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REVIEW

Role of etelcalcetide in the management of secondary hyperparathyroidism in hemodialysis patients: a review on current data and place in therapy

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Claudia Friedl[1]
Emanuel Zitt[2]

[1]Department of Internal Medicine, Clinical Division of Nephrology, Medical University of Graz, Graz, [2]Department of Internal Medicine III, Nephrology and Dialysis, Feldkirch Academic Teaching Hospital, Feldkirch, Austria

Abstract: Secondary hyperparathyroidism (sHPT) is a frequently occurring severe complication of advanced kidney disease. Its clinical consequences include extraskeletal vascular and valvular calcifications, changes in bone metabolism resulting in renal osteodystrophy, and an increased risk of cardiovascular morbidity and mortality. Calcimimetics are a cornerstone of parathyroid hormone (PTH)-lowering therapy, as confirmed by the recently updated 2017 Kidney Disease: Improving Global Outcomes chronic kidney disease – mineral and bone disorder clinical practice guidelines. Contrary to calcitriol or other vitamin D-receptor activators, calcimimetics reduce PTH without increasing serum-calcium, phosphorus, or FGF23 levels. Etelcalcetide is a new second-generation calcimimetic that has been approved for the treatment of sHPT in adult hemodialysis patients. Whereas the first-generation calcimimetic cinacalcet is taken orally once daily, etelcalcetide is given intravenously thrice weekly at the end of the hemodialysis session. Apart from improving drug adherence, etelcalcetide has proven to be more effective in lowering PTH when compared to cinacalcet, with an acceptable and comparable safety profile. The hope for better gastrointestinal tolerance with intravenous administration did not come true, as etelcalcetide did not significantly mitigate the adverse gastrointestinal effects associated with cinacalcet. Enhanced adherence and strong reductions in PTH, phosphorus, and FGF23 could set the stage for a future large randomized controlled trial to demonstrate that improved biochemical control of mineral metabolism with etelcalcetide in hemodialysis patients translates into cardiovascular and survival benefits and better health-related quality of life.

Keywords: calcimimetic, chronic kidney disease, dialysis, etelcalcetide, secondary hyperparathyroidism

Introduction

Secondary hyperparathyroidism (sHPT) is common in hemodialysis patients. This complication of chronic kidney disease (CKD) is caused by an attempt to control the disturbed calcium, phosphorus, and vitamin D metabolism. sHPT causes vascular and soft-tissue calcification and leads to disturbances of mineral metabolism. Combining these mineral, bone, and cardiovascular abnormalities, the clinical syndrome is now known as CKD-related mineral and bone disorder (CKD-MBD).

Clinically, sHPT causes vascular and valvular calcification and changes in bone metabolism that lead to renal osteodystrophy.[1] Furthermore, in large international observational studies, an independent association between increasing parathyroid hormone (PTH) and cardiovascular and all-cause mortality was found, especially

Correspondence: Emanuel Zitt
Department of Internal Medicine III, Nephrology and Dialysis, Feldkirch Academic Teaching Hospital,
47 Carinagasse, Feldkirch 6800, Austria
Tel +43 5522 303 2700
Fax +43 5522 303 7506
Email emanuel.zitt@lkhf.at

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for PTH >600 pg/mL.[2,3] sHPT-associated high FGF23 is independently associated with left ventricular hypertrophy,[4] cardiovascular events,[5] and premature death.[6] CKD-MBD abnormalities have also been implicated as risk factors for the very rare but devastating calcific and thrombotic arteriolopathy calciphylaxis[7] and lead to reduced health-related quality of life (HRQoL). The indication for sHPT treatment results from these clinical consequences.

In this article, we briefly summarize the pathogenesis of sHPT in CKD, with emphasis on the key molecular regulators that are targeted by calcimimetics, briefly touch on sHPT treatment options with regard to the updated Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD practice guidelines, review the lessons learnt from the oral first-generation calcimimetic cinacalcet with a focus on drug adherence, and finally describe preclinical and clinical data of the new intravenous second-generation calcimimetic etelcalcetide.

Pathogenesis of secondary hyperparathyroidism in chronic kidney disease

sHPT generally develops in stage 3 CKD with an estimated glomerular filtration rate <60 mL/min/1.73 m^2. Almost all hemodialysis patients suffer from sHPT.[8,9] It is characterized by normal or slightly decreased serum-calcium levels, initial normophosphatemia followed by hyperphosphatemia, low $1,25(OH)_2D_3$ (calcitriol) concentration, increasing levels of FGF23, a decrease in plasma-soluble Klotho and the development of renal osteodystrophy.[9,10] These changes cause parathyroid-cell hyperplasia accompanied by increased synthesis and secretion of PTH.[11] Reduced renal phosphorus-excretion capacity leads to transient increases in serum phosphorus and concomitantly decreased ionized calcium concentrations. To counteract these alterations, increased PTH corrects these changes in mineral metabolism as it reduces the tubular reabsorption of phosphorus and increases the reabsorption of calcium.[12] Additionally, the phosphatonin FGF23 decreases serum-phosphorus levels, due to reduced tubular phosphorus reabsorption independent of PTH. For full activity and activation of its receptors FGFR1 and FGFR3, it requires the presence of its coreceptor Klotho.[13] Contrary to increasing FGF23 levels, tubular Klotho expression and levels of soluble Klotho decrease with declining kidney function.[14] PTH itself stimulates FGF23 secretion directly and indirectly through enhanced synthesis of calcitriol secondary to the PTH-induced stimulation of tubular 1α-hydroxylase.[15–17] On the other hand, FGF23 lowers the secretion of PTH, although decreased Klotho and FGFR1 expression on hyperplastic parathyroid cells attenuate this effect.[18,19]

The key molecular regulators of parathyroid function and PTH secretion are the cell-surface calcium-sensing receptor (CaSR) and nuclear vitamin D receptor (VDR). A reduction in blood ionized calcium concentration rapidly stimulates the secretion of preformed PTH, prolonged hypocalcemia increases PTH synthesis, and this causes parathyroid-cell hyperplasia.[20] Activation of the VDR lowers PTH transcription, whereas decreased calcitriol stimulates PTH synthesis.[21]

Elevated phosphorus reduces the activity of tubular 1α-hydroxylase and lowers the synthesis of calcitriol.[22] Also, it stimulates PTH production independently of changes in calcium and calcitriol concentration[23] and directly increases parathyroid-cell proliferation,[24] due to downregulation of parathyroid CaSR and VDR.[25] Low serum concentrations of calcium and phosphorus and high PTH stimulate 1α-hydroxylase and increase calcitriol production, whereas FGF23 and calcitriol itself reduce enzyme activity.[26] With progressive sHPT, parathyroid-cell hyperplasia is characterized by reduced expression of CaSR, VDR, and FGFR1.[18,19,27,28] This parathyroid resistance promotes and aggravates the development of severe sHPT.

sHPT treatment: 2017 KDIGO CKD-MBD guidelines

Current treatment options for sHPT include: reducing oral phosphorus uptake by dietary phosphorus restriction, especially limiting phosphate additives in processed foods and favoring plant-based protein sources, and by the use of phosphate binders; the inhibition of PTH synthesis and secretion by the supplementation of calcitriol or other VDR activators (VDRAs) or the use of calcimimetics; finally, surgical parathyroidectomy is a valuable option in refractory cases after pharmacotherapy has failed. Unchanged, the recently updated KDIGO CKD-MBD clinical practice guidelines suggest for chronic hemodialysis patients maintenance of PTH levels in the range of approximately two to nine times the upper limit of normal for the particular PTH assay in use. In these patients, calcimimetics, VDRAs, or a combination of calcimimetics with VDRAs can be used to achieve this recommended target range.[29] With an evidence level of 2B, no single approach is preferred over another. Until now, there have been no prospective randomized controlled trials (RCTs) of phosphate binders or VDRAs indicating a benefit on patient-level outcomes except improvements in bone disease with alfacalcidol.[30] Contrary to VDRAs, which tend

to increase serum-calcium, phosphorus, and FGF23 levels, while decreasing PTH, the first-generation calcimimetic cinacalcet effectively reduces PTH without increasing calcium, phosphorous, or FGF23.[31,32] Treatment with cinacalcet improves biochemical parameters of sHPT, with significantly more patients achieving recommended target levels compared to patients treated with a standard regimen containing calcitriol or another VDRA.[33,34] Even in patients with persistent or recurrent HPT after parathyroidectomy, cinacalcet is effective.[35] Experimental data has found calcitriol and paricalcitol induce soft-tissue and aortic calcification in uremic rats, while cinacalcet monotherapy did not cause extraskeletal calcifications and attenuated the deleterious effect when given in combination with these VDRAs.[36]

Lessons learnt from the first-generation calcimimetic cinacalcet

Cinacalcet is the first calcimimetic drug approved for the treatment of sHPT in adult dialysis patients. It has been commercially available in the US since 2004, in Europe since 2005, and in Japan since 2008. As an allosteric modulator, cinacalcet increases the sensitivity of the CaSR to extracellular ionized calcium, leading to decreased PTH synthesis and secretion.[37] It is taken orally once daily, with a recommended starting dose of 30 mg. To achieve PTH targets, uptitration to a maximum of single-dose 180 mg is possible.[31]

In prevalent hemodialysis patients with moderate–severe sHPT and preexisting vascular or valvular calcification, treatment with cinacalcet in combination with low-dose VDRAs attenuated the progression of coronary artery and aortic valve calcification over 52 weeks compared to a treatment regimen based on flexible doses of a VDRA alone when assessed by the calcium-volume score, but slightly missed statistical significance with the Agatston score (P=0.07) in the ADVANCE trial.[38] In a post hoc analysis of protocol-adherent patients in the same study, significantly attenuated progression of cardiovascular calcification was found, even using the Agatston score.[39] In the large randomized placebo-controlled, double-blind EVOLVE trial conducted in 3,883 dialysis patients with sHPT, patients treated with cinacalcet on top of standard care showed better control of sHPT and lower risk of developing severe unremitting HPT compared to the placebo group.[40] However, the unadjusted primary composite end point (time to death or first occurrence of a nonfatal cardiovascular event, including myocardial infarction, hospitalization for unstable angina, heart failure, and peripheral vascular event) showed a nonsignificant reduction in intention-to-treat analysis with cinacalcet. Adjusted for imbalances in baseline characteristics or nonadherence, a nominally significant reduction in the primary composite end point was found.[41] Additionally, further prespecified secondary analyses of EVOLVE demonstrated a significant risk reduction for parathyroidectomy[40] or the development of calciphylaxis[42] with the use of cinacalcet.

With regard to bone turnover and histology, cinacalcet has been shown to decrease histomorphometric markers of bone turnover after 6–12 months of treatment in 77 dialysis patients with biopsy-proven high bone turnover. It generally improved bone histology, with most of the patients presenting with mild hyperparathyroid bone disease or mixed uremic osteodystrophy, and significantly increased the proportion of patients with normal bone histology (from 0 patients at baseline to 20 patients after 12 months).[43]

No definite answer can be given to the question of whether cinacalcet has an impact on patient-reported outcome HRQoL. In a combined analysis of data from three similarly designed Phase III RCTs enrolling a total of 1,136 patients (665 cinacalcet, 471 controls), HRQoL improved slightly for the Medical Outcomes Study Short Form 36 physical component-summary score and the specific domains of bodily pain and general health perception.[44] A systematic review about the effect of cinacalcet on QoL in patients with end-stage KD (ESKD) and sHPT, including two observational studies and one EVOLVE-based RCT, found no significant change from baseline in HRQoL with cinacalcet treatment.[45] HRQoL is influenced by many factors, and it remains difficult to assess the true and sole benefit of one single intervention. Moreover, most RCTs exploring patient-reported HRQoL as a secondary end point are not adequately powered to detect small or modest differences in this outcome.

Drug adherence with oral cinacalcet

Despite improved control of sHPT using cinacalcet in combination with or without other treatment options for sHPT, one demanding challenge is poor adherence to cinacalcet therapy, which can impair long-term sHPT control. In the literature, nonadherence to cinacalcet varies: 45.6%–71%.[46–48] Gincherman et al investigated the refill-based adherence rate for cinacalcet in 79 hemodialysis patients, and found a 1-year medication-possession rate >80% (indicating consistent medication use) of 29% for cinacalcet.[46] The authors hypothesized that the lower adherence rate with cinacalcet had been the result of the high incidence of gastrointestinal side effects. The most frequent side effects of cinacalcet are gastrointestinal, primarily nausea and vomiting. In an RCT by Block et al, the frequency of nausea was 32% in patients

treated with cinacalcet versus 19% in the placebo group ($P<0.001$).[31] These results were in line with those obtained from an RCT conducted by Lindberg et al (nausea 30% vs 22%).[49] In both trials, vomiting was more common in the cinacalcet arm compared to placebo (30% vs 16% and 23% vs 12%, respectively).[31,49] In observational studies of daily clinical practice, the reported frequency of gastrointestinal side effects with cinacalcet was lower than in RCTs. In the observational ECHO trial conducted in 1,865 dialysis patients receiving cinacalcet, nausea was experienced by 5% and vomiting by 3% of the study cohort.[50] The rate of treatment discontinuation due to these gastrointestinal side effects was <5% in the study by Block et al[31] and 3% in the ECHO trial.[50] Therefore, the high nonadherence to cinacalcet could not be explained only by its side effects.

Economic factors may also contribute to poor cinacalcet adherence. In a retrospective study, Park et al analyzed the data of more than 11,700 Medicare beneficiaries on dialysis in the USA. Only 35% of these patients were adherent to cinacalcet (medication-possession rate ≥80%). Additionally, they observed differences between dialysis-specific medications and non-dialysis-specific medications, with higher adherence and persistence to non-dialysis-specific medications. These differences in adherence may be attributable to different medication costs by therapeutic classes. The costs of dialysis medications were significantly higher compared to non-dialysis-specific medications.[48]

A further possible explanation for high nonadherence to cinacalcet could be the high oral drug load in dialysis patients. Chiu et al found a median daily pill burden of 19 in chronic dialysis patients, and a quarter of them were prescribed more than 25 pills per day. Drugs for the treatment of sHPT accounted for about half the daily pill burden.[51] Since the consequences of nonadherence to medications in the treatment of sHPT are generally not immediately noticed by the patient, one could speculate that this may be a further reason for lower adherence to cinacalcet compared to other medication. Importantly, higher adherence to cinacalcet was associated with inpatient savings of US$4,000–$8,900/patient/year in a retrospective study on 4,923 dialysis patients.[47] Therefore, better adherence may not only influence patients' health but has also high economic impact.

Given the fact that poor long-term adherence to prescribed medication is a common problem in dialysis patients[52,53] and associated with higher morbidity and mortality, as well as increased treatment costs,[54] strategies to improve adherence in dialysis patients are of particular importance. One strategy to decrease nonadherence could be the intravenous application of drugs during or after hemodialysis. Such an approach has become possible with etelcalcetide. The hope to avoid gastrointestinal side-effects and improve drug adherence with intravenous administration during hemodialysis have been drivers in the development of the second-generation calcimimetic etelcalcetide, which is described in detail in the following sections.

Mode of action and preclinical data of etelcalcetide

Etelcalcetide (Parsabiv; Amgen, Thousand Oaks, CA, USA), formerly known as AMG416 or velcalcetide, is a new second-generation calcimimetic that was approved for the treatment of sHPT in adult hemodialysis patients in the EU in November 2016, in Japan in December 2016, and in the US in February 2017. Etelcalcetide is a small peptide containing eight amino acids with a molecular weight of 1,048 Da. It causes long-lasting allosteric activation of the CaSR through the formation of a covalent disulfide bond between the D-cysteine in etelcalcetide and cysteine 482 in the extracellular domain of the CaSR.[55]

Similarly to cinacalcet, etelcalcetide causes rapid and dose-dependent decrease of PTH (maximal reduction within 2 hours in healthy subjects; after approximately 30 minutes in hemodialysis patients), calcium, phosphorus, and FGF23 levels. But in contrast to cinacalcet, etelcalcetide can activate the CaSR even under calcium-free conditions, indicating its additional function as a direct CaSR agonist. However, approximately 30 times as much ligand is required to generate the same magnitude of response as observed in the presence of calcium. The pharmacokinetic profile of etelcalcetide in patients with CKD differs from cinacalcet. Etelcalcetide is almost exclusively cleared by the kidney through glomerular filtration. Therefore, its plasma-elimination half-life significantly increases with declining renal function, with a short effective half-life of 3–5 days in patients with ESKD. A single intravenous dose can lower PTH levels for up to 72 hours in patients on hemodialysis. This longer half-life allows intravenous administration thrice weekly at the end of each hemodialysis session. After administration of a single intravenous dose, regular 4-hour hemodialysis sessions three times a week are responsible for around 60% of its clearance, whereas 3% are eliminated in urine, 6% in feces, and 31% by nonspecific mechanisms. Etelcalcetide is resistant to enzymatic degradation by proteases and does not interact with cytochrome P450. It undergoes biotransformation by disulfide exchange with endogenous thiols, resulting in the reversible formation of albumin–peptide conjugates.

Table 1 Differences between first- and second-generation calcimimetics

	Cinacalcet	Etelcalcetide
Class	First-generation calcimimetic type II Small organic molecule	Second-generation calcimimetic type II Octapeptide
Molecular formula	$C_{22}H_{23}F_3N$	$C_{38}H_{73}N_{21}O_{10}S_2$
Molecular weight	394 Da	1,048 Da
Mode of action at CaSR	Allosteric modulator	Allosteric modulator and direct agonist
Location of interaction with CaSR	Transmembrane domain	Extracellular domain
Mode of administration	Daily oral	Thrice-weekly intravenously at the end of hemodialysis session

Abbreviation: CaSR, calcium-sensing receptor.

These conjugates are not dialyzable, because of their molecular weight of 67 kDa. In the presence of L-cysteine, reverse disulfide exchange reforms etelcalcetide, the forward reaction forming the conjugate being faster than the reverse reaction.[56] Table 1 provides a short overview of the key differences between first- and second-generation calcimimetics.

In addition to its biochemical effects on mineral and bone metabolism, etelcalcetide has also been shown to reduce parathyroid-cell proliferation and increase expression of the CaSR, VDR, and FGFR1 in parathyroid cells in a rodent uremic model.[57] Despite a similar PTH-lowering effect, etelcalcetide treatment significantly lowered aortic calcium content and prevented medial aortic calcification in uremic rats with sHPT, whereas paricalcitol did not show these beneficial effects.[58] A direct effect on vascular endothelial[59] or smooth-muscle cells[60] expressing the CaSR or an FGF23-dependent pathway could be responsible for these effects. Furthermore, animal experimental data have provided the first evidence that etelcalcetide might be beneficial in the management of renal osteodystrophy. In nephrectomized rats with established sHPT, etelcalcetide attenuated sHPT-associated increase in cortical bone porosity, mineralization defects, and bone-marrow fibrosis and improved bone strength.[61]

Clinical data

The efficacy and safety of etelcalcetide in sHPT treatment in dialysis patients have been investigated in several RCTs.[62–66] In a single-dose crossover Phase II trial by Martin et al,[66] the efficacy of etelcalcetide was investigated in 28 hemodialysis patients suffering from sHPT. Patients were enrolled in one of five cohorts and received either a single intravenous dose of etelcalcetide (5, 10, 20, 40, 60 mg) or placebo. Treatment with etelcalcetide was well tolerated and resulted in dose-dependent decreases in PTH levels. In addition, administration of etelcalcetide at doses ≥10 mg was associated with dose-dependent reductions in FGF23 and serum-calcium concentrations and resulted in diminished interdialytic increase in serum phosphorus compared to placebo.

In 2015, Bell et al[62] reported on results of a multicenter, double-blind, randomized, placebo-controlled, dose-escalating trial. This Phase II study included 78 hemodialysis patients with baseline PTH levels ≥350 pg/mL. Subjects were divided into three cohorts: patients in cohort 1 received either 5 mg etelcalcetide or placebo thrice weekly after each hemodialysis session for 2 weeks, and those in cohorts 2 and 3 were treated with 10 mg or 5 mg etelcalcetide or placebo at the end of each dialysis for 4 weeks. The primary end point for cohorts 2 and 3 was defined as mean percentage change in PTH levels from baseline. After 4 weeks, PTH had decreased significantly by 49.4% with 10 mg of etelcalcetide and by 33.0% with 5 mg. The proportion of patients with ≥30% PTH reduction was 76.2% in etelcalcetide-treated patients vs 9.5% in the placebo group ($P<0.0001$). Treatment with etelcalcetide was also associated with a decrease in serum-calcium and FGF23 levels. Approximately 40% of study participants reported at least one treatment-emergent adverse event (TEAE), but the incidence of TEAEs was not dose-dependent and no patient discontinued the study due to a TEAE.

Block et al[64] conducted two parallel, Phase III, double-blind, RCTs of 1,023 dialysis patients from six nations with moderate–severe sHPT (PTH >400 pg/mL). Patients received either etelcalcetide or placebo after each hemodialysis session for 26 weeks in addition to conventional sHPT therapy. The primary end point was the proportion of patients attaining >30% PTH reduction from baseline during the efficacy-assessment phase from week 20 to 27. The starting dose of etelcalcetide was 5 mg, and treatment was adjusted according to PTH and calcium levels to a maximum dose of 15 mg. In the first trial, 508 patients were enrolled, of whom 254 received etelcalcetide (median per-session dose 7.1 mg). The second trial included 515 patients, with 255 randomized to the study drug (median per-session dose 5.0 mg). In both trials, patients receiving etelcalcetide were significantly more likely to achieve the primary efficacy end point: 74.0% vs 8.3% ($P<0.001$) and 75.3% vs 9.6% ($P<0.001$), respectively. In addition, more patients in the etelcalcetide group achieved a mean PTH level ≤300 pg/mL (49.6% vs 5.1% and 53.3% vs 4.6%, $P<0.001$). Compared to placebo,

serum-calcium levels decreased significantly in the etelcalcetide group, but the proportion of patients receiving calcium supplements, calcium-containing phosphate binders, or VDRAs increased. Dialysate-calcium concentrations were found to be higher in etelcalcetide-treated patients. The calcium-lowering effect of the calcimimetic was observed early, with the lowest calcium concentrations found during treatment weeks 10–12. Furthermore, etelcalcetide decreased serum-phosphorus and FGF23 levels. In terms of adverse events, diarrhea (10.7% vs 8.6%), nausea (10.7% vs 6.2%), vomiting (8.9% vs 5.1%), and symptomatic reduction in corrected serum calcium <8.3 mg/dL (7.0% vs 0.2%) were more common in patients with etelcalcetide.

The results of a further Phase III trial investigating the efficacy and safety of etelcalcetide were recently reported by Fukagawa et al.[65] This multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted in 155 Japanese hemodialysis patients with PTH levels ≥300 pg/mL. Patients randomized to the study drug received etelcalcetide thrice weekly after each hemodialysis. The starting dose was 5 mg, and according to PTH and calcium levels, the dose was subsequently adjusted to single doses of 2.5–15 mg at 4-week intervals for 12 weeks. The mean dose of etelcalcetide was 7.8 mg at the end of the study. The primary end point was the proportion of patients with PTH levels of 60–240 pg/mL on day 85, the PTH target range recommended by the Japanese Society for Dialysis Therapy. Compared to placebo, patients randomized to etelcalcetide more often achieved this primary end point (59.0% vs 1.3%). With etelcalcetide, a higher proportion of patients achieved ≥30% reduction in PTH from baseline (76.9% vs 5.2%). In addition, treatment with etelcalcetide was associated with a decrease in serum calcium, phosphorus and FGF23. Drug-related AEs were reported in 19.2% of patients receiving etelcalcetide versus 3.9% in the placebo group.

In a head-to-head Phase III study, Block et al[63] investigated the efficacy and safety of etelcalcetide versus cinacalcet in 683 hemodialysis patients with moderate–severe sHPT (PTH ≥500 pg/mL). Patients randomized to etelcalcetide (n=340) received the drug thrice weekly intravenously at the end of each hemodialysis session and oral placebo daily for a total duration of 26 weeks. Patients in the control group received daily oral cinacalcet and thrice-weekly intravenous placebo after hemodialysis. The starting dose of etelcalcetide was 5 mg, and cinacalcet was administered with an initial dose of 30 mg. Dose titrations were performed every 4 weeks during the first 4 months (etelcalcetide 2.5–5 mg titration, final dose range 2.5–15 mg; cinacalcet 30 mg titration, final dose range 30–180 mg) with a centrally measured target PTH level of 100–300 pg/mL. The primary end point of this randomized, double-blind, double-dummy trial was noninferiority of etelcalcetide at achieving >30% PTH reduction from baseline during the efficacy-assessment phase (weeks 20–27). Key secondary end points included superiority in attaining biochemical end points (>50% and >30% reduction in PTH) and mean number of weekly days with self-reported nausea and vomiting over the first 8 weeks. The median weekly dose of etelcalcetide was 15.0 mg and the median daily cinacalcet dose 51.4 mg. Etelcalcetide was noninferior to cinacalcet in reducing PTH levels, and demonstrated superiority for several end points. The proportion of patients achieving >30% reduction in PTH was 68.2% in the etelcalcetide group versus 57.7% in the cinacalcet group (P=0.004). Significantly more patients in the etelcalcetide group achieved >50% reduction in PTH levels (52.4% vs 40.2%, P=0.001). Furthermore, the proportion of patients with >30% reduction in FGF23 was higher in the etelcalcetide-treated group (74.4% vs 57.5%, P<0.0001). Compared with cinacalcet, treatment with etelcalcetide was also associated with greater reduction in serum-calcium and phosphorus levels. The use of calcium supplements, calcium-containing phosphate binders, and VDRAs, as well as the proportion of patients treated with a higher dialysate-calcium concentration, increased in both groups. No significant difference was observed in self-reported nausea and vomiting between the etelcalcetide- and cinacalcet-treated group. Therefore, these gastrointestinal side effects seem to be a systemic effect rather than a local class effect of calcimimetics, maybe mediated by an activation of the CaSR in non-parathyroid target organs. The overall safety and tolerability were similar between the two groups (Table 2). As predicted by Phase II trials, application of etelcalcetide was frequently accompanied by reduced serum calcium concentrations (based

Table 2 Incidence of adverse events in head-to-head comparison between cinacalcet and etelcalcetide

	Cinacalcet (n=341)	Etelcalcetide (n=338)
	n (%)	n (%)
Calcium reduction[a]	204 (59.8)	233 (68.9)
Hypocalcemia[b]	8 (2.3)	17 (5.0)
Muscle spasms	20 (5.9)	22 (6.5)
Pain in extremity	14 (4.1)	17 (5.0)
Paresthesia	6 (1.8)	7 (2.1)
Nausea	77 (22.6)	62 (18.3)
Vomiting	47 (13.8)	45 (13.3)
Diarrhea	35 (10.3)	21 (6.2)
Heart failure	2 (0.6)	10 (3.0)
Death	6 (1.8)	9 (2.7)

Notes: [a]Defined as reduction in serum albumin-corrected calcium <8.3 mg/dL that resulted in a medical intervention; [b]defined as symptomatic reduction in serum albumin-corrected calcium <8.3 mg/dL.

Table 3 Summary of controlled etelcalcetide Phase II and III trials

Study	Study design	Country/region	Study population (n)	Study duration	Comparator	Etelcalcetide intervention	Changes in iPTH: results of etelcalcetide vs comparator
Martin et al[66]	Double-blind, randomized placebo-controlled, multicenter	USA	28 (total) 12 (cohort 1–3) 16 (cohort 4–5)	28 days	Placebo	Single dose of study drug Cohorts 1–3: two-period crossover design with 7–14 days interdose interval: cohort 1, 5 mg; cohort 2, 10 mg; cohort 3, 20 mg Cohorts 4 and 5: 1:1 randomization; cohort 4, 40 mg; cohort 5, 60 mg	Mean change from baseline at discharge (~3 days after application): cohort 3, −48.5%; cohort 4, −49.3%; cohort 5, −62.6%
Bell et al[62]	Double-blind, randomized placebo-controlled, multicenter	USA	78	2 weeks (cohort 1), 4 weeks (cohorts 2, 3)	Placebo	Cohort 1: 5 mg thrice weekly Cohort 2: 10 mg thrice weekly Cohort 3: 5 mg thrice weekly	Mean change from baseline to efficacy period: cohort 2, −49.4% ($P<0.05$); cohort 3, −33.0% ($P<0.05$)
Block et al[64]	Two parallel, multicenter, randomized, double-blind, placebo-controlled trials	USA, Canada, Europe, Israel, Russia, Australia	1,023 (trial A 508, trial B 515)	26 weeks	Placebo	Starting dose 5 mg thrice weekly; titration in 2.5 or 5 mg increments at weeks 5, 9, 13, 17; maximum dose 15 mg thrice weekly	Proportion of patients achieving >30% reduction: trial A, 74.0% vs 8.3% ($P<0.001$); trial B, 75.3% vs 9.6% ($P<0.001$)
Block et al[63]	Randomized, double-blind, double-dummy active clinical trial	USA, Canada, Europe, Russia, New Zealand	683	26 weeks	Cinacalcet	Starting dose 5 mg thrice weekly, titration in increments of 2.5 or 5 mg at weeks 5, 9, 13, 17, maximum dose 15 mg Starting dose of oral cinacalcet 30 mg daily, titration in increments of 30 mg at weeks 5, 9, 13, 17, maximum dose 180 mg daily	Proportion of patients achieving >30% reduction: 68.2% vs 57.7% (noninferiority, $P<0.001$; superiority, $P=0.004$)
Fukagawa et al[65]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group	Japan	155	12 weeks	Placebo	Starting dose 5 mg thrice weekly, titration at 4-week intervals, maximum dose 15 mg thrice weekly	Proportion of patients achieving target range of 60–240 pg/mL: 59.0% vs 1.3% ($P<0.001$)

Abbreviation: iPTH, intact parathyroid hormone.

on albumin-corrected total calcium), reflecting asymptomatic hypocalcemia in Phase III trials. Not surprisingly, a reduction in serum calcium <8.3 mg/dL was the most common AE. Overt symptomatic hypocalcemia was found in 6.7%–7.2% of etelcalcetide-treated patients in the placebo-controlled trials (compared to 0%–0.4% of placebo-treated patients) and in 5% of patients in the head-to-head comparison with cinacalcet (2.3%). The clinical significance of calcimimetic-induced hypocalcemia remains unclear, as it is rarely associated with clinical sympoms.[31,50] The 2017 KDIGO CKD-MBD practice guidelines no longer recommend the maintenance of serum calcium concentration within the normal reference range in dialysis patients; rather, it suggests avoiding hypercalcemia and tolerates mild and asymptomatic calcimimetic-associated hypocalcemia to avoid inappropriate calcium loading in these patients.[29] This approach is supported by a very recent post hoc analysis of the EVOLVE trial, which found severe hypocalcemia (total serum calcium <7.5 mg/dL) within the first 16 weeks after the first administered dose in 18.4% of patients in the cinacalcet group versus 4.4% in the placebo group.[67] This event was not dose-dependent, but associated with higher baseline PTH values, reflecting an increased likelihood of developing hypocalcemia with increasing sHPT severity. In the majority of patients, hypocalcemia resolved within 14 days without modification of sHPT treatment (reduction/discontinuation of cinacalcet, initiation/increase of VDRAs, initiation of calcium-containing phosphate binder). Further studies are necessary to determine the effect of etelcalcetide on vascular and skeletal health considering the hypocalcemic effect and associated changes in VDRA therapy or calcium supplementation. Nevertheless, a baseline albumin-corrected serum calcium level ≥8.3 mg/dL, in accordance with the Phase III trials, should be a prerequisite prior to the initiation of etelcalcetide in our opinion.

Cinacalcet should be discontinued for at least 7 days prior to the initiation of the intravenous calcimimetic in patients who switch to etelcalcetide. Table 3 briefly summarizes the key characteristics of published controlled Phase II and III trials of etelcalcetide.

To date, no controlled studies directly comparing etelcalcetide with placebo, cinacalcet, or surgical parathyroidectomy with regard to hard clinical end points, such as mortality, cardiovascular events, fractures and parathyroidectomy in patients with ESKD have been conducted. The same holds true for parathyroidectomy, which has never been compared to calcimimetics in an RCT. This renders cost-effectiveness analyses more difficult. With rising healthcare costs and limited resources, such analyses focusing on economic and clinical value of a specific treatment become more and more important.

Recently, a decision-analysis model was developed to assess the lifetime cost-effectiveness of etelcalcetide versus cinacalcet, excluding dialysis costs.[68] In this model, the long-term efficacy of etelcalcetide was extrapolated from its effect on PTH reduction in three Phase III trials (versus placebo and cinacalcet)[63,64] and from clinical event-rate data from EVOLVE.[41] Compared with cinacalcet, the incremental cost-effectiveness ratio (cost per quality-adjusted life year [QALY]gained) of etelcalcetide was €1,355/QALY assuming the same weekly calcimimetic drug cost, €24,521/QALY assuming 15% higher weekly costs for etelcalcetide, and €47,687/QALY assuming 30% higher weekly costs for etelcalcetide. Definite cost-effectiveness of etelcalcetide may vary from one country to another, dependent on country-specific drug costs, clinical event costs, reimbursement policy, and the willingness-to-pay threshold.

Conclusion

The new second-generation calcimimetic etelcalcetide effectively reduces PTH, phosphorus, calcium, and FGF23 in hemodialysis patients with an acceptable safety profile. Intravenous administration at the end of a hemodialysis session promises better drug adherence, reduces pill burden, and might thus allow improved management of sHPT compared to previous standard care. Enhanced adherence and better control of sHPT could set the stage for a future large RCT to demonstrate that improved biochemical control of mineral metabolism with etelcalcetide translates into affordable cardiovascular and survival benefits and better QoL for hemodialysis patients.

Disclosure

EZ has received speakers' honoraria from Amgen. CF reports no conflicts of interest in this work.

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