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Calcimimetics in chronic kidney disease: evidence, opportunities and challenges

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Secondary hyperparathyroidism (SHPT) remains a highly prevalent and important complication in patients with chronic kidney disease (CKD). Indeed, SHPT may compromise bone health and contribute to the increased cardiovascular risks of these patients. Calcimimetic agents may help to control SHPT and to achieve the stringent mineral metabolism targets in patients with CKD stage 5D. Whether this will translate in improved patient-level outcomes remains to be demonstrated in adequately powered prospective intervention studies. These studies are currently ongoing. Additional investigations are required to define how calcimimetics fit best in the expanding armamentarium to treat SHPT. The role of vitamin D (analogs) and parathyroidectomy needs to be reevaluated in the calcimimetic era. Persistent hyperparathyroidism after successful renal transplantation may also become an important indication for therapy with calcimimetics. In patients with this complication, calcimimetics may help to improve bone health both by suppressing bone turnover and demineralization and may retard or prevent nephrocalcinosis of the graft. The evidence for using calcimimetics in CKD patients not yet on dialysis, conversely, is less straightforward. In these patients, therapy for SHPT should rather be focused on the primary trigger, i.e. the high phosphate load relative to the functional nephron mass.

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Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney disease (CKD). SHPT is generally associated with abnormally high rates of bone resorption and is often accompanied by pain and fractures.[1,2] Extraskeletal manifestations of the disease include vascular calcification, hypertension, anemia, pruritus, and sexual dysfunction.[3–5] Epidemiological data demonstrate significant relations among elevated parathyroid hormone (PTH), calcium (Ca), and phosphorus (P) and mortality and morbidity.[6–10] Block *et al.*[8] showed in a large hemodialysis cohort that PTH concentrations >600 pg/ml are associated with an increase in the risk for death compared with PTH concentrations <600 pg/ml; higher PTH was also associated with higher risks for cardiovascular disease and fracture. In the same analysis, hyperphosphatemia and hypercalcemia were associated with mortality as well.[8] It should be noted that the PTH–mortality relation was weaker than the phosphorus–mortality or calcium–mortality relations.

Guidelines from the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) recognize the intimate relations between bone mineral disease, vascular calcification, and mortality, and propose stringent targets for serum PTH, calcium, and phosphorus.[11] Unfortunately, the exact interplay between these biomarkers is unknown and the relationship between combinations of biomarkers and long-term clinical outcomes remains poorly characterized.[12]

Treatment for SHPT should maintain a PTH concentration compatible with normal turnover of bone, prevent the development of parathyroid hyperplasia, maintain physiological concentrations of phosphorus and calcium, and be free of any tendency to accelerate the development and progression of vascular and soft tissue calcification.

Besides dietary phosphate restrictions, phosphate-binding agents and vitamin D sterols have been the cornerstone for managing SHPT for a long time. With this treatment regimen, however, K/DOQI targets are difficult to achieve on a constant basis. One large study of hemodialysis patients from seven countries found that only 21% of patients satisfied the guidelines' criteria for PTH concentration and 5% met combined targets for calcium, phosphorus, PTH, and Ca $\times$ P.[9]

In recent years, novel therapeutic agents such as calcium-free phosphate binders and vitamin D analogs have become

available that will facilitate control of hyperphosphatemia and hyperparathyroidism while the calcium load is minimized. Calcimimetics are the latest acquisition in the expanding therapeutic armamentarium of SHPT.[13] Calcimimetics allosterically modulate the Ca-sensing receptor (CaSR), a G-protein-coupled receptor that is present on the parathyroid gland, increasing its sensitivity to extracellular Ca and thereby lowering PTH secretion from the parathyroid gland.[14,15] Calcimimetics also mediate reductions in serum PTH levels by decreasing PTH gene expression.[16] Finally, recent data indicate that calcimimetics reduce PTH synthesis also indirectly through increasing the vitamin D receptor expression in the parathyroid glands.[17]

Cinacalcet HCl is at present the only commercially available calcimimetic agent. It was approved by the United States Food and Drug Administration in 2004 and by the European Medicines Agency in 2005 for the treatment of SHPT of dialysis patients and parathyroid carcinoma. Manufactured by Amgen, cinacalcet HCl is marketed as Sensipar (Amgen Inc., Thousand Oaks, CA, USA) in the US and as Mimpara (Amgen Inc.) in Europe.

This review aims to summarize the available clinical experience with calcimimetic therapy and to touch on future opportunities and threats.

SHPT IN CKD STAGE 5D

Biochemical outcomes

In early studies, single doses of cinacalcet given to hemodialysis patients simultaneously reduced PTH and serum calcium.[18] It is important to note that PTH levels decreased already during the first hour after dosing to reach a nadir (72% reduction in the 100 mg group) at approximately 4 h post-dose. PTH levels did not return to baseline in the subsequent 28 h. Reductions in serum calcium followed a similar pattern to those of PTH.[18] In a small longitudinal study in hemodialysis patients with uncontrolled SHPT, PTH increased by 3% in the placebo group and fell by 33% in the cinacalcet group; Ca $\times$ P rose by more than 11% in the placebo-treated patients but fell by almost 8% in the treatment group.[19] A similar picture has emerged from subsequent larger studies with longer follow-up. In 741 patients treated for 26 weeks, there was a 30% reduction in PTH from baseline values in two-thirds of cinacalcet-treated patients, compared with in 11% of those receiving standard care. Ca $\times$ P was unchanged with standard care, but fell 15% in the treatment arm. The likelihood of achieving a PTH level of $\leqslant$250 pg/ml was independent of gender, race, age, duration of dialysis, baseline biochemical variables, the presence of diabetes, or the use of vitamin D sterols.[20] The differential response among those who received cinacalcet may point to genetic influences. These remain to be explored.

The mechanism underlying the declines of calcium and phosphorus remains incompletely understood. In the absence of substantial residual renal function, alterations in the exchange of these minerals between extracellular fluid and the miscible pool in bone are most likely responsible. Studies in parathyroidectomized and/or thyroidectomized rats clearly indicate that the calcimimetic NPS R-568 induces hypocalcemia not only by inhibiting PTH secretion but also by stimulating calcitonin secretion.[15] This dual action may explain the different kinetics of serum calcium levels after parathyroidectomy and cinacalcet administration. Finally, functioning CaSRs within the skeleton could potentially play a role as well.

With respect to the changes in serum calcium and phosphorus, calcimimetic agents differ from calcium-containing phosphate binders (which raise calcium and lower phosphorus and PTH) and vitamin D compounds (which raise calcium and phosphorus and lower PTH). Obviously, cinacalcet facilitates the achievement of the K/DOQI-recommended targets for PTH, calcium, phosphorus, and Ca $\times$ P in CKD stage 5D.[21,22] Recent data show that cinacalcet can effectively maintain reductions in PTH for up to 3 years, without increasing concentrations of serum calcium and phosphorus and without any attenuation.[23] Recent clinical research mainly focuses on strategies for optimization of the management of SHPT with cinacalcet. Chertow *et al.*[24] demonstrated that control of PTH levels was maintained by substituting active vitamin D by cinacalcet. Moreover, the introduction of cinacalcet significantly improved control of Ca $\times$ P, resulting in an increase in the proportion of patients who simultaneously achieved the PTH and Ca $\times$ P target levels (17–47% during the course of the study). In Europe, two post-registrational studies including a total of more than 1200 dialysis patients have been conducted to investigate strategies for optimization of the management of SHPT with cinacalcet. In the recently completed OPTIMA phase IIIB trial, a new cinacalcet-based treatment algorithm that allowed for reductions in vitamin D dose was demonstrated to increase the achievement of K/DOQI treatment targets in dialysis patients in whom conventional therapy was no longer effective.[25] In the SENSOR phase IIIB trial, patients were randomized to cinacalcet intake during dialysis or with the first major meal after dialysis. The same cinacalcet-based treatment algorithm as in the OPTIMA trial is applied to optimize cinacalcet, vitamin D, and phosphate binder use.[26] Results of the latter trial are expected in the near future.

Clinical outcomes

The aforementioned trials provide convincing evidence that the introduction of calcimimetic drugs represents a real opportunity to improve the paradigm of managing the biochemical variables associated with SHPT. While the effective treatment of hypercalcemia and SHPT is of clinical interest, it remains to be demonstrated whether this will translate into improvement in hard end points such as bone health or cardiovascular morbidity and mortality.

Calcimimetics and bone health. Epidemiological data have clearly demonstrated an increased fracture risk in hemodialysis patients.[1,27] Two main mechanisms may account for the increased fracture risk: either a lower resistance of bone after relative minor traumas or an increased propensity to fall.[28]

Renal osteodystrophy, being a prevalent complication of CKD, accounts to a large extent for a lower resistance of bone in hemodialysis patients. Renal osteodystrophy comprises a number of histologically distinct bone abnormalities that are generally classified as either high-turnover (osteitis fibrosa, mild, and mixed) or low-turnover (osteomalacia and adynamic) lesion. So far, the utility of biochemical markers of bone turnover to predict the type of skeletal lesions is disappointing. A bone biopsy with dynamic tetracycline labeling remains the 'gold standard' to evaluate bone health in humans.

In the presence of elevated PTH concentrations, hyperparathyroid bone disease (osteitis fibrosa) most typically develops. Treatment with the calcimimetic agent NPS R-568 has been shown in uremic rats to reduce serum PTH levels, to eliminate osteitis fibrosa, and to return cortical bone strength toward normal.[29]

Over the past decade, the prevalence of different forms of renal osteodystrophy has shifted. Whereas hyperparathyroid bone disease was the most common abnormality observed in the 1980s, the prevalence of adynamic bone disease has risen over the past decade.[30] The reported prevalence of low bone turnover varies from 5 to 61%.[31–33] Diabetes, the administration of pharmacologic doses of vitamin D sterol, and large doses of calcium-containing phosphate binders have been implicated in the pathogenesis of adynamic bone disease.[34–36] The clinical relevance of adynamic bone remains controversial. Nevertheless, several lines of evidence indicate a link with increased fracture risk and with accelerated cardiovascular calcification.[37–39] Animal studies indicate that cinacalcet might play a role in the treatment of this entity as well. In rats exhibiting a low-turnover bone lesion resembling osteomalacia despite the presence of mild SHPT, NPS R-568 had an 'anabolic-like' action when administered by daily gavage. It is speculated that intermittent decreases in the serum level of PTH are sufficient to reverse the phenomenon known as 'homologous receptor desensitization'; that is, prolonged exposure to PTH in itself may cause the desensitization of the PTH receptors.[40] Miller and Fox[41] showed that daily transient decreases in PTH levels induced by NPS R-568 slow the rate of bone loss but do not increase bone mass in ovariectomized rats with normal PTH. Elevated serum levels of PTH before treatment, therefore seem critical for stimulating bone formation. In some respects, the findings by Ishii *et al.*[40] parallel those obtained when the serum levels of PTH are increased intermittently.[42,43]

Clinical data on the impact of calcimimetics on bone mineral density and on bone histomorphometry are limited. A small placebo-controlled 1-year repeat bone biopsy study in 32 hemodialysis patients with SHPT showed favorable trends in bone turnover and fibrosis in the cinacalcet-treated subjects but failed to show significance most probably due to lack of power.[44] Moreover, preliminary clinical data suggest a beneficial effect on bone mineral density in patients with SHPT treated with cinacalcet.[45]

The ongoing Bone Histomorphometry Assessment For Dialysis Patients with Secondary Hyperparathyroidism of End Stage Renal Disease (BONAFIDE study) will give a definite answer to the question whether cinacalcet has a beneficial effect on bone health in patients with CKD 5D and established hyperparathyroid bone disease. The primary end point of this multicenter, uncontrolled, descriptive bone biopsy study is the change from baseline in bone formation rate. Eighty-five subjects are scheduled for inclusion. Results of this study are to be expected by 2009.

Even if the outcome of the BONAFIDE study is favorable for cinacalcet treatment, it remains to be seen whether this treatment will result in a decreased fracture risk. The recent *post hoc* analysis of all randomized controlled trials of cinacalcet versus placebo (in both arms with standard treatment of SHPT) showed a significantly lower actuarial risk of fracture in the cinacalcet group (relative risk 0.46, 95% CI 0.22–0.95).[46] This *post hoc* analysis requires confirmation by randomized trials, including fractures in the pre-defined major end points.

Modification of calcification and other cardiovascular risk factors by calcimimetics

Cardiovascular calcification. Both in uremic and in non-uremic individuals, the extent and the progression of cardiovascular calcification increase the risk for cardiovascular morbidity and mortality.[47–50] Although the causes of vascular calcification in CKD remain to be elucidated, abnormalities in mineral metabolism are increasingly recognized to play an important role.[51–54] In this regard, the close relationship between bone disease and vascular calcification should be acknowledged.[37,55,56] Oversuppression of PTH and calcium loading, for example, due to the overzealous use of calcium-containing phosphate binders or vitamin D analogs, have been associated with accelerated cardiovascular calcification in several studies.[54,57] Calcimimetics, conversely, have been shown to reduce elevated PTH levels without inducing vascular calcification and to prevent calcitriol-induced vascular calcifications.[58,59] The mechanisms of action that are responsible for the anticalcification effect of the calcimimetics are poorly understood. Both an indirect effect through control of PTH levels without increasing the Ca $\times$ P product and a direct effect at the cellular level on the arterial vessel wall are plausible.

In a recent uncontrolled clinical trial in hemodialysis patients, Messa *et al.*[60] observed increased osteoprotegerin and decreased fetuin-A levels following the initiation of cinacalcet treatment. This is an important observation as both fetuin-A and osteoprotegerin are acknowledged to be key factors in the pathogenesis of vascular calcification in CKD.[61] The changes reported by Messa *et al.* confer an increased risk of vascular calcification.[62,63] Alternatively these changes reflect a reduced demand for feedback defense mechanisms, which may be secondary to improved mineral metabolism. This hypothesis was proposed by Mehrotra *et al.*[64] to explain observations made in non-dialysed diabetic nephropathy patients. Undoubtedly, additional controlled (longitudinal) trials are needed for clarification.

Hypertension and dyslipidemia. Hypertension and dyslipidemia are prevalent in renal failure and contribute to the increased cardiovascular risk. In experimental renal failure, abrogation of SHPT by administration of a calcimimetic mitigates the development of hypertension, dyslipidemia, and cardiac remodeling.[65,66] Similar changes have been reported after parathyroidectomy both in animals and patients.[65,67] The underlying pathophysiological mechanisms are only poorly understood.

Calcimimetics may result in reduced peripheral vascular resistance either directly via activation of the CaSR or indirectly by the decrease of ionized calcium. Alternatively, the blood pressure-lowering effect may be mediated via suppression of the PTH serum levels.[66,68,69] Clinical studies with calcimimetic agents available so far have not been designed to evaluate effects on blood pressure, and none of the published trials has reported any impact on blood pressure.[18,20,70]

Decreased activity of both lipoprotein[71] and hepatic[72] lipase has been implicated in the pathogenesis of dyslipidemia related to hyperparathyroidism. These changes in lipase metabolism were corrected by parathyroidectomy (PTX)[71,72] and calcium channel blockade.[72] The latter supports a causative role of cytosolic calcium concentrations. The observation that administration of insulin corrected the disturbed metabolism of triglyceride-rich particles indicates that the effect of PTH at least partially involves inhibition of insulin secretion or interference with its peripheral action.[73]

Cardiovascular morbidity and mortality

It is well recognized that cardiovascular morbidity and mortality in patients with CKD is a problem of epidemic proportion. The abovementioned data suggest that calcimimetics may beneficially modify several risk factors and thus improve cardiovascular outcomes in CKD stage 5D. Data from a *post hoc* analysis showing a significant reduction in hospitalization for cardiovascular disease and a trend toward improved mortality among patients who were randomly assigned to cinacalcet versus placebo corroborate this hypothesis.[46] The ongoing Evaluation of Cinacalcet Therapy to Lower cardiovascular Events (EVOLVE) trial is designed to prospectively test the hypothesis that cinacalcet improves cardiovascular outcomes in hemodialysis patients. Approximately 3800 CKD stage 5D patients from 22 countries will be randomly assigned to cinacalcet or placebo. Flexible use of traditional therapies is permitted. The study is event driven, with an anticipated duration of approximately 4 years.[74] Whether the EVOLVE trial will come to the high expectations of the nephrology community remains to be seen. Prudence is justified. Indeed, prior large randomized intervention trials in CKD stage 5D, including those on lipid reduction,[75] normalization of hematocrit,[76] and increased dialysis dosage,[77] and the recent Dialysis Clinical Outcomes Revisited (DCOR) trial[78] failed to show a benefit despite the wealth of available evidence in favor of the intervention at the time of conception of these studies.

SHPT IN PATIENTS WITH CKD NOT YET ON DIALYSIS

NKF-K/DOQI guidelines recognize that early treatment of SHPT in patients with CKD not receiving dialysis is likely to improve long-term outcomes and reduce disease severity.[11]

The complexity of hyperparathyroidism physiopathology is well recognized. Recent clinical studies demonstrate a high fractional phosphate excretion along with elevated PTH and fibroblast growth factor 23 (FGF-23) levels in patients with early CKD despite the presence of normophosphatemia.[79–81] These findings indicate that in progressive renal failure compensatory increases in renal phosphate excretion are recruited before the development of hyperphosphatemia. This increase in renal phosphate excretion is driven, at least partly by PTH and FGF-23, a recently discovered important phosphaturic hormone.[80,82–84] Renal 1-α-hydroxylase activity is impaired by FGF-23 leading to decreased calcitriol synthesis and reduced calcitriol levels.[85] Inadequate calcitriol synthesis provides a physiological explanation for impairments in intestinal calcium absorption and for the hypocalciuria and modest hypocalcemia that characterize untreated patients with moderate renal insufficiency.[86–88] Inadequate calcium absorption prompts adaptive responses by the parathyroid glands to maintain blood ionized calcium concentrations.[89] Overall, the well-known 25-year-old tradeoff theory, according to which hyperparathyroidism is the price to pay for preventing hyperphosphatemia and hypocalcemia, seems to remain valid.[90]

In a recent study in patients with CKD not yet on dialysis, the addition of cinacalcet significantly decreased PTH levels compared to controls.[91] The observed reductions in PTH levels were similar to those observed in dialysis patients treated with cinacalcet. In addition, the 24-h phosphaturia decreased, whereas serum phosphorus concentrations increased (4.0 to 5.0 mg per 100 ml, $P<0.05$) in the cinacalcet-treated patients. This observation was not unexpected given the phosphaturic effects of PTH, but contrasts to what is seen in hemodialysis patients (Table 1). The long-term impact of these biochemical changes on relevant outcome variables such as progression of renal disease and cardiovascular morbidity and mortality remains to be investigated.

In several animal studies, suppression of PTH levels has been shown to attenuate the progression of renal failure.[65,93] This beneficial effect on progression may be mediated by hemodynamic changes induced by PTH.[94] Alternatively, suppression of PTH may prevent or retard nephrocalcinosis. The 'calcification–precipitation' hypothesis proposes that

Table 1 | Effects of cinacalcet on parameters of mineral metabolism in CKD patients

	CKD stage 5D	CKD 3–5 (T)	Reference
Serum calcium	↓	↓	20,91,92
Serum phosphorus	↓	↑	20,91,92
PTH	↓	↓	20,91,92
Bone-specific AP	↓	↑	44,92
FE_{PO_4}	—	↓	92

AP, alkaline phosphatase; FE, urinary fractional excretion; PTH, parathyroid hormone.

phosphate absorbed in excess of residual nephron excretory capacity produces precipitation and deposition of calcium phosphate microcrystals in the tubular lumen, peritubular space, capillaries, and interstitium and is thus responsible for progressive functional deterioration in CKD.[95,96] Suppression of PTH by calcimimetics may cause the tubular phosphate concentrations to drop below a critical threshold and thereby may prevent precipitation to occur. At least in furosemide-treated young rats, NPS R-467 has been shown to prevent the development of hyperparathyroidism and to attenuate nephrocalcinosis.[97] Additional animal and/or clinical renal biopsy studies are required to clarify whether, and if so to what extent calcimimetics prevent nephrocalcinosis and progression of renal disease.

As in patients with CKD stage 5D, high levels of serum phosphate have been associated with increased cardiovascular morbidity and mortality in predialysis patients.[98–100] For example, in the recent PREPARE study, a prospective observational cohort study conducted in The Netherlands, a 62% increase in mortality for each milligram per 100 milliliter increase in plasma phosphate concentration was observed independent of age, gender, primary kidney disease, baseline estimated glomerular filtration rate, and comorbidity at baseline.[100] It should be acknowledged that the design of these studies does not allow conclusions on causality. Nevertheless, recent findings in Klotho-knockout mice corroborate the association between hyperphosphatemia and cardiovascular morbidity and mortality. Klotho converts canonical FGF receptor into a specific receptor for FGF-23. When Klotho-knockout mice are fed a phosphate-containing diet, these mice develop severe hyperphosphatemia[101] and cardiovascular calcification similar to those seen in dialysis patients.[102] When phosphate is restricted from the diet, Klotho-knockout mice develop normally, which confirms an important role of phosphate in increased cardiovascular mortality in (early) CKD patients.[103]

In summary, the rationale for using calcimimetics for the treatment of SHPT in CKD patients not yet on dialysis is obviously less clear than it is in dialysis patients.

PERSISTENT HYPERPARATHYROIDISM AFTER SUCCESSFUL RENAL TRANSPLANTATION

Successful kidney transplantation corrects the endocrine and metabolic imbalances and the main abnormalities responsible for SHPT in the first months.[104–106] PTH levels show a biphasic decline after successful renal transplantation: a rapid drop (by approximately 50%) during the first 3–6 months, attributed to a reduction of the parathyroid functional mass,[105] followed by a more gradual decline.[107] The long lifespan of parathyroid cells (approximately 20 years) with a cell renewal rate of approximately 5% per year contributes to the very slow involution of the gland after renal transplantation.[108] As a result, elevated intact PTH levels are observed in more than 25% of patients 1 year after successful renal transplantation.[107,109] Substantial evidence indicates that persistent hyperparathyroidism is implicated in the pathogenesis of post-transplant hypercalcemia, hypophosphatemia, and most probably also bone disease.[110–113] Furthermore, recent data indicate that persistent hyperparathyroidism may be involved in the pathogenesis of nephrocalcinosis of the renal transplant, which, in turn, is independently associated with chronic allograft nephropathy.[114]

Data from several small series indicate that cinacalcet is an effective agent for the treatment of hypercalcemia secondary to persistent hyperparathyroidism in renal transplant recipients.[92,115–120] The mechanism of calcium reduction is most probably a decrease in the PTH effect on the bone. A decreased tubular reabsorption as a result of lower PTH levels and/or a direct effect of the calcimimetic on the CaSR in the kidney is unlikely to play a relevant role as enhanced calciuria is not universally observed in patients or animals following treatment with calcimimetics.[92,121] Cessation of the calcimimetic therapy results in the return of serum calcium and PTH levels to pretreatment values in most transplant patients.[115,117]

Overall the drug is well tolerated. Some groups, however, observed a limited but significant drop of the glomerular filtration rate following the initiation of cinacalcet. Especially the cyclosporine-treated patients seem to be at risk for renal function deterioration.[122] Renal function restores after cessation of the calcimimetic.[115] This suggests a hemodynamic rather than a structural mechanism. Renal function deteriorations have also been described in the first weeks following parathyroidectomy.[67,123] It is important to note that in the long-term a parathyroidectomy had no detrimental effect on graft outcome.[124]

Although cinacalcet interacts with CYP1A2, 2D6, 3A4 when metabolized and inhibits CYP2D6, clinically relevant interactions with the standard immunosuppressive drugs cyclosporine, tacrolimus, sirolimus, and everolimus have not been reported.[92,122,125]

Appropriately designed and powered clinical trials, examining the impact of calcimimetics on hard end points or relevant surrogate markers, such as bone mineral density, cardiovascular calcification or nephrocalcinosis, are required to further define the role of this novel class of drug in the treatment of persistent hyperparathyroidism after successful renal transplantation.

CALCIMIMETICS AND PARATHYROID GLAND SIZE

It is well known that parathyroid enlargement due to parathyroid cell proliferation (hyperplasia) is a major determinant of PTH hypersecretion.[89,108] An important question that remains to be answered is whether calcimimetics affect gland size and if so, at what rate?[126] Wada *et al.*[127] performed short- and long-term studies in rats with chronic renal failure and showed that the oral administration of the calcimimetic NPS R-568 prevented excessive parathyroid cell proliferation and gland hyperplasia, when given at the time of renal mass reduction. Recent data confirm and extend these observations.[128–130] Colloton *et al.*[128] demonstrated that that orally administered cinacalcet arrested

parathyroid cell proliferation in rats with established chronic renal failure and even induced the regression of parathyroid hyperplasia. The drug was given to animals for 4 weeks, starting 6 weeks after the surgical induction of uremia. This study was the first to demonstrate regression of parathyroid gland volume in a uremic rat model within a relatively short time period. Very recently, Mizobuchi *et al.*[130] demonstrated that high concentrations of the calcimimetic compound R-568 accelerate the apoptosis of parathyroid cells from uremic rats *in vitro*.

Clinical studies are urgently needed to confirm these animal studies. Such studies are hampered by the lack of an accurate, reliable method for measuring the parathyroid gland size.[89] A few studies have established a relationship between functional mass parameters derived from the iCa-PTH suppression/stimulation test and the parathyroid gland size evaluated by ultrasonography[131] or measured at the time of parathyroidectomy in transplant patients.[132] The iCa-PTH suppression/stimulation test is currently the best tool available to evaluate the parathyroid functional mass.[105]

TOXICITY/SIDE EFFECTS

Several studies have shown that long-term treatment with cinacalcet is generally well tolerated. The two most common adverse events are hypocalcemia and gastrointestinal side effects. Hypocalcemia is considered to result from decreased calcium mobilization from the bone under lowered PTH conditions. This hypocalcemia was found to be generally asymptomatic and could be readily managed by modest adjustments to the dialysate calcium content or to the doses of calcium-containing phosphate binders, vitamin D sterols, or cinacalcet.[20] These measures warrant caution as they contribute to a positive calcium balance with potentially harmful consequences in the long term.

Over the last two decades, the focus of attention in the treatment of SHPT has shifted from the control of PTH levels toward the prevention of cardiovascular calcification. As a result of this paradigm shift, calcium-containing phosphate binders, calcitriol supplements, and high calcium dialysate baths (1.5–1.75 mmol/l) are increasingly replaced by non-calcium-containing phosphate binders, novel vitamin D analogs (presumed to be less calcemic), and low calcium dialysate baths (1.25 mmol/l or less), respectively. These changes in therapy may cause the serum calcium levels to drop toward the lower end of the target range. Caution is warranted when initiating calcimimetics in these patients. One should indeed be aware that after administration of cinacalcet, serum calcium levels follow a similar time course to those of PTH, that is, a pronounced decrease reaching a nadir at 4 h post-dose.[18] When superimposed on an already low baseline calcium level, temporary but severe hypocalcemia may occur, which may become clinically relevant (malignant arrhythmia, cardiac failure) especially in cardiovascular vulnerable patients.[133,134] Besides temporary hypocalcemia, prolonged hypocalcemia may also occur due to an increased shift of calcium from the circulation to the bone tissues.[135,136] This condition which results from the transient quantitative uncoupling between bone formation and resorption[137] is often encountered after parathyroidectomy[138] and is often referred to as the 'hungry bone syndrome'.[139]

The mechanisms underlying the gastrointestinal side effects are unclear. The CaSR is expressed on numerous cell/tissue types present in the gastrointestinal tract. However, no antiproliferative actions on intestinal epithelial cells were observed in cinacalcet-treated animals.[127] Interference with the production/secretion of gastrointestinal hormones or the gastrointestinal transit represents alternative explanations. Further basic and clinical investigations are required to clarify the pathophysiological mechanisms underlying the gastrointestinal side effects.

PHARMACOKINETICS

The calcimimetic agent NPS R-568 was efficacious in primary and SHPT and in parathyroid carcinoma;[15] however, the unpredictable pharmacokinetics of this compound led to its replacement by cinacalcet hydrochloride. The metabolism and disposition of cinacalcet have been examined in experimental animals and human volunteers.[140] In patients on dialysis, a once daily administration is appropriate.[141] Changes in plasma PTH levels correlated inversely with changes in cinacalcet levels. Importantly, the pharmacokinetic properties of cinacalcet after a single administration are not influenced by the hemodialysis procedure.[142] Pharmacokinetic studies suggest that shorter dosing intervals should be advised in patients with preserved renal function.[143]

THERAPY WITH CALCIMIMETICS VERSUS PTX

Therapy with cinacalcet may be considered an alternative for parathyroidectomy in patients with severe SHPT. In fact, therapy with calcimimetics is often referred to as a 'reversible chemical parathyroidectomy'.

Biochemical parameters of mineral metabolism show comparable changes after PTX[144,145] and during therapy with cinacalcet. The fact that hypoparathyroidism is less likely to occur with cinacalcet treatment than with PTX may be considered an advantage of the medical approach. Whether iatrogenic hypoparathyroidism will inevitably result in adynamic bone disease remains to be demonstrated. Studies addressing this issue are scanty and, overall, have yielded conflicting results.[146–151] Hampl *et al.*, for example, provided evidence that even 20 years after total PTX a normal bone metabolism can be maintained in hemodialysis patients by adequate substitution with oral calcium and vitamin D supplements despite almost undetectable PTH levels. In addition, several surgical case studies have reported an increase in bone mineral density after PTX.[152] These data, together with the recent observation of a lower fracture risk among hemodialysis patients who underwent PTX compared with matched controls, suggest that the amelioration of biochemical consequences of SHPT by PTX may outweigh potential risks of long-term hypoparathyroidism at least in

terms of bone health.[153] In addition, several authors observed a regression or stabilization of soft tissue calcification following parathyroidectomy.[146,154] Finally, data from the United States Renal Data System and Dialysis Morbidity and Mortality Study demonstrated that PTX is associated with lower long-term mortality rates among US patients receiving chronic dialysis.[155,156]

In the absence of prospective studies comparing outcomes of cinacalcet plus standard therapy versus parathyroidectomy, both approaches should be considered complementary rather than competitive.[157] Indeed, therapy with calcimimetics may be the only option in high-risk patients and those unwilling to undergo surgery. Calcimimetics may also be effective in controlling relapses of SHPT after PTX.[158] On the other hand, some patients with severe hyperparathyroidism may be refractory to cinacalcet treatment and therefore still need to be referred for surgery. In the post-hoc study by Cunningham *et al.*,[46] the PTX rate in the cinacalcet-treated patients was 0.3 per 100 subject years versus 4.1 per 100 subject years in those receiving standard therapy (relative risk 0.07, CI 0.01–0.55).

COST–UTITLITY

Besides efficacy, the budgetary impact of a therapeutic measure has also to be considered, as health-care resources are under continuous pressure. It has been calculated that the overall use of cinacalcet in the United States will increase the overall cost of health care by $300 million/year.[159] The additional cost per month per patient is estimated to vary from about $300 (30 mg) to $ 1800 (180 mg).[23,160] The cost–utility of cinacalcet in addition to standard therapy compared to standard care alone has recently been investigated by Garside *et al.*[161] These authors concluded that according to directives from the UK National Institute for Health and Clinical Excellence (NICE), cinacalcet—at its current costs—cannot be considered a cost-effective treatment for people with SHPT.[161] Narayan *et al.*[162] compared the cost–utility of parathyroidectomy versus cinacalcet in patients with CKD stage 5D. For patients with uncontrolled hyperparathyroidism who are good candidates for either drug therapy or surgery, cinacalcet is the most cost-effective modality if the patient is to remain on dialysis therapy for $\leqslant 7.25 \pm 0.25$ months. Cinacalcet may be more optimal if used in patients who have high risk of mortality or who would expect to receive a kidney transplant quickly. For other subgroups, parathyroidectomy is more cost-effective. These authors assumed no rebound of the parathyroid function after cessation of the calcimimetic at the time of transplantation. This assumption is questioned by recent clinical evidence.[113]

CONCLUSION

Secondary HPT remains an important complication in patients with CKD. It may compromise bone health and contribute to the increased cardiovascular risks of these patients. The treatment options of SHPT have expanded substantially in recent years, with calcimimetic agents being the most recent acquisition. Several strengths, weaknesses, opportunities, and threats of calcimimetic treatment can be discerned (Figure 1). Undoubtedly, calcimimetics may help to achieve the stringent mineral metabolism targets in patients with CKD stage 5D. It should however be of note that these targets are largely opinion based. Much controversy remains on what is the optimal PTH level in CKD stage 5D. The correlation between PTH levels and bone turnover is generally acknowledged to be weak. Target levels may furthermore differ depending on the end organ (bone, heart, vascular tree). It therefore remains to be awaited whether the improved achievement of current mineral metabolism targets by calcimimetic treatment will translate into improved bone health and cardiovascular morbidity and mortality. Current evidence, though indirect, is encouraging, but—as always—the proof of the pudding will be in the eating.

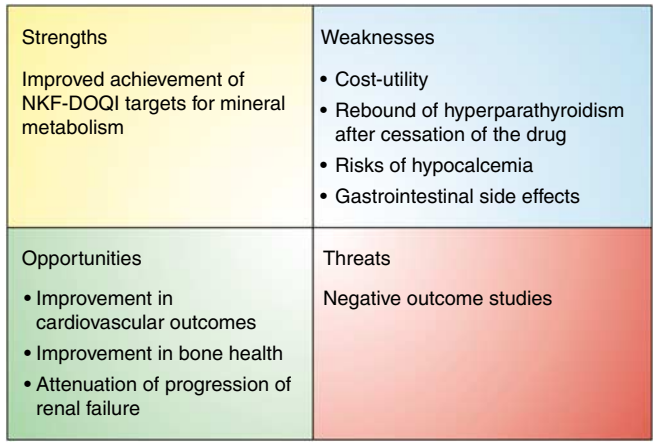

Figure 1 | SWOT analysis of calcimimetic agents.

The rationale for using calcimimetics in CKD patients not yet on dialysis is less clear. In these patients, therapy for SHPT should rather be focused on the primary trigger, that is, the high phosphate load relative to the functional nephron mass.

In patients with persistent HPT after successful renal transplantation, therapy with calcimimetics may be useful. Calcimimetics may help to improve bone health both by suppressing bone turnover and demineralization and may retard or prevent nephrocalcinosis of the graft. Further clinical studies are urgently needed to test these hypotheses.

Additional investigations are required to define how calcimimetics fit best in the expanding armamentarium to treat SHPT (diet, calcium-containing and calcium-free phosphate binders, naïve and active vitamin D analogs, parathyroidectomy).[163] Given the many pleiotropic effects of vitamin D and considering recent epidemiological data,[164–170] one should beware of completely substituting vitamin D (analogs) for calcimimetics. Combining these two drugs may proof to be advantageous to the patients. Evidently, also the role of PTX needs to be reevaluated in the calcimimetic era. The lower incidence of iatrogenic hypoparathyroidism associated with the use of cinacalcet in comparison with

parathyroidectomy might be considered an advantage of the calcimimetics. However, lacking studies comparing outcomes of cinacalcet plus standard therapy versus parathyroidectomy, both approaches should be considered complementary rather than competitive. Indeed, therapy with calcimimetics may be the only option in high-risk patients and those patients who are unwilling to undergo surgery. On the other hand, some patients with severe hyperparathyroidism may be refractory to calcimimetic treatment and therefore still need to be referred for surgery. Finally, in an era of health-care resources being under continuous pressure, cost–utility is a major issue. Taken together, calcimimetic agents compliment, rather than replace, current treatment options for SHPT.

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