New Perspectives in the Management of Secondary Hyperparathyroidism

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Abstract: The traditional treatment of secondary hyperparathyroidism, which affects many patients with chronic kidney disease and is associated with an increased risk of morbidity and mortality, is not very effective. Recent approaches to its management include the use of vitamin D analogues, non-calcium non-aluminium containing phosphate binders, and calcimimetics.

Key Words: Hyperparathyroidism, bone metabolism, chronic kidney disease, end-stage renal disease, vitamin D, calcium-sensing receptor, calcimimetics, cinacalcet HCl.

INTRODUCTION

The clinical outcomes of patients with end-stage renal disease (ESRD) remain poor: estimated 5-year survival in Europe is only 47.5% [1], and equivalent data from the United States suggest that the expected remaining lifetimes of prevalent dialysis patients are between one-third and one-sixth of those of members of general population. Furthermore, cardiac disease accounts for about half of all deaths in patients on dialysis [2,3].

The mineral abnormalities related to secondary hyperparathyroidism (SHPT) due to chronic kidney disease (CKD) have been associated with increased morbidity and mortality in ESRD patients, and there is growing evidence that SHPT plays a critical role in the pathophysiology of cardiovascular diseases (CVD) in such patients [4-11].

SHPT is characterised by decreased serum calcium (Ca) and increased serum phosphorus (P) concentrations, and reduced levels of active vitamin D calcitriol. These mentioned are closely interrelated. Declining kidney function reduces the production of calcitriol and the renal excretion of phosphate that leads to increased P levels; hyperphosphataemia reduces the production of calcitriol and increases parathyroid hormone (PTH) secretion [12]; and calcitriol deficiency decreases the inhibition of PTH secretion, reduces the duodenal absorption of calcium and bone calcium release; thus calcium concentrations decrease promoting PTH release.

A recently identified circulating polypeptide, fibroblast growth factor-23 (FGF23) may play an important role in the development of SHPT. FGF23 is secreted by osteoblasts and osteocytes in response to hyperphosphataemia as well as to dietary phosphorus load and promotes the urinary excretion of phosphate [13]. In CKD, as kidney function declines serum FGF23 progressively increases even before the development of a frank hyperphosphataemia [14]. FGF23 may suppress the production of calcitriol and consequently represent a further stimulus to PTH secretion in CKD [13].

An additional factor of SHPT progression is the skeletal resistance to PTH induced by various causes including down-regulation of PTH receptor gene expression and dysfunction of osteoblasts, and accumulation of circulating non-1-84 PTH fragments which antagonise the biological activity of PTH [15].

Acting through the G protein-coupled Ca-sensing receptor (CaR), Ca plays a central role in regulating PTH secretion [16,17]. The increase in ionised Ca concentration inhibits PTH synthesis/secretion, whereas low ionised Ca levels increase its production and release.

The only physiologically active form of Ca is ionised Ca. Total Ca exists in two forms: a protein-bound (predominantly albumin-bound) fraction that accounts for about 40%, and a non protein-bound fraction. About 90% of the non protein-bound form is ionised Ca, whose levels are affected by plasma albumin concentration and plasma pH. When the ionised Ca concentration is not available the albumin correct calcium should be estimated by a specific formula. Among the various simplified formulae proposed with this intent one of the widely used is: albumin-corrected Ca mg/dL = Ca mg/dL + 0.8 × (4 – serum albumin g/dL) [23]. In particular, the albumin-corrected Ca value is useful when albumin levels are low and, in such cases, Ca concentrations are low although ionised Ca levels may be normal.

Prolonged stimulation of the parathyroid glands, mainly as a result of low Ca and high P levels, and calcitriol deficiency, leads to cell proliferation and diffuse parathyroid hyperplasia. As CKD progresses to stage 5 (Glomerular filtration rate <15 ml/min or dialysis), the parathyroid hyperplasia may evolve even further to nodular hyperplasia [15]. In these large nodular parathyroid glands, CaR and vitamin D receptors (VDR) are under-expressed and so they cannot respond adequately to changes in extracellular Ca ion concentrations and the suppressive action of calcitriol [18,19]. The control of PTH synthesis/secretion by calcium and vitamin D is thus reduced, and SHPT may become refractory to physiological regulation and current medical therapy [20]. High PTH levels and spontaneous hypercalcaemia due to the release of large amounts of Ca and P from skeletal stores characterise refractory SHPT.

CURRENT CHALLENGES IN SHPT TREATMENT

Epidemiological studies have shown that increases in PTH, Ca and P levels, and in the calcium × phosphorus

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product (Ca × P), are independently associated with a higher risk of death [5-10]. Interestingly, it has been found that the risk is increased not only across serum P categories, but also across albumin-adjusted serum Ca categories, and so low Ca levels have been associated with a lower risk of mortality [5]. This finding is not in line with the results of a previous prospective study that followed 433 ESRD patients for an average of 41 months [21], in which chronic hypocalcaemia was strongly associated with mortality and cardiovascular events. These observations are in agreement with the results of two recent analysis that used multivariable time-varying models to evaluate the relationship between mortality and Ca levels in the more than 29,600 haemodialysis (HD) patients participating in the Dialysis Outcomes and Practice Patterns Study (DOPPS) [Albert, J.; Akiba, T.; Akizawa, T.; Goodkin, D.; Jacobson, S.; Jadoul, M.; Port, F.; Young, E. Presented to XLII Congress of the European Renal Association - European Dialysis and Transplantation Association (ERA-EDTA), Glasgow, United Kingdom, 2006 (MO004)] and 58,000 HD patients belonging to a U.S. national cohort [22] respectively. Further investigations are therefore necessary to improve the definition of the risk of mortality associated with low Ca levels.

In 2003, the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) established guidelines for managing SHPT in patients with CKD at different stages [23] and recommended treatment targets for PTH, Ca and P levels, as well as Ca × P. The suggested P levels for patients with stage 3 or 4 CKD are 0.87-1.49 mmol/l; the target range in patients with stage 5 CKD is higher but near the normal range (1.13-1.78 mmol/l), and is often difficult to reach in everyday clinical practice. The target range for albumin corrected-Ca is normal with stage 3 or 4 CKD, but 2.1-2.37 mmo/l for patients in stage 5. In these patients, the PTH target is high (16.5-33 pmol/L or 150-300 pg/ml) because observational data suggest that adequate bone turnover is more likely if PTH levels are moderately high [23].

The effectiveness of traditional SHPT therapy is limited, as is shown by the relatively small proportion of patients reaching the proposed targets. The DOPPS observational study of representative HD facilities and patients from 12 countries showed that relatively few HD patients met the K/DOQI guideline targets for PTH, serum P, albumin-corrected serum Ca or Ca × P: only 21.4% of patients in DOPPS I and 26.2% in DOPPS II achieved the PTH target, and approximately 40% achieved the target for P (40.8% in DOPPS I, and 44.4% in DOPPS II) and albumin-corrected Ca (40.5% in DOPPS I, and 42.5% in DOPPS II). The results were basically similar across countries, and it was rare for patients to fall within the recommended ranges for all four indicators of mineral metabolism: only 4.6-5.5% [24,25].

Furthermore, the percentage of dialysis patients undergoing parathyroidectomy because of refractory SHPT remains high and has not changed over recent years [26,27]. These observations suggest that conventional therapy is scarcely effective in managing mineral metabolism abnormalities or preventing the progression of parathyroid gland hyperplasia.

TRADITIONAL SHPT THERAPY

The traditional treatment of SHPT includes maintaining calcium balance by modulating dialysate calcium concentrations and dietary calcium supplementation, administering vitamin D and the management of hyperphosphataemia by means of dietary phosphate restriction, optimising dialysis phosphate removal, decreasing gastrointestinal phosphate absorption by means of phosphate-binders. Parathyroidectomy may be necessary in patients who are refractory to therapy.

The control of P levels is often difficult in CKD patients. Dietary phosphate restriction alone is not usually sufficient to maintain serum P control and may be associated with risk of malnutrition. Standard HD treatment is generally incapable of removing all the absorbed phosphorus from a patient with an optimal protein intake (1.2 g/kg/day), and the use of alternative dialysis techniques (daily or nocturnal dialysis) that remove much greater quantities of phosphorus is limited by economic and organisational problems. The use of oral phosphate binders is therefore necessary in majority of patients with stage 5 CKD.

Intestinal phosphate absorption accounts for approximately 70% of dietary intake, but may be lower in patients with ESRD. Phosphate binding should occur in the stomach or in the small bowel before absorption, which mainly takes place in the jejunum and ileum.

Aluminum-based phosphate binders, such as aluminum hydroxide, were widely used after the 1970s because of their effectiveness in binding P in the gastrointestinal tract [25] but unfortunately, a relatively high fraction of aluminum is absorbed. In patients with normal renal function, this is excreted by the kidneys, but it accumulates in the skeleton, nervous system, haematopoietic system and parathyroid tissue of dialysis patients, and may cause the development of a particular syndrome characterised by an association of bone disease (osteomalacia or adynamic bone disease), encephalopathy and microcytic hypochromic anemia. As aluminum salts are extremely potent phosphate binders, their clinical use is still recommended for short periods of time in CKD patients whose P levels are poorly controlled by other therapies.

Since the 1980s, increasing awareness of aluminum toxicity has led to the replacement of aluminum-containing agents by calcium-containing salts (calcium acetate and calcium carbonate), and calcium-based phosphate binders are now recommended as the initial therapy of hyperphosphataemia in patients with stage 3-4 CKD by the NKF-K/DOQI guidelines and the most widely used in clinical practice. They are less efficient in binding P than aluminum salts because, unlike ionised aluminum, ionised calcium binding to phosphorus depends on pH [28], which has opposite effects on the solubility of calcium carbonate (the calcium salt most widely used in Europe) and the calcium-phosphate reaction. Calcium carbonate dissolves best at an acid gastric pH, but calcium binding to phosphorus requires a pH of more than 5 [28]. The results of *in vitro* and *in vivo* studies suggest that calcium acetate is a more efficient phosphorus binder than calcium carbonate because a given dose of elemental cal-

cium administered as calcium acetate binds twice as much phosphorus as the same dose of calcium given as calcium carbonate [29-32]. Some studies also suggest that, when the same amounts of elemental calcium are given as either calcium acetate or calcium carbonate, calcium acetate binds more phosphate and so less calcium is adsorbed [29,30]. However, one drawback of calcium acetate is its taste, which may reduce patient compliance.

Because of their limited efficacy in controlling P levels, some patients may require very high doses of calcium-containing binders, which are also associated with Ca absorption. When the elemental Ca load exceeds 2 g/day, calcium-containing phosphate binder therapy may lead to positive calcium balance and hypercalcaemia, especially in patients on vitamin D therapy, which promotes the intestinal absorption of calcium and phosphorus. Concerns have been raised by recent observations of increased coronary and large vessel calcification related to the calcium intake of HD patients treated with calcium-containing binders [11,33,34]. For example, Goodman *et al*. found that coronary artery calcification, as determined by means of electron-beam computed tomography, was greater in young HD patients than control subjects, and that the daily intake of calcium was higher among the HD patients with coronary artery calcification [11]. Guerin *et al*. found that arterial calcification density, measured as a calcification score in different arterial districts, increased with the prescribed dose of calcium-based phosphate binders [33].

Unfortunately, there is no simple laboratory test to assess calcium balance and determine a safely administrable maintenance or cumulative dose of calcium salts [35].

Until recently, vitamin D calcitriol [$1,25(OH)_2D_3$] therapy has been the main pharmacological means of effectively lowering PTH levels. Vitamin D down-regulates PTH gene transcription and thus decreases PTH synthesis acting through the vitamin D receptor (VDR).

The other main action of vitamin D is to enhance intestinal calcium and phosphorus absorption, and bone calcium mobilisation [36]. This effect may lead to undesirably high serum Ca and P concentrations, which limit the doses of calcitriol that can be safely given and may even require treatment discontinuation. The use of calcitriol is therefore often precluded because of its calcaemic and phosphataemic effects.

Furthermore, the prolonged administration of high doses of vitamin D may lead to reduced bone turnover (adynamic bone disease) [37].

When marked parathyroid hyperplasia has developed, patients may become refractory to vitamin D therapy because of the resistance of parathyroid cells to vitamin D [38].

NON-ALUMINUM AND NON-CALCIUM PHOSPHATE BINDERS

Sevelamer Hydrochloride

Non-aluminum and non-calcium phosphate binders have been developed in an attempt to overcome the problems of aluminum toxicity or excessive calcium intake, and avoid the risk of vascular calcification, and their efficacy is usually compared with that of calcium-based phosphate binders.

Sevelamer hydrochloride is a widely used cross-linked (allylamine hydrochloride) exchange resin of this class which, unlike other phosphate binders, does not release absorbable metal cations. It is a cationic polymer that binds the phosphate anion and releases chloride, and is most effective at pH values of 5-7; it is also a bile acid sequestrant, and therefore has favourable effects on the lipid profile. When compared with calcium-containing phosphate binders in clinical studies with a follow-up of up to two years, sevelamer hydrochloride has been found to lead to similar control of P and Ca × P, with less frequent hypercalcaemic episodes and a reduced risk of over-suppressing PTH [36] or higher PTH levels [40]. In addition, it decreases total and LDL-cholesterol levels (as expected) and reduces the levels of C-reactive protein (CRP) [39]. Taken together, these effects can plausibly explain the slower advance of coronary and aortic calcification observed in dialysis patients [39,40], and it is interesting to note that this was observed despite the similar control of Ca and P levels, and the Ca × P product.

An analysis restricted to the patients randomised to receive sevelamer or calcium acetate in order to assess whether the specific preparation of calcium based-binders might affect the results confirmed the same findings [41]. A similar study evaluated the progression of the calcification score as measured by means of electron beam computed tomography in 129 patients new to dialysis [42]. The calcification score of the subjects with no coronary calcifications at baseline did not increase over 18 months, but increased in the patients with baseline calcifications in both treatment groups. However, the increases were more rapid and severe in the calcium-treated patients than in those treated with sevelamer.

The findings of studies of the efficacy of sevelamer in controlling P levels vary. One study with a follow-up of eight weeks found that the sevelamer-treated patients had lower Ca levels and less frequent hypercalcaemic episodes, but higher P and Ca × P values than those treated with calcium acetate [43]. However, it needs to be pointed out that some of the patients on calcium acetate received a calcium dose that was higher than that recommended by the guidelines. Furthermore, methodological concerns about the above studies include their lack of blinding, the variety of calcium salts used, and the fact that variables such as dialysate calcium or vitamin D were not controlled. Longer and better-controlled studies are therefore necessary to confirm these data.

A prospective, open-labelled, randomised trial with a 3-year follow-up investigated whether sevelamer hydrochloride treatment was associated with less mortality and morbidity than calcium-based binders in 2103 dialysis patients [Suki, W.; Zabaneh, R.; Cangiano, J.; Reed, J.; Fisher, D.; Swan, S.; Block, G.; Dillon, M.; Blair, A.; Burke, S. Presented to the 38th Annual Meeting of the American Society of Nephrology. Philadelphia, PA, USA, 2005 (TH-PO745)]. The analysis of the defined primary end-point in the entire study population showed no significant difference between the two treatments. A *post hoc* analysis found that, although mortality was similar in the patients treated for less than two

years, sevelamer was associated with a 34% reduction in the risk of mortality in those treated for more than two years (p=0.02), and a 22% reduction in the patients aged more than 65 years (p=0.03). Sevelamer therefore seemed to be associated with a benefit that increased over time and was greater in older patients . However these findings need to be confirmed as they derive from a *post hoc* analysis of data.

Unfortunately, sevelamer hydrochloride is often associated with high pill burdens that may reduce the patient compliance. Another drawback is that it is associated with an increased acid load [43] because, when it binds phosphate, some of the chloride released is absorbed together with a proton. This may worsen metabolic acidosis and limit its use in patients not yet on dialysis.

Lanthanum Carbonate

Lanthanum carbonate is a new phosphate binder recently approved in U.S. and Europe. Lanthanum is a rare element that is detectable in the human body as low levels are naturally present in food and water. This trivalent cation has a high affinity for phosphate across a wide pH range (pH 3-7), a characteristic that makes lanthanum as potent a phosphate binder as aluminum [Damment, SJP; Webster, I. Presented to 36th annual meeting of the American Society of Nephrology, San Diego, 2003 (FPO654)]. Clinical trials have shown that it is as effective as calcium carbonate in reducing P concentrations, and leads to a lower incidence of hypercalcemic events [44]. It is tolerable and efficacious in controlling P levels for up to three years. The most common adverse events are gastrointestinal [45].

Lanthanum is excreted largely unabsorbed in the feces, although small amounts are absorbed and then excreted mainly in bile (80%) or across the gut wall [46]. Concerns have been raised about its possible accumulation and toxicity because, in rat models, it is associated with increased tissue accumulation, mainly in the liver (i.e. its primary excretory organ). This accumulation seemed to be markedly enhanced by CKD [47,48].

Studies of different methods of administering lanthanum have led to contradictory deposition profiles in rodents, particularly in relation to brain penetration. A recent study of rats dosed *via* diet, gavage or i.v. showed brain deposition only in the rats given lanthanum in their food, which suggests that dietary administration may be accompanied by a risk of contamination that may lead to misleading tissue deposition profiles [Damment, SJP, Seker, R.; Cox, A.G. Presented to XLII Congress of the European Renal Association - European Dialysis and Transplantation Association (ERA-EDTA), Glasgow, United Kingdom, 2006 (SO017)].

Given the toxic effects of mineral and metal accumulation reported in the past, bone biopsies have been obtained from patients who had received lanthanum carbonate for more than four years, and showed no evidence of aluminum-like effects on bone [Malluche, H.H.; Faugere, M.C.; Wang, G.; Damment, S.J.P.; Webster, I. Presented to 37th annual meeting of the American Society of Nephrology, St. Luis, Mo, USA, 2004 (F-PO944)]. Conversely there are data indicating that lanthanum carbonate may improve renal bone disease: a study of patients undergoing bone biopsy before and one year after the start of treatment found a reduction in the frequency of the more extreme forms of renal osteodystrophy (hyperparathyroidism, adynamic bone disease and osteomalacia), whereas the patients treated with calcium carbonate during the same period experienced an increase in these forms [49]. Histological assessment of the livers of uremic and normal rats given lanthanum carbonate revealed typical findings of the spectrum of changes observed in the liver of normal laboratory rats and there was no increase in the incidence of such changes in the lanthanum-treated rats. The same study found that serum enzyme activities showed no changes indicative of liver toxicity [Damment, S.J.P.; Secker, R.; Downes, N. Presented to the ERA-EDTA Congress, Glasgow, United Kingdom, 2006 (SP389)]. Data from randomised, controlled clinical trials show no evidence of haepatotoxity after two years of lanthanum carbonate therapy [Finn WF. Presented to the 38th Annual Meeting of the American Society of Nephrology. Philadelphia, PA, USA, 2005 (SA-PO950)].

Clinicians should be aware that lanthanum may produce artifacts on standard x-rays radiographies of abdomen where it can be seen as diffuse opacifications throughout the colon [50].

MCI-196

One of the new non-aluminum and non-calcium phosphate binders under investigation is MCI-196, or colestilan (2-methylimidazole polymer with 1-chloro-2, 3-epoxypropane), a non-absorbed, anion exchange resin used as an antihypercholesterolemic drug in Japan. A short-term, double-blind, randomised, placebo-controlled trial involving 79 Japanese ESRD patients showed that MCI-196 significantly decreased P levels [51], and also decreased Ca × P, PTH and (as expected) LDL-cholesterol. Another study randomised 119 ESRD patients to receive fixed doses of MCI-196 or placebo for more than three weeks, and confirmed the efficacy of MCI-196 in decreasing P and Ca × P, and total and LDL-cholesterol [Locatelli, F.; Pontoriero, G.; Dimkovic, N.; Chambard, A.; Manning, A.; Nakajiama, S.; Sano, H. Presented to the XLII Congress of the European Renal Association - European Dialysis and Transplantation Association (ERA-EDTA), Istanbul, Turkey, 2005 (SO08)].

Nicotinamide

Nicotinamide, a circulating form of the nicotinic acid widely used as antihyperlipidemic agent, represents a potential alternative for treating iperphosphataemia *via* the inhibition of intestinal phosphate absorption. Nicotinamide has been found to be able decrease serum P levels by inhibiting the intestinal sodium dependent phosphate co-transporter. In an open label study nicotinamide administration in 65 haemodialysis patients led to a progressive decrease in serum phosphorus over a time period of 12 weeks [52]. In another 8-week prospective open label study [53] nicotinic acid therapy decreased P and Ca × P but increased Ca levels in 34 haemodialysis patients.

It remains to be clarified whether absorbed nicotinamide may block sodium-phosphate co-transport in other tissues of the body causing unwanted adverse effects. Thus further

studies are required to evaluate its long-term effects and safety profile.

VITAMIN D ANALOGUES

Recent years have seen the development of new vitamin D analogues, such as paricalcitol [19-nor-1,25$(OH)_2D_2$], doxercalciferol [1α-$(OH)D_2$], alfacalcidol [1α-$(OH)D_3$], falecalcitriol [1,25-$(OH)_2$26,27F6D_3], and maxacalcitol [22-oxa-1,25$(OH)_2D_3$], with the aim of retaining the same suppressive action of vitamin D on the parathyroid glands while reducing its calcaemic and phosphataemic effects. The mechanism of the latter action is attributed to their tissue selectivity: for example, paricalcitol does not seem to up-regulate the intestinal VDR and seems to be less active in mobilising calcium from bone [54-56]. Preclinical studies found that paricalcitol had less hypercalcaemic and hyperphosphataemic effects than calcitriol [50], but the available clinical evidence supporting these favourable effects is still weak. A double-blind, randomised study has shown that paricalcitol decreases PTH levels more rapidly than calcitriol [57]. The proportion of patients who became hypercalcaemic and/or experienced a high Ca × P at least once was similar in the two groups, although sustained episodes were less frequent in the paricalcitol-treated patients. There was no difference in the incidence of hyperphosphataemia between the two groups [57].

Three recent randomised, placebo-controlled studies have investigated the effects of oral paricalcitol in 220 patients with stage 3 and 4 CKD [58]. There was no between-group difference in the incidence of hypercalcaemia, hyperphosphataemia or a high Ca × P, nor in urinary calcium and phosphorus excretion. Similar results were found in a study comparing doxercalciferol and placebo [59]. However, in subjects treated with doxercalciferol, mean urinary calcium levels increased significantly after 24 weeks of therapy. No randomised comparative studies of different vitamin D sterols have been performed.

Some retrospective studies have evaluated mortality in patients treated with vitamin D sterols. One study of a historical cohort of incident hemodialysis patients in the United States suggested that patients who received any form of injectable vitamin D had a significant survival advantage over patients who did not [60], and the same question was evaluated in an analysis of the DOPPS data. While any vitamin D therapy was associated with a lower unadjusted risk of mortality, the magnitude and significance of the protective effect of vitamin D diminished after adjusting for patients demographics, comorbidities and laboratory values [Young, E.W.; Albert, J.M.; Akiba, T.; Greenwood, R.; Kimata, N.; Levin, N.W.; Piera, L.; Saran, R. Presented to the 38th Annual Meeting of the American Society of Nephrology. Philadelphia, PA, USA, 2005 (TH-PO735)]. The differences in the findings of these studies may perhaps be explained by differences in study populations and adjustments factors.

Other retrospective studies have found lower mortality and hospitalisation rates in paricalcitol- and doxercalciferol-treated patients than in calcitriol-treated patients [61,62] [Tentori, F. Hunt, W.C.; Stidley, C.A.; Rohrscheib, M.R.; Meyer, K.B.; Zager, P.G. Presented to the 38th Annual Meeting of the American Society of Nephrology. Philadelphia, PA, USA, 2005 (TH-PO737)./ Tentori, F. Hunt, W.C.; Rohrscheib, M.R.; Stidley, C.A.; Meyer, K.B.; Zager, P.G. Presented to the 38th Annual Meeting of the American Society of Nephrology. Philadelphia, PA, USA, 2005 (TH-PO738)]. Research over the last 20 years has revealed a range of biological actions of vitamin D that include the induction of cell proliferation, the inhibition of cell growth, immunomodulation, and control of other hormonal systems [36], but it is not clear what mechanisms may explain why vitamin D therapy can be associated with a lower mortality rate and what vitamin D analogue therapy can be associated with a further survival advantage. Prospective, randomised clinical trials are needed to confirm these findings.

CALCIMIMETICS

Calcimimetics are a new class of therapeutic agents that act directly on the CaRs that regulate PTH synthesis and secretion. When the CaRs in the parathyroid gland detect high serum Ca levels, they mediate the suppression of PTH levels; when Ca levels are low, they up-regulate PTH secretion.

Cinacalcet HCl [(alpha R)-(-)-alpha-methyl-N-[3-[3-[trifluoromethylphenyl]propyl]-1-napthalenemethanamine hydrochloride)], the first and currently the only calcimimetic agent approved for clinical use, acts as a positive allosteric modulator of CaRs. It enhances intracellular signal transduction and thus maximises the physiological effect of endogenous Ca, thus reducing PTH synthesis and secretion from the chief parathyroid gland cells, and decreasing serum Ca levels [63]. The clinical efficacy of cinacalcet HCl in treating SHPT has been demonstrated in three randomised, double-blind, placebo-controlled, phase III trials carried out in the United States, Europe, Canada and Australia [64-66] that involved 1,136 stage 5 CKD patients on dialysis with SHPT and uncontrolled PTH levels (>31.8 pmol/L [300 pg/mL]) despite the use of conventional SHPT therapy. The patients were randomised to receive cinacalcet HCl or placebo plus conventional therapy. In each trial, a significantly greater proportion of the patients in the cinacalcet HCl group achieved the predefined target PTH level of <26.5 pmol/L (250 pg/mL), and a pooled analysis of all three trials showed that 40% of the cinacalcet HCl-treated patients achieved the predefined PTH target against only 5% of the control patients. In comparison with baseline, PTH levels decreased by 50% in the patients treated with cinacalcet HCl but increased by 4.1% in the standard treatment control group. In comparison with conventional therapy alone, the addition of cinacalcet HCl not only reduced PTH, but also simultaneously decreased P and Ca levels, and the Ca × P. In relation to K/DOQI targets (although the studies began before the release of the K/DOQI guidelines), 33% of the cinacalcet HCl-treated subjects and 9% of the control subjects had a mean PTH value of 150-300 pg/ml (15.9-31.8 pmol/L), and 65% of the patients receiving cinacalcet HCl achieved a Ca × P of <55 mg^2/dL^2 (4.4 $mmol^2/L^2$) compared with 36% of the control subjects (P<0.001). Calcimimetics therefore improved the control of PTH while complying with the K/DOQI targets for serum calcium and phosphorus levels.

PTH decreased during calcimimetic treatment regardless of disease severity: the proportion of patients in whom PTH levels decreased by at least 30% was similar in the groups whose baseline PTH values were in the ranges 300-500 pg/ml, 500-800 pg/ml or >800 pg/ml. The proportion of patients achieving the fixed PTH target was higher in the cinacalcet HCl group regardless of the use of vitamin D and calcium-containing phosphate binders [Goodman, W.G.; Fadda, G.Z.; Filkelstein, F.O.; Mittman, N.; Lien, Y.H.; Leblanc, M.; Locatelli, F.; Frazao, J.M.; Olgaard, K.; Olson, K.A.; McCary, L.C.; Tuner, S.A.; Quarles, L.D. Presented to 36th annual meeting of the American Society of Nephrology, San Diego, 2003 (SA-PO741)], thus suggesting that cinacalcet HCl can be used alone or together with traditional therapy.

In an open-label study of hemodialysis patients who had controlled PTH levels but a high Ca × P, and were receiving moderate-high doses of vitamin D derivates, the administration of cinacalcet HCl decreased mean Ca, P and Ca × P levels. Cinacalcet HCl maintained control of PTH and increased the proportion of patients who achieved the Ca × P target (21% at baseline; 72% after 16 weeks of treatment). At the end of the study, 21% of the patients had stopped taking vitamin D, and the mean dose of vitamin D was decreased in the remainder. Conversely, the dose of calcium-based phosphate binders prescribed after starting cinacalcet HCl was increased to normalise Ca levels. This study suggests that cinacalcet HCl in combination with low-dose vitamin D derivates may improve the control of mineral metabolism in patients who have controlled PTH but high Ca × P levels when treated with vitamin D derivates alone [67].

In order to reduce the possible gastro-intestinal sides effects cinacalcet HCl should be administered during meals. Moreover clinicians should be cautious in administering calcimimetics at the beginning of the dialysis session, especially when a low concentration of calcium in the dialysis bath is used. In this case, the rapid decrease in Ca levels together with the other quick changes induced by the dialytic procedure (hypokalaemia,, dehydration, alkalosis, etc.) may favour cardiac arrhythmias [68].In some cases, calcimimetics need to be combined with calcium-based binders and/or vitamin D in order to counterbalance an excessive reduction in Ca levels or further suppress PTH levels. In such cases, it must be borne in mind that it is possible that a higher calcium balance could increase the risk of cardiovascular calcification, particularly if a higher calcium balance is coupled with an excessive reduction in PTH that may favour bone turnover suppression.

Novel cinacalcet HCl-based treatment algorithms are currently under study, one of which was specifically designed to obtain better control of PTH, Ca and P by introducing cinacalcet HCl and reducing vitamin D doses. This algorithm has been tested in 552 European dialysis patients with PTH levels of 300-800 pg/ml and a high Ca × P and, in comparison with conventional therapy, it enabled simultaneous improvements in PTH, Ca, P and Ca × P levels [Locatelli, F.; Macario, F.; Brink, H.S.; Dhaene, M.; Pai, P.; Holzer, H.; Zani, V.; Carter, D.; Molemans, B.; Reichel, H. Presented to XLII Congress of the European Renal Association - European Dialysis and Transplantation Association (ERA-EDTA), Glasgow, United Kingdom, 2006 (SP357)].

It is possible that the use of calcimimetics combined with vitamin D sterols could provide an additional benefit by enhancing the effect of vitamin D on the parathyroid glands. Parathyroid gland hyperplasia in CKD is associated with a decrease in VDR expression in parathyroid cells. An *in vitro* and *in vivo* study has shown that administering the R-568 calcimimetic alone or with calcitriol is associated with an increase in VDR mRNA expression [Almaden, Y.; Rodriguez, M.E.; Canalejo, A.; Canadillas, S.; Lopez, I.; Aguilera-Tejero, E.; Rodriguez, M. Presented to the XLII Congress of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Istanbul, Turkey, 2005 (SP017)], which suggests that calcimimetic treatment may increase VDR levels, thus improving the response to vitamin D and reducing the need for high vitamin D sterol doses.

The efficacy of cinacalcet HCl does not seem to decrease with long-term treatment, as its effects were maintained in patients treated for up to three or four years [Moe SM, Goodman WG, Cunningham J, Drueke, T.; Adler, S.; Rosansky, S.J.; Albizem, M.B.; Olson, K.A.; Addison, J.; Sprague, S.M. Presented to the 38th Annual Meeting of the American Society of Nephrology. Philadelphia, PA, USA, 2005 (F-PO755)] [69], with no signs of tolerance or emerging resistance. The most frequent adverse events were nausea and vomiting, which may lead to poor compliance or treatment discontinuation. Their pathophysiology is not clear, but it has been hypothesised that they may be due to an interaction between cinacalcet HCl and CaRs in the gastrointestinal tract. Marked hypocalcaemia (Ca concentrations of <7.5 mg/dl or 1.88 mmol/L) occurred on at least two consecutive occasions in 5% of the cinacalcet HCl-treated subjects, but was rarely symptomatic and led to the withdrawal of only one patient. Post-marketing surveillance is necessary in order to exclude other possible unknown effects caused by the interaction of calcimimetics with the CaRs in other organs.

The data from short-term, randomised, double-blind, placebo-controlled, phase II studies of patients with stage 3-4 CKD show that the reductions in PTH are comparable with those observed in patients on dialysis: patients with stage 3-4 CKD more frequently experienced hypocalcaemic episodes and, unlike dialysis patients, their mean P concentrations increased. It can be assumed that the reduction in PTH in patients with residual renal function was associated with an increase in the tubular reabsorption of phosphorus that leads to increased P levels. Phase III trials are currently ongoing to evaluate the use of cinacalcet HCl in stage 3-4 CKD. Further studies are needed to confirm these findings, evaluate safety profiles, and define the metabolic characteristics of the patients who could benefit from calcimimetics while avoiding the risk of hypocalcaemia and hyperphosphataemia.

The use of cinacalcet HCl in patients with stage 3-4 CKD is of interest because, if the data concerning the possible beneficial effects of calcimimetics on parathyroid hyperplasia [70,71], bone disease [Malluche HH, Monier-Faugere MC, Wang G, Frazao, J.M.; Charytan, C.; Coburn, J.W.; Coyne, D.W.; Kaplan, M.R.; baker, N.; McCary, L.C.; Turner, S.A.; Goodman, W.G. Presented to XLI Congress of the European Renal Association - European Dialysis and

Transplantation Association (ERA-EDTA), Lisbon (Portugal) 2004 (MO16)] [72,73] and vascular calcifications [74,75] are confirmed, they will reduce the risk of adverse outcomes from the time of early-stage CKD.

A *post hoc* analysis [76] of clinical outcomes in 1184 patients treated with cinacalcet HCl for 6-12 months revealed significant reductions in the risk of parathyroidectomy, fracture and cardiovascular hospitalisation, although there was no difference in all-cause hospitalisation or the risk of mortality. These results are consistent with the above findings supporting the effects of cinacalcet HCl in reducing parathyroid cell proliferation and hyperplasia, improving bone turnover parameters and mitigating vascular calcifications. However, the analysis has a number of methodological limitations: the studies were not designed to evaluate difference in event rates, and the follow-up periods were probably too short to assess such clinical outcomes. Further long-term studies of large populations are needed to determine clinical outcomes and assess whether calcimimetic therapy changes SHPT-related morbidity and mortality.

Cinacalcet HCl therapy has also been evaluated in renal transplant patients with persistent hyperparathyroidism. Despite their apparently normalised renal function, some kidney transplant patients show normal/high PTH concentrations, increased serum Ca levels, enhanced phosphate excretion and decreased bone mass [77]. In a small number of renal transplant recipients [78,79], cinacalcet HCl significantly decreased serum Ca and PTH levels, but there was considerable inter- and intra-individual variability in response. Mean P levels increased or remained unchanged, and Ca × P remained unchanged. Prospective controlled studies are necessary to determine the possible effects of the drug on long-term renal and general outcomes in such patients.

CONCLUSIONS

Adequately controlling mineral metabolism abnormalities is difficult in a considerable number of patients with SHPT. Because of the complex relationships between PTH, Ca and P, a therapy that is effective in controlling one of these parameters often has negative effects on the others.

New therapeutic options, such as non calcium- and non aluminium-containing phosphate binders, the new vitamin D analogues, and calcimimetics are now available.

In particular, calcimimetics offer a distinctly new choice because, unlike traditional therapies, they not only decrease PTH levels, but also reduce Ca and P, and Ca × P levels, which are associated with increased morbidity and mortality.

The combined use of these new agents represents a basis for innovation in the treatment of SHPT that may profoundly change the management of deranged Ca and P homeostasis in patients with CKD.

Further prospective studies are required to evaluate whether they will decrease the risk of vascular calcification, favourably affect bone, slow down progression to parathyroid hyperplasia, and have a positive impact on morbidity and mortality.

ABBREVIATIONS

ESRD	=	End-stage renal disease
SHPT	=	Secondary hyperparathyroidism
CKD	=	Chronic kidney disease
CVD	=	Cardiovascular disease
Ca	=	Serum calcium
P	=	Serum phosphorus
PTH	=	Parathyroid hormone
FGF23	=	Fibroblast growth factor-23
CaR	=	Ca-sensing receptor
VDR	=	Vitamin D receptors
Ca × P	=	Calcium × phosphorus product
NKF-K/DOQI	=	National kidney foundation-kidney disease outcomes quality initiative
DOPPS	=	Dialysis outcomes and practice patterns study
HD	=	Haemodialysis
CRP	=	C-reactive protein
ERA-EDTA	=	European renal association - european dialysis and transplantation association

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