a decrease of serum calcium within 4 to 8 h in patients with renal disease, but not in patients with parathyroid adenoma. Long-term administration of cinacalcet to patients with primary hyperparathyroidism induces a progressive decrease in serum calcium toward the normal range and an increase in serum phosphorus, despite only minor changes in serum PTH (42). In contrast, predialysis serum values of PTH, calcium, and phosphorus all decrease progressively with time in ESRD patients in response to cinacalcet, when given in addition to optimal standard treatment consisting of active vitamin D derivatives and phosphate binders alone (32). Importantly, in ESRD patients cinacalcet effectively controls secondary hyperparathyroidism over prolonged time periods, up to at least 3 yr (43). Of note, the pathologic rightward shift of the Ca2+-PTH curve seen in many dialysis patients with secondary hyperparathyroidism can be reversed by cinacalcet treatment (44,45).

Role of Cinacalcet and Vitamin D Derivatives in the Management of Hyperparathyroidism in Patients with ESRD

Both active vitamin D derivatives and cinacalcet allow long-term control of secondary hyperparathyroidism in patients with ESRD. An important question is whether there are reasons to prefer one to the other, and whether combined administration offers advantages compared with each drug (or drug class) given in isolation. Potential arguments for the latter approach, which has been proposed by Levi and Silver (17), may be the findings that active vitamin D increases Ca++ sensitivity of the parathyroid (46) and that the CaR is regulated by vitamin D but not by calcium (47).

In terms of PTH control, the efficacy of the two drug classes can be considered equal, although a recent meta-analysis cast some doubt on the consistent efficacy of vitamin D compounds in reducing PTH levels in patients with CKD (48). Vitamin D and its active derivatives attenuate the severity of secondary hyperparathyroidism, often, however, at the price of an increase in serum calcium and phosphorus, resulting from enhanced intestinal absorption (49,50). In contrast, cinacalcet generally decreases both serum calcium and phosphorus, in addition to a reduction of PTH (see below).

Case in Favor of Vitamin D or Active Vitamin D Derivatives Alone

The hypercalcemic and hyperphosphatemic effect of therapeutic doses of active vitamin D derivatives is generally not a major problem in early stages of CKD, which are already characterized by progressive impairment of renal calcitriol synthesis. This effect may constitute an advantage when serum calcium and phosphorus are at the lower end of the normal range or below. In addition, one has to point out that the only currently available calcimimetic, cinacalcet, is licensed for use in patients with CKD stage 5D. In patients with CKD stages 2 to 5, clinicians have to rely on the use of calcitriol, its analog 1-alpha 25 OH vitamin D (alfacalcidol), or other active vitamin D sterols, either alone or in combination with oral calcium supplements and/or non–calcium containing phosphate binders, to arrest or retard the steady increase in plasma PTH levels associated with the progression of chronic renal failure (51,52). These treatments are equally effective in CKD 5D patients with moderate to severe hyperparathyroidism (53–56). Although this is the case in the majority of patients, it is not true in all of them, as shown in a recent prospective study from Japan: 120 dialysis patients with secondary hyperparathyroidism were treated de novo with intravenous calcitriol for up to 48 wk. The treatment goal of decreasing serum intact PTH to levels <300 pg/ml could be achieved only in 79 patients (57).

The administration of excessive amounts of calcitriol or alfalcacidol may induce adynamic bone disease and arterial calcification, as do excessive oral doses of calcium salts (58). It remains to be demonstrated in patients with CKD whether treatment with high doses of the novel active vitamin D derivatives such as paricalcitol has similar adverse effects on bone, or whether, on the contrary, it is useful to prevent bone loss (in part by stimulating bone formation) and to prevent vascular calcification. The latter claims are based on experimental data obtained in cell cultures and experimental animals (59–61).

It has recently been widely appreciated that administration of native vitamin D or its hepatic metabolite, 25 OH vitamin D (calcifediol), may be useful in CKD patients with vitamin D deficiency (33,62). Insufficient or deficient levels of circulating 25(OH) vitamin D and/or 1,25(OH)2 vitamin D in CKD patients are associated with an increased prevalence of vascular calcification (63) and arterial stiffness (64), as well as with higher mortality (63,65 to 67). For many years, some authors had advised that calcifediol should be administered early in the course of CKD to hyperparathyroid patients with CKD, even when they are vitamin D replete (68). In recent years, it has become apparent that most, if not all, patients with advanced stages of CKD have vitamin D insufficiency or deficiency (69), and the same is true even in the general population (70). Therefore, some authors recommend supplementation with native vitamin D in all CKD patients. This advice is based on pathophysiological considerations and numerous observations of pleiotropic vitamin D effects, including cardiovascular, antiproliferative, and immunomodulatory actions (71). Recently, circulating 25(OH)D and 1,25(OH)2D levels have been found to be related to cardiac outcome and survival even in nonrenal patients with coronary heart disease (65).

In line with this concept, in several retrospective studies, treatment with calcitriol, alfalcacidol, or paricalcitol has been reported to be associated with beneficial effects on survival in CKD patients, both before (72) and after (73–77) the initiation of dialysis treatment. Moreover, the results of one of these observational studies in hemodialysis patients suggested a survival advantage with paricalcitol as compared with calcitriol (74), but another failed to identify such a difference (76). These effects appeared to be independent of changes in serum calcium and phosphorus. A major problem with historical cohort analyses of drug effects, however, is the risk of residual and unmeasured confounding by indication (48,76,78). Unfortunately, definite controlled, prospective evidence for the benefit of administration of native vitamin D or vitamin D derivatives in CKD patients on outcome, that is, morbidity or mortality, is not yet...
The main theoretical advantage of cinacalcet over active vitamin D derivatives in dialysis patients is that it decreases not only serum PTH, but also serum calcium and phosphorus and hence the Ca × P product. A recent study in chronic hemodialysis patients with moderate to severe secondary hyperparathyroidism addressed the issue of whether treatment with cinacalcet combined with low doses of vitamin D sterols improves control of both serum PTH and Ca × P (86). The results documented that combined therapy with cinacalcet and low-dose vitamin D sterols improved achievement of the biochemical targets for CKD-related mineral and bone disorder (CKD-MBD) recommended by the K/DOQI guidelines. Moreover, the study provided evidence in favor of cinacalcet being equivalent to combined treatment in those patients whose serum values of PTH and Ca × P product could be well controlled according to K/DOQI guidelines. This might be particularly true for ESRD patients with mild to moderate degrees of hyperparathyroidism.

Case in Favor of Combination of Vitamin D and Cinacalcet
Several controlled trials documented that in patients with ESRD, the addition of cinacalcet treatment on top of optimal standard therapy with active vitamin D derivatives and phosphate binders provides better control of secondary hyperparathyroidism than standard therapy alone (32,87). The K/DOQI treatment goals were achieved in a higher proportion of dialysis patients with elevated serum PTH and Ca × P levels in one such study (88). The superiority of the combination of standard therapy with cinacalcet was also demonstrated in the OPTIMA trial, in which dialysis patients with poorly controlled hyperparathyroidism were randomly allocated to receive either conventional care or a cinacalcet-based regimen (89). Again, a higher proportion of patients receiving cinacalcet in addition to conventional therapy versus conventional care alone achieved the targets for serum PTH, calcium, and phosphorus. Moreover, cinacalcet treatment allowed a 22% reduction of the vitamin D dose in patients who had received vitamin D at baseline. Another trial was conducted in hemodialysis patients with controlled PTH and elevated Ca × P to evaluate whether treatment with low-dose active vitamin D derivatives plus cinacalcet enhanced the proportion of patients achieving K/DOQI serum PTH and Ca × P targets (90). At the start of the study, the dose of active vitamin D derivatives was lowered and cinacalcet was titrated from 30 mg/d to a maximum possible dose of 180 mg/d. At the end of the study, K/DOQI targets for biointact PTH were achieved in 85% of patients, and for Ca × P in 72% of patients. Concurrent achievement of both targets occurred in 47% of patients. Thus cinacalcet enabled improved control of mineral metabolism with a combination of low-dose active vitamin D derivatives.

Adverse Effects of Vitamin D Derivatives and Cinacalcet
Vitamin D, both its natural active derivatives and its active analogs, are generally better tolerated than cinacalcet and cause fewer gastrointestinal side effects. Thus in a recent double-blind, placebo-controlled, multicenter study aimed to evaluate the long-term safety and efficacy of cinacalcet, nausea was observed in 13% patients receiving cinacalcet versus 5% patients on standard therapy alone, vomiting in 9% versus 2%, dyspepsia in 5% versus 4%, and diarrhea in 5% versus 2% (91).

Investigator-reported hypocalcemia was seen in 11% of cinacalcet-treated patients, but in only 1% of patients on standard therapy (91). In contrast, active vitamin D sterols often induce hypercalcemia and/or hyperphosphatemia (83–85). The frequency of these side effects may be less with so-called nonhypercalcemic active vitamin D derivatives such as paricalcitol (92) or doxercalciferol (93), but it clearly has not been reduced to zero (94,95).

In a recent uncontrolled clinical trial in hemodialysis patients, cinacalcet treatment was associated with an increase in serum osteoprotegerin and a decrease in serum fetuin-A levels (96). Because in CKD, both fetuin-A and osteoprotegerin play an important role in the pathogenesis of vascular calcification, the changes induced by cinacalcet could be interpreted as conferring an increased risk of vascular calcification. Alternatively, they could reflect a reduced demand for feedback defense mechanisms, which may be secondary to improved mineral metabolism (97).

Perspectives
A major problem remains in assessing the effectiveness of cinacalcet/vitamin D treatment, namely the absence of prospective randomized trials to document that in CKD patients, better control of secondary hyperparathyroidism translates into fewer hard end-points such as fractures, cardiovascular morbidity, and mortality. As outlined above, several observational studies point to a survival advantage in CKD patients receiving vitamin D treatment. This concerned mostly active derivatives. Some studies showed better survival with the more recently developed vitamin D analogs than with the parent substance, that is, calcitriol. It must not be forgotten, however, that observational, retrospective studies show association but do not prove causality (78). The outcome of direct, head-on comparisons would be of considerable interest.

Of note, two randomized controlled trials (RCT) are underway that examine the question of whether cinacalcet is superior to optimal standard therapy. The first trial (ADVANCE), a randomized, open label, parallel assignment, efficacy study, is aimed at reducing the progression of aortic valve calcification in a cohort of 330 dialysis patients (http://clinicaltrials.gov/
ct2/show/record/NCT00379899). The second (EVOLVE) is aimed at improving global outcome in 3800 chronic dialysis patients. The primary endpoints are time to all-cause mortality or first nonfatal cardiovascular event (98). Unfortunately, apparently no RCT are underway to prove the hypothesis that intravenously administered active vitamin D steroids confer a survival advantage in patients with CKD. Only RCT like the above two trials with cinacalcet will eventually show whether one or the other of the currently available treatment modalities should be preferred for the control of secondary hyperparathyroidism in ESRD patients.

Disclosures

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