The Role of the Old and the New Calcimimetic Agents in Chronic Kidney Disease-Mineral and Bone Disorder

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Introduction

Chronic kidney disease (CKD) is an increasingly disease and a public health issue, affecting 8–16% of the population worldwide [1]. During the course of CKD, the decline of renal function leads to the development of calcium and phosphate metabolism disorders, causing a condition—"Mineral Bone Disease associated with CKD" (CKD-MBD) [2]. This condition develops with the incapacity of the kidney to excrete phosphate properly, leading to its retention and accumulation. Phosphate load stimulates Fibroblast Growth Factor 23 (FGF-23) and serum parathyroid hormone (PTH) [3]. FGF-23, a peptide hormone produced mainly in the osteocytes, is able to reduce phosphate levels using three different pathways: decreasing tubular epithelial cells reabsorption with the subsequent increase in renal excretion, stimulating PTH secretion with its additional phosphaturic effect

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and inhibiting calcitriol synthesis and subsequently decreasing phosphate intestinal absorption. Also, the latter leads to a decreased gastrointestinal absorption of calcium with the subsequent development of hypocalcemia. The low calcitriol levels and hipocalcemia also stimulate PTH secretion in the parathyroid glands and induce the development of parathyroid gland hyperplasia and secondary hyperparathyroidism (SHPT).

Secondary hyperparathyroidism is associated with increased bone remodeling due to stimulation of the bone cells osteoblasts and osteoclasts. The result is the development of a high turnover bone disease called *osteitis fibrosa*. This bone disease is associated with increased risk of fractures, vascular calcifications, cardiovascular and all-cause mortality [4]. Recent observational data indicates that uncontrolled SHPT is associated with a higher risk of cardiovascular mortality as well as all-cause cardiovascular hospitalizations [5]. It is interesting to note that patients have better outcomes the longer the time they have controlled SPTH with intact PTH (iPTH) levels within the recommended range. Indeed consistent control of the bone metabolism parameters (iPTH, calcium and phosphate serum levels) within published recommended targets is a strong predictor of survival in hemodialysis patients [6].

The classical treatment for SHPT includes active vitamin D compounds and phosphate binders to limit gastrointestinal phosphate absorption [7]. However, achieving the optimal laboratory targets is often difficult because active vitamin D sterols have a small therapeutic window, suppressing PTH secretion, but simultaneously increasing calcium and phosphate intestinal absorption and serum levels.

Calcium sensing receptor (CaSR) is essential for maintaining systemic calcium homeostasis, becoming an excellent target for treating bone and mineral disorders. This receptor is expressed in several tissues including parathyroid gland cells [8]. Its ligands are called calcimimetics and can be classified as type 1 (agonists) such as ionized calcium and other divalent anions that directly stimulate CaSR or type 2 (positive allosteric modulators)—binding to a site that is distinct from the physiological ligand increasing the sensitivity of CaSR to ionized calcium, leading to the decrease of the set-point for systemic calcium homeostasis (homeostasis is achieved with lower concentrations of ionized calcium) [8]. This enables a decrease in plasma PTH levels, and consequently of calcium levels (Table 1). Additionally, lower levels of phosphorus and Calcium × Phosphorus are also seen [9], demonstrating the capability of calcimimetics to improve the four critical disease biomarkers associated with SHPT (phosphorus and calcium lowering effect distinguishes calcimimetics from active vitamin D) [10].

Table 1 Effect of PTH-suppressive therapies on biochemical parameters

	PTH	Calcium	Phosphorus	FGF-23
Vitamin D analogs	↓	↑	↑	↑
Cinacalcet	↓	↓	↓	↓
Etelcalcetide	↓↓	↓↓	↓	↓↓
Evocalcet	↓	↓	↓	↓

First generation compounds include phenylalkylamines R-567 and R-568 that were tested in hemodialysis patients but pharmacokinetics issues halted further clinical development [7]. Second generation calcimimetic drugs includes cinacalcet, and others never achieving clinical use such as calindol and AC-265347. Cinacalcet Hydrochloride was the first type 2 calcimimetic oral administered agent approved for clinical use [11].

Cinacalcet treatment effectively reduces PTH, calcium and phosphorus [12]. After more than 15 years from its approval, cinacalcet demonstrated that effectively reduces PTH and improves biochemical control of CKD-MBD.

Etelcalcetide is a new second generation calcimimetic. As a novel intravenous formulation with a pharmacokinetic profile that allows thrice-weekly dosing (at the time of hemodialysis), etelcalcetide was developed to improve efficacy and adherence and reduce gastrointestinal adverse effects relative to cinacalcet. It was recently approved in Europe and is regarded as a second opportunity to improve outcomes in CKD-MBD optimizing the treatment for SHPT using this promising new calcimimetic [13].

Evocalcet is the newly developed oral calcimimetic agent with less gastrointestinal adverse effects than cinacalcet and may be an alternative option for the treatment of secondary hyperparathyroidism in dialysis patients [14].

In this chapter, we summarize the impact of cinacalcet in biochemical and relevant clinical outcomes. We discuss the possible implications of etelcalcetide in the quest for improving outcomes for CKD patients. We also explore available data of the new oral calcimimetic evocalcet.

Cinacalcet Effectively Controls Secondary Hyperparathyroidism

Cinacalcet efficacy and safety was tested in several randomized controlled trials (RCTs) [11, 12, 15]. Cinacalcet treatment on addition to active vitamin D in patients with SHPT that are inadequately controlled despite standard therapy effectively decreases PTH levels along with reductions in serum calcium and phosphorus. Post hoc analysis demonstrated that treatment with cinacalcet improves achievement of biochemical targets recommended by international societies [16]. In a meta-analysis [17] involving 8 trials (1429 patients) comparing cinacalcet treatment plus standard therapy with placebo plus standard therapy end-of-treatment values for PTH (−290.49 pg/mL, 95% CI: −359.91 to −221.07), calcium (−0.85 mg/dL, 95% CI: −1.14 to −0.56), phosphorus (−0.29 mg/dL, 95% CI: −0.50 to −0.08) and calcium × phosphorus product (−7.90 mg^2/dL^2, 95% CI: −10.25 to −5.54) were significantly lower with cinacalcet compared with placebo.

To allow an objective assessment of the cinacalcet lowering effect of PTH, active vitamin D analogs dose was constant. However, subsequent clinical studies have confirmed the PTH-lowering effect of cinacalcet used in varying doses or

constant doses of active vitamin D. This was an important finding considering that in clinical practice, cinacalcet is used often with vitamin D sterols [18]. Cinacalcet adverse effects are described in Table 2.

Besides the suppressive effect on PTH levels, data suggest that cinacalcet treatment can induce a volume reduction of the enlarged parathyroid glands with nodular hyperplasia seen in SHPT patients [19]. Meola et al. using high resolution color Doppler sonography measured parathyroid gland volume in nine hemodialysis patients with severe SHPT (mean baseline PTH 1196 ± 381 pg/mL) [20]. Patients were treated with cinacalcet, with a follow-up period of 24–30 months. Cinacalcet treatment led to a reduction in parathyroid gland volume in 68% in glands with a baseline volume < 500 mm^3 and in 54% in glands with a baseline volume ≥ 500 mm^3. In fact, cinacalcet exerts inhibitory effect on parathyroid cell proliferation in animal models of SPHT [21]. It is interesting to note that this inhibitory effect on cellular proliferation is specific for parathyroid cells and it is not observed in other cells expressing CaSR.

Table 2 Lateral effects of calcimimetic agents and suggested actions to take

Side effect	Frequency	Proposed action
Gastrointestinal events		
Nausea	Very common	Give Cinacalcet with main meal after dialysis/in the evening Decrease or fractionate the dose if symptoms appear after a dose increase Caution is advised with antiemetics, including metoclopramide (QT prolongation)
Vomiting	Very common	
Diarrhea and dyspepsia	Uncommon	
Anorexia	Common	
Hypocalcemia and nervous system disorders		
Hypocalcemia	Common	Withhold or reduce Cinacalcet until serum Calcium levels reach 8 mg/dl or symptoms have resolved Use of Calcium-based phosphate binders, Vitamin D sterols or adjustments of dialysis fluid calcium have been suggested by some authors, according to clinical judgment
Dizziness and paraesthesia	Common	
Seizures	Uncommon	
Others		
Skin and cutaneous disorders Rash	Common	Seek other causes. Consider discontinuing drug
Musculoskeletal, connective tissue and bone disorders Myalgia	Common	Seek other causes. Consider discontinuing drug
Immune-system disorders Hypersensitivity reactions	Uncommon	Seek other causes. Consider discontinuing drug

Cinacalcet Reduces FGF-23 Levels

FGF-23 levels have been associated with adverse clinical outcomes [22–27] progression of CKD, arterial calcification, left ventricle hypertrophy, cardiovascular events and increased mortality. A pharmacologic intervention capable of reducing FGF-23 holds the promise to have a beneficial effect on those important clinical outcomes.

CUPID (Cinacalcet Study for Peritoneal Dialysis Patients in Double Arm on the Lowing Effect of iPTH Level), a prospective, randomized controlled study, evaluated the effect of cinacalcet on FGF-23 levels [28] enrolled peritoneal dialysis patients for a period longer than 3 months and PTH > 300 pg/mL. Patients were randomized to cinacalcet therapy or vitamin D. Cinacalcet group had a reduction in FGF-23 levels (3960–2325 RU/mL) and the control group had an increase in FGF-23 concentration (2085–2415 RU/mL). ACHIEVE (ACHIEVE: Optimizing the Treatment of Secondary Hyperparathyroidism: A Comparison of Sensipar and Low Dose Vitamin D versus Escalating Doses of Vitamin D Alone), a phase 4, open-label, placebo-controlled, multicenter, RCT, was designed to compare treatment results with escalating doses of cinacalcet plus fixed low-dose calcitriol (cinacalcet-D group) versus escalating doses of calcitriol alone (Flex-D group) [29]. Using data of 91 subjects from this study, Wetmore et al. verified that the percentage change of FGF-23 between the two groups differed significantly ($p = 0.002$) [30]. In the Cinacalcet-D group the percentage change decreased (-9.7 ± 18.2; $p = 0.021$), while in the Flex-D group an increased tendency was found, however the results were not significant (4.1 ± 16.5).

The mechanism for this effect of cinacalcet on decreasing FGF-23 levels remains to be clarified. CUPID investigators concluded that cinacalcet treatment was independently associated with FGF-23 reduction, and not related with the drug's effect on PTH, calcium and phosphorus serum levels. Others observed that the decrease of FGF-23 levels is concomitant with the decrease in phosphorus levels (but not to PTH or calcium levels) [31]. Wetmore et al. suggested that calcium and phosphorus are responsible for cinacalcet's effect on FGF-23 levels [30]. Further investigation is needed in order to understand how exactly cinacalcet therapy results in greater reductions in serum FGF-23, when comparing to traditional drugs.

Recently, a post hoc evaluation of the EVOLVE (Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events) study added some more information to the FGF-23 issue [32]. When analyzing the results from the cinacalcet treated patients group ($n = 1338$) a decrease in FGF-23 levels was seen (5555–2255 pg/mL; $p < 0.001$), in opposition to the control group ($n = 1264$) where the levels remained unchanged (5600–5580 pg/mL). Moreover, when comparing to control group, a larger proportion of patients in the cinacalcet group had a meaningful decline ($\geq 30\%$) of FGF-23 (28% vs. 64%; $p < 0.001$). This finding is relevant, because the reduction $\geq 30\%$ of the FGF-23 levels was associated with a decreased risk of cardiovascular mortality ($p < 0.001$), sudden death ($p < 0.001$) and heart failure ($p = 0.04$).

Cinacalcet and Fractures

Patients with CKD have increased risk of fractures compared with the general population [33, 34]. Also there is a high rate of death and hospitalization following bone fracture among hemodialysis patients [35]. Abnormities in bone structure which affects bone quality are observed in patients with CKD-MBD. Malluche et al. demonstrated that bone with high turnover had material and nanomechanical abnormalities such as reduced mineral to matrix ratio [36]. The turnover-related alterations in bone quality may contribute to the diminished mechanical competence of bone in CKD.

Iimori et al. [37] in their single center cohort study demonstrated a U-shaped correlation between PTH and risk of fracture—only decreased [PTH < 150 pg/mL; Hazard ratio (HR) 3.27] or increased levels (PTH > 300 pg/mL; HR 2.69) were related to a superior hazard of clinical fracture.

There is no RCT specifically designed to evaluate whether any compound used in treatment of SHPT (phosphate binders, vitamin D analogs or calcimimetics) decreases the risk of fracture in CKD patients. However, treatment with cinacalcet has been associated with reduced risk of fractures. A combined post hoc analysis of safety data from four phase 3 RCTs enrolling 1184 patients with end-stage renal disease (ESRD) and uncontrolled SHPT (defined as PTH > 300 pg/mL) showed that randomization to cinacalcet on addition to conventional treatment with active vitamin D, resulted in significant reduction in the risk of fracture [Relative risk (RR) 0.46, 95% CI 0.22–0.95, $p = 0.04$] compared with placebo and conventional treatment [38].

In the EVOLVE trial, in the intention-to-treat (ITT) analysis cinacalcet did not significantly reduced the risk of fractures [39]. During the study, more than two thirds of patients in both groups discontinued the treatment, so a predetermined lag-censoring analysis (censoring time > 6 months after stopping the study drug) was performed and a relative hazard for fracture of 0.72 (95% CI 0.58–0.90; $p = 0.003$) was obtained. When participants were censored at the time of co-interventions, such as parathyroidectomy and kidney transplant, the relative hazard was 0.71 (95% CI 0.58–0.87; $p = 0.001$). Moreover, when considering the risk of all clinical fractures (not only the first, but also the subsequent) the multivariable-adjusted relative hazard was 0.83 (95% CI 0.72–0.98; $p = 0.02$). Concluding, when taking into account events prompting discontinuation of the study drug, co-interventions and cumulative clinical fractures, cinacalcet reduced the rate of clinical fracture by 17–29% [39]. These data provide suggestive evidence that cinacalcet reduces risk of fracture in patients with SHPT.

This effect of cinacalcet in reducing fractures is not a surprising one considering two reports using bone histomorphometry from different groups describing improved histology in patients treated with cinacalcet [40, 41]. In BONAFIDE (Bone Biopsy Study for Dialysis Patients with Secondary Hyperparathyroidism of End Stage Renal Disease) [41] dialysis patients ($n = 77$) with PTH > 300 pg/mL and biopsy-proven high-turnover bone disease were treated with cinacalcet and

a second bone biopsy was performed after 6–12 months of cinacalcet treatment. Bone formation and bone reabsorption indices were improved; most impressive was that the number of patients with normal bone histology increased from none at baseline from 20 to 12 months.

The role of bone mineral density (BMD) evaluation in chronic kidney patients is evolving. Unlike previous ones, current KDIGO guidelines suggest BMD testing in patients with CKD G3a-G5D with CKD-MBD and/or risk factors for osteoporosis if results will impact therapeutic decisions [42]. Evidence-based information is scarse about effect of cinacalcet on BMD in CKD patients. Some of available data showed a positive effect of cinacalcet on BMD, namely on femoral neck [43] and proximal femur [44]. However, others revealed that cinacalcet therapy showed no effect on BMD lumbar spine [44] or a detrimental effect with associated bone loss on femoral neck and lumbar spine [45]. The effect and significance of cinacalcet on BMD remains to be clarified.

Cinacalcet and Vascular Calcification

Secondary hyperparathyroidism is associated with vascular calcification. Once established in hemodialysis patients, it generally progresses much faster than in the general population, leading to an increased risk of all-cause and cardiovascular mortality [2].

In a single-center prospective cohort study (n = 23), Nakayama et al. [46] evaluated the impact of cinacalcet in abdominal aortic calcification by calculating aortic calcification area index (ACAI) before and after treatment (−12, 0, 12, 24 and 36 months). The mean ACAI values were not decreased during the observation period (21.4% at baseline, 23.9% at 12 months, 23.7% at 24 months and 24.3% at 36 months). Tsuruta et al. [47] compared coronary artery calcification in a cinacalcet group (n = 8) and a control group (n = 60), verifying a decreasing tendency (−0.094/year) in the coronary artery calcification score when using cinacalcet, while in the control group the opposite was seen (+0.034/year). However, the results were not statistically significant (p = 0.102).

ADVANCE (A Randomized Study to Evaluate the Effects of Cinacalcet Plus Low Dose Vitamin D on Vascular Calcification in Subjects with Chronic Kidney Disease) [48], compared vascular and cardiac valve calcification progression in 360 adult hemodialysis patients with SHPT, treated either with cinacalcet plus low-dose vitamin D (n = 180) or flexible doses of vitamin D alone (n = 180). The primary endpoint was changes in the Agatston Total Coronary Artery Calcification (CAC) score (uses the concept of plaque density, therefore reflecting the amount of calcium deposited within a calcified lesion). The median percent increase in Agatston total CAC score was not different between the two treatment groups. Similarly, Agatston Score changes in the thoracic aorta and mitral valve were not statistically significant. Aortic valve, on the other hand, had a stratified median treatment difference of −44.7% (95% CI: −85.8% to −6.1%; p = 0.014).

The ADVANCE study had some limitations. A substantial number of patients assigned to cinacalcet group received doses of vitamin D higher than specified in protocol. A post hoc analysis [49] comparing CAC progression among protocol-adherent patients treated with cinacalcet showed that percentage increase in CAC and aortic valve calcification was significantly slower in cinacalcet group. Other limitations include the open-label design and short period of follow-up—12 months are unlikely to be sufficient to detect substantial changes in vascular calcification. Finally, the reduced observed calcification progression cannot be attributed solely to cinacalcet; we have to consider also the lower doses of vitamin D sterols in cinacalcet group.

Cinacalcet, Cardiovascular Disease and All-Cause Mortality

Elevated serum levels of phosphorus, calcium, PTH and FGF-23 have been linked to death and cardiovascular outcomes [50–52]. Cunningham et al. [38] in a post hoc analysis, combined data on clinical outcomes from four randomized phase 3, controlled trials and showed that treatment with cinacalcet resulted in a significant reduction in the risk of cardiovascular hospitalizations (HR = 0.61, 95% CI 0.43–0.86) and a non-significant tendency to reduce all-cause mortality. Another observational study including 19,186 hemodialysis patients from a large dialysis provider [53] receiving intravenous vitamin D analogs (as surrogate for the diagnosis of SHPT) found that the treatment with cinacalcet was associated with significant reductions in all-cause mortality, cardiovascular mortality, with more pronounced survival benefits founded in patients with more severe SHPT. In a prospectively observational study, Block et al. [50] described a significant survival benefit associated with cinacalcet prescription. These and others observations [54, 55] lead to the development of a prospective RCT evaluating the effect of cinacalcet treatment on cardiovascular mortality. The EVOLVE [56] was a RCT enrolling 3883 hemodialysis patients with moderate to severe SHPT (median PTH 693 pg/mL) assigned to receive cinacalcet (n = 1948) or placebo (n = 1935). All patients were eligible to receive conventional treatment including phosphate binders, vitamin D sterols. The primary composite end point was time until death, myocardial infarction, hospitalization for unstable angina, heart failure or a peripheral vascular event. In an unadjusted ITT analysis, the primary end point was reached in 48.2% of patients in cinacalcet group and 49.2% in placebo group (relative HR in the cinacalcet group 0.93; 95% CI 0.85–1.02; p = 0.11). After adjusting for baseline characteristics the relative HR for the primary composite end point was 0.88 (95% CI 0.79–0.97; p = 0.008). In fact, despite randomization there was an unexpected 1-year difference in age between groups (median age 55 years in cinacalcet group and 54 years in placebo group). As age is one of strongest predictions of death, this difference may have affected the results.

Also, the statistical power of EVOLVE was hampered by high rates of treatment crossover because discontinuation in the cinacalcet group (dropout) and use of commercially available cinacalcet in placebo group (drop-in). A pre-specified lag-censoring analysis in which data censored 6 months after patients stopped cinacalcet was performed. This analysis found a significant reduction in the risk of primary composite end point (HR 0.85; 95% CI 0.76–0.95; p = 0.003) and risk of death (HR 0.83; 95% CI 0.73–0.96; p = 0.009) in the cinacalcet group.

Another pre-determined protocol analysis compared younger (<65 years) and older patients (≥65 years) [57]. Cinacalcet reduced the risk of death and major CV events in older, but not younger patients.

Although the primary analysis of EVOLVE trial was negative, pre-specified additional analysis showed significant reduction in the risk of death or cardiovascular outcomes which suggests a potential benefit of cinacalcet.

Palmer et al. [58] published a metanalysis of randomized trials evaluating effects of calcimimetic therapy on mortality and adverse events in adults with CKD. Including 18 trials and a total of 7446 patients, they found cinacalcet had little or no effect on all-cause mortality (RR 0.97; 95% CI 0.89–1.05) and an imprecise effect on cardiovascular mortality (RR 0.67; 95% CI 0.16–2.87). The results of this metanalysis should be interpreted with caution. More than half of patients were derived from EVOLVE trial and this metanalysis only included the results from primary analysis with the potential setbacks that we discussed above. Also all trials included, except EVOLVE trial, were small and not specifically designed to assess clinical relevant outcomes such as mortality or cardiovascular events.

Etelcalcetide, A Novel Intravenous Calcimimetic Agent

Etelcalcetide is a novel second generation calcimimetic agent recently approved for the treatment of SHPT [13]. Etelcalcetide is a 8 amino acids peptide agonist of CaSR, which binds to CaSR by a covalente disulfide bond resulting in allosteric activation of CaSR and consequently reduced circulating levels of PTH and calcium [59]. In contrast to cinacalcet, etelcalcetide functions as a direct agonist of CaSR, slightly activating CaSR even under calcium-free conditions (Table 3). However, downstream signaling is stronger in the presence of calcium; thus the main action of etelcalcetide is mediated through its effects as allosteric activator [60].

Etelcalcetide has a favorable pharmacokinetic profile, with a longer elimination half-life than cinacalcet, with half-life elimination exceeding 7 days in ESRD patients [61]. It is administered by intravenous route at the end of hemodialysis session, with plasma concentration of etelcalcetide decreasing over time but remains relatively constant from 24 h post-dose to the next dialysis session [13]. It is a molecule dialysable during hemodialysis and with the doses of

Table 3 Comparison between cinacalcet and etelcalcetide. Values are expressed in percentage unless indicated otherwise. EAP: efficacy assessment phase

	Cinacalcet	Etelcalcetide
Class	Calcimimetic	Calcimimetic
Year of approval (Europe)	2004	2016
Mechanism of action	Interacts with membrane-spanning segments of CaSR and enhances signal transduction, thereby reducing PTH secretion	Peptide agonist of the CaSR that interacts with and activates the receptor thereby reducing PTH secretion
Mode of administration	Daily oral	IV at the end of dialysis
Half-life	30–40 h	>7 days
Excretion	Renal (80%), Fecal (15%)	Renal
Interaction with CYPs	Metabolized by CYP3A4, and to a lesser extent, CYP1A2; inhibits CYP2D6 (*caution is advised when prescribing potentially interacting drugs*)	No significant interactions
Daily dosing (starting; maximal)	30–180 mg	2.5–15 mg/dialysis
Efficacy endpoints >30% reduction from baseline in mean serum PTH level during the EAP >50% reduction from baseline in mean serum PTH during the EAP	63.9 40	77.9 52 ($p = 0.001$)
Adverse effects		
Nausea	22.6	18.3
Vomiting	13.8	13.3
Diarrhea	10.3	6.2
Headache	7.0	6.5
Hypertension	6.7	6.2
Hypotension	2.9	6.8
Muscle spasms	5.9	6.5
Pain in extremity	4.1	5.0
Asymptomatic hypocalcemia	59.8	68.9
Symptomatic hypocalcemia	2.3	5.0

etelcalcetide between 2.5 and 5 mg at the end of dialysis session, plasma concentrations of etelcalcetide reaches steady-state by week 4. Although clinical experience is of course limited, in vitro data shows data etelcalcetide is not an inhibitor, inducer or substrate of hepatic cytochrome (CYP) enzymes neither is an inhibitor or substrate of common efflux and uptake human transport proteins such as P-glycoprotein [62]. Thus, etelcalcetide is expected to have a low risk for CYP or transporter-mediated drug interactions.

Immunogenicity risk of etelcalcetide has been evaluated [63]. While both pre-existing and developing after treatment anti-etelcalcetide antibodies were detected, there are no consequences reported for clinical exposure, efficacy or safety of etelcalcetide.

Pivotal trials testing etelcalcetide in the treatment of SHPT were recently published [64, 65]. Two parallel, phase 3, placebo-controlled trials were conducted in 1023 hemodialysis patients with moderate to severe hyperparathyroidism. Intravenous administration of etelcalcetide (n = 503) or placebo (n = 513) after each hemodialysis session for 26 weeks was done. Patients randomized to etelcalcetide were significantly more likely to achieve primary efficacy end point (reduction greater than 30% in baseline PTH) 74.0–75.3% in etelcalcetide group versus 8.3–9.6% in placebo group. Also, patients randomized to etelcalcetide were significantly more likely to achieve a PTH level of 300 pg/mL or lower (49.6–53.3% in etelcalcetide group versus 4.6–5.1% in placebo group). The median dose of etelcalcetide during efficacy assessment phase was 5.0 and 7.1 mg. Patients randomized to etelcalcetide were more likely to experience substantial lowering of FGF-23 despite more frequent provision of calcium and vitamin D. Treatment with etelcalcetide decreased bone specific alkaline phosphatase and collagen type 1 cross-linked C-telopeptide. Patients randomized to etelcalcetide had more muscle spasms, nausea and vomiting than placebo group. Hypocalcemia occured in 63.8% of patients but symptomatic hypocalcemia was reported in only 7% of patients assigned to etelcalcetide. Similar results were obtained in a placebo-controlled trial from Japan, testing efficacy and safety of etelcalcetide [66].

A randomized, double-bind, double-dummy active clinical trial was conducted comparing intravenous etelcalcetide and oral placebo versus oral cinacalcet and intravenous placebo in 683 hemodialysis patients with PTH higher than 500 pg/mL [65]. The primary efficacy end point was non-inferiority of etelcalcetide at achieving more than a 30% reduction from baseline in mean predialysis PTH concentration and secondary end points included superiority in achieving biochemical end points (>50 and >30% reduction in PTH) and self-reported nausea or vomiting. Etelcalcetide was not inferior to cinacalcet in reducing PTH concentration and also met superior criteria. The proportion of patients who achieved >30% PTH reduction was 68.2% in etelcalcetide group and 57.7% in cinacalcet group. There was also a significant difference in proportions of patients who achieved >50% reduction of PTH. Hypocalcemia was more frequent in etelcalcetide group (68.9% vs. 59.8%) and the mean days of vomiting or nausea were not significantly different. Overall safety and tolerability between etelcalcetide and cinacalcet were similar. There was a numerically higher number of heart failure episodes in the etelcalcetide group, but overall the event rates were very low and similar to those observed in the EVOLVE trial.

The effect of etelcalcetide on FGF-23 levels is also noteworthy. Etelcalcetide treatment yielded more pronounced reduction in FGF-23 levels than cinacalcet. As discussed above, FGF-23 is elevated in CKD patients and it has been associated to adverse outcomes such as left ventricular hypertrophy and cardiac failure. Also in

the EVOLVE trial a 30% reduction of FGF-23 levels was associated with significant reduction of primary composite end point, heart failure and death [32]. This promising finding in the etelcalcetide group raises the possibility of a more pronounced impact in cardiovascular outcomes.

There are some important clinical aspects to consider in the results of the referred trials we want to highlight. Etelcalcetide is superior to cinacalcet in achieving reduction of PTH and FGF-23 concentrations in ESRD patients, however also leading to more frequent episodes of hypocalcemia. Data suggests that this hypocalcemic effect could be more pronounced at beginning of treatment when PTH is highest. Indeed, in the multinational placebo-controlled trial, the calcium-lowering effect of etelcalcetide was evident early after treatment initiation and reached a nadir at weeks 10–12. This calcium-lowering effect was observed despite an increased use of oral calcium containing binders, active vitamin D analogs and increases in dialysate calcium concentration in an important proportion of patients. This observation might raise legitimate concerns regarding the possible cumulative positive calcium balance. Etelcalcetide is given at the end of hemodialysis session which improves medication adherence and reduces pill burden. Unlike previously anticipated, etelcalcetide does not seem to have fewer gastrointestinal symptoms related to calcimimetic treatment despite intravenous administration. The nausea and vomiting induced by cinacalcet and etelcalcetide appears to be a systemic effect rather than local gastrointestinal class effect.

Finally, it is tempting to consider that the longer elimination half-life could lead to a more stable control of biochemical parameters like PTH, calcium, phosphate and this sustained suppression of PTH could translate into improved bone turnover and metabolism, decreased vascular calcification and ultimately improved cardiovascular patient outcomes. This impact in such important outcomes remains to be proved.

Etelcalcetide—Questions to Resolve and (Some) Evidence from Outside the Clinical Trial World

There is still a paucity of published data of etelcalcetide in real world setting. However, there are some questions that remain to be answered and some emerging data that we want to highlight.

Etelcalcetide and Regression of Parathyroid Gland Size

Yoshimura et al. [67] reported a single case of dramatic reduction in parathyroid gland in a hemodialysis patient with uncontrolled SHPT in spite of treatment with active vitamin D and cicalcalcet. Oral cinacalcet was stopped and the patient was treated with etelcalcetide resulting in a decrease of total parathyroid

glands volume from 1549 to 82.6 mm^3 after 9 months of treatment. Although this is an anecdotal report, it raises the hope that etelcalcetide can reduce the size of parathyroid gland even in patients who did not respond to cinacalcet. However, it remains to clarify if etelcalcetide induces apoptosis in hyperplastic parathyroid cells.

Etelcalcetide and Gastrointestinal Adverse Effects

Perhaps the most disappointing result of etelcalcetide pivotal trials was the absence of improved tolerance as it was anticipated considering the IV administration route. In the previously describe trial comparing cinacalcet with etelcalcetide, the adjusted mean weekly days of vomiting or nausea in the first 8 weeks of treatment were not significantly different for patients randomized to cinacalcet (0.3) and etelcalcetide (0.4) [65]. Of the 341 patients treated with cinacalcet, 77 (22.6%) reported nausea and 47 (13.8%) vomiting. Of the 338 patients randomized to etelcalcetide 62 (18.3%) reported nausea and 45 (13.3%) vomiting. Overall safety and tolerability between etelcalcetide and cinacalcet were similar.

In our personal clinical experience, etelcalcetide seems to perform better than cinacalcet regarding to nausea and vomiting. In future, further clinical evidence will confirm or refute this first clinical practice impression. In meantime, Mima et al. described 9 hemodialysis patients, with mean baseline PTH levels 626 ± 326 pg/mL, treated with etelcalcetide with an observation period of 4.4 ± 1.0 months [68]. The mean etelcalcetide dose was 6.1 ± 2.2 mg/hemodialysis session. Serum PTH levels decreased to 258 ± 207 pg/mL. In this very small study, no adverse events were reported during the observation period—nausea, vomiting, hypotension, headache, muscle spasms, anemia or abnormal 12-lead electrocardiograms.

Etelcalcetide and Theoretical Concerns of Its Use in Diabetics Undergoing Hemodialysis

There are some authors considering that until more clinical experience with etelcalcetide is available, the clinicians should be cautious when treating SHPT in diabetic hemodialysis patients with this new calcimimetic agent [69]. This is due to the theoretical possibility that etelcalcetide plasma protein binding may compete with oral hypoglycemic and insulins detemir and degludec, increasing the risk for hypoglycemia or hypocalcemia. Also hypocalcemia may cause decompensation of preexisting cardiac failure and lead to hypotension-related cardiac events, such as myocardial ischemia. Insulin-related hypoglycemia and hemodialysis prolong QT interval as well as hypocalcemia. So diabetic patients should be strictly monitored for hypocalcemia and associated effects.

Hypocalcemia in Hemodialysis Patients Treated with Calcimimetics

The 2009 KDIGO guidelines suggested in patients with CKD stages 3-5D to maintain serum calcium in normal range [2]. The revised 2017 KDIGO guidelines states that "in adult patients with CKD G3a-5D, we suggest avoiding hypercalcemia". The suggestion to avoid hypercalcemia is justified by novel evidence linking higher calcium levels to increased mortality in adults with CKD [42]. But there were doubts about the generalizability of the previous suggestion to correct hypocalcemia because of 2 arguments. First, there is the potential harm for some adults associated with positive calcium balance—it is important to remember that serum calcium levels do not necessarily reflect calcium balance [70, 71]. Second, the prevalence of hypocalcemia may have increased after introduction of cinacalcet [9, 72]. Most importantly, no negative signals were associated with the persistently low serum calcium levels in the cinacalcet arm of the EVOLVE trial [56]. So the clinical implications of hypocalcemia in the patients treated with calcimimetics is uncertain, but it may be less harmfull.

Floege J. et al. published an interesting work aiming to investigate incidence, predictors and therapeutic consequences of hypocalcemia by a post hoc analysis of EVOLVE [73]. At least one episode of hypocalcemia occurred within 16 weeks after the first administered dose of cinacalcet in 58.3% of patients compared to 14.9% of patients randomized to placebo. Hypocalcemia was severe (defined as total serum calcium < 7.5 mg/dL) in 18.4% in cinacalcet group compared with 4.4% in placebo group. In the majority of patients, hypocalcemia was asymptomatic and resolved spontaneously within 14 days with no modification of therapy. Among patients who received an intervention, the most common was an increase in active vitamin D dose. Interestingly, there were no increase in PTH following the hypocalcemia episode.

In summary, we agree with the KDIGO recommendation that is not necessary to correct hypocalcemia in all patients but significant or symptomatic hypocalcemia still should be addressed. Severe or symptomatic hypocalcemia could translate into adverse consequence such as bone disease, hyperparathyroidism and QT interval prolongation.

Evocalcet—A New Alternative Oral Calcimimetic Agent

Evocalcet is a newly synthesized oral calcimimetic agent [74]. In a rat model of renal failure, evocalcet and cinacalcet suppressed the secretion of PTH. However, cinacalcet induced a significant delay in gastric emptying while evocalcet did not. Evocalcet also induced less emesis compared with cinacalcet in common marmosets.

Recently a head-to-head comparison of efficacy and safety of evocalcet to cinacalcet was performed in Japanese hemodialysis patients with secondary hyperparathyroidism [14]. It was a phase 3, randomized double-blind, double-dummy

trial. This study enrolled Japanese patients with SHPT that were randomized to evocalcet or cinacalcet for 30 weeks (317 patients each arm). The primary efficacy endpoint was non-inferiority of evocalcet to cinacalcet in the proportion of patients achieving a mean PTH level of 60–240 pg/mL. In the evocalcet arm, 72.7% of patients achieved PTH target compared with 76.7% of patients with cinacalcet group (between-group difference: −4% [confidence interval −11.4%; 3.5%], for non-inferiority). Gastrointestinal-related adverse effects occurred in 18.6% of patients treated with evocalcet and in 32.8% of patients treated with cinacalcet (between-group difference: −14.2% [−20.9%, −7.5%], significant for superiority). Other endpoints, serum calcium, serum phosphate, and FGF-23 decreased over time similarly in both groups.

Further studies are necessary to prove efficacy and safety of this new agent, namely in other populations and with different baseline and target PTH levels. We believe that evocalcet could be an interesting alternative to cinacalcet in hemodialysis, peritoneal dialysis patients, and possibly in other clinical contexts like primary hyperparathyroidism and parathyroid carcinoma.

Conclusion

In conclusion, SHPT is associated with increased bone turnover, risk of fractures, vascular calcifications, cardiovascular and all-cause mortality. Cinacalcet, the first calcimimetic approved for clinical use, effectively reduces PTH and improves biochemical control of mineral and bone disorders in chronic kidney patients. However, the effect of cinacalcet on hard outcomes remains to be proved.

Etelcalcetide, the new second generation calcimimetic, is superior to cinacalcet in achievieng reduction of PTH and FGF-23 concentrations in ESRD patients. Also leads to more frequent episodes of hypocalcemia that could be more pronounced at beginning of treatment. Etelcalcetide is given at the end of hemodialysis session which improves medication adherence and reduces pill burden. Etelcalcetide has also unmet needs—besides hypocalcemia and unlike previously anticipated, etelcalcetide did not prove to have fewer gastrointestinal symptoms despite intravenous administration.

In our view, etelcalcetide represents significant advances in treatment of SHPT—better control of PTH, FGF-23, improved adherence. However if this improved biochemical control translates into improved clinical outcomes such as bone fractures rate, cardiovascular morbidity and mortality remains to be elucidated by prospective randomized trials.

Evocalcet is the new calcimimetic agent for the treatment of secondary hyperparathyroidism. In Japanese hemodialysis patients, this compound was better tolerated than cinacalcet.

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