НОВЫЕ ВОЗМОЖНОСТИ ЛЕЧЕНИЯ ВТОРИЧНОГО ГИПЕРПАРАТИРЕОЗА У ПАЦИЕНТОВ С ТЕРМИНАЛЬНОЙ СТАДИЕЙ ХРОНИЧЕСКОЙ БОЛЕЗНИ ПОЧЕК, ПОЛУЧАЮЩИХ ЗАМЕСТИТЕЛЬНУЮ ПОЧЕЧНУЮ ТЕРАПИЮ ГЕМОДИАЛИЗОМ

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Обзор литературы посвящен проблеме лечения вторичного гиперпаратиреоза (ВГПТ) у пациентов с терминальной стадией ХБП на гемодиализе. В основе патогенеза ВГПТ лежит депривация D-гормона с запуском патофизиологических механизмов нарушения костного ремоделирования, повышения ФРФ-23, ПТГ, изменениями содержания фосфора и кальция в сыворотке крови, нарушениями в чувствительности и регуляции кальций-чувствительного рецептора (КЧР), что в последующем приводит к значимым изменениям структуры костной ткани и кардиоваскулярным осложнениям. В списке препаратов, применяемых для лечения ВГПТ у диализных больных, значимое место занимают агонисты КЧР, до недавнего времени представленных единственным препаратом для приема внутрь – цинакальцетом с убедительно доказанной эффективностью. В настоящее время в США, Европе и России зарегистрирован новый кальцимиметик для внутривенного введения 3 раза в неделю – этелкальцетид. В обзоре представлены результаты клинических исследований этого препарата, показавшего преимущества в эффективности в сравнении с цинакальцетом и аналогичный профиль по побочным эффектам. Предполагается повышение приверженности к лечению ВГПТ у диализных пациентов за счет снижения кратности введения препарата и возможности его введения в диализных центрах.

КЛЮЧЕВЫЕ СЛОВА: Вторичный гиперпаратиреоз; хроническая болезнь почек; гемодиализ; кальцимиметики; этелкальцетид; цинакальцет;

NOVEL TREATMENT OPTIONS FOR SECONDARY HYPERPARATHYROIDISM IN END-STAGE KIDNEY DISEASE PATIENTS ON HEMODIALYSIS THERAPY

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Pathogenesis of secondary hyperparathyroidism is based on D-hormone deprivation, leading to bone remodeling impairment, increase in FGF-23, PTH levels, changes in blood calcium and phosphorus levels. Taken together with alteration of calcium-sensing receptor (CaSR) sensitivity, these changes result in alteration of bone structure and cardiovascular complications. CaSR agonists are one of the most important medications for treatment of secondary hyperparathyroidism in dialysis patients. Until recently, there was only one CaSR agonist with proven effectiveness – cinacalcet, which is administered per os, daily. Now, a new drug is registered in US, Europe and Russia – etelcalcetide, which is administered intravenously 3 times a week. In this review we focus on results of clinical trials regarding etelcalcetide effectiveness and possible compliance benefits.

KEYWORDS: Secondary hyperparathyroidism; chronic kidney failure; hemodialysis; calcimimetic agents;

INTRODUCTION

Secondary hyperparathyroidism (SHPT) refers to the overproduction of parathyroid hormone (PTH) in response to chronic hypocalcemia. The most severe forms of persistent secondary hyperparathyroidism develop in patients with end-stage renal disease [1].

According to the National Health and Nutrition Examination Survey (NHANES), the prevalence of end-stage renal disease (ESRD) in the US population increased from 0.6 to 1.1% between 1992 and 2002 [2]. The screening tests indicate that the frequency of diagnosing chronic kidney disease (CKD) stages is comparable and independent on the country and population, and CKD affects about 10-17% of the adult population with only 1% diagnosed with the disease. Recent data suggest that SHPT accounts for 20 – 56% of all phosphorus and calcium metabolic disorders in CKD [3].

PATHOGENESIS OF SECONDARY HYPERPARATHYROIDISM IN CHRONIC KIDNEY DISEASE

Functioning nephron loss in chronic renal failure (CRF) results in hyperphosphatemia accompanied by a reciprocal decrease in ionized calcium in the blood. Hypocalcemia and hyperphosphatemia stimulate PTH secretion by the parathyroid glands. Hyperphosphatemia is associated with the onset of skeletal resistance to PTH-induced bone resorption which leads to a bone metabolism disorder and aggravates hypocalcemia. Calcium modulates PTH secretion through calcium-sensing receptors in the parathyroid glands (PTG). The receptors show low levels and decreased sensitivity to extracellular calcium in uremic patients. As CRF progresses, decreased calcitriol synthesis in the kidneys and reduced levels of receptors to calcitriol in the PTG contribute to a lower inhibitory action of calcitriol on PTH synthesis and secretion [4].

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Based on the recent data, renal parenchymal atrophy is not the only cause of reduced calcidol 1-alpha-hydroxylation, since a drastic elevation in fibroblast growth factor-23 (FGF-23) levels, a key regulator in phosphorus homeostasis in the body, has the same action. FGF-23 is secreted by osteocytes (bone cells) and has a pronounced phosphaturic effect due to its suppression of proximal tubule phosphate reabsorption. In addition, FGF-23 significantly inhibits vitamin D activation and converts it into an inactive form by increasing hydroxylation at position 25 [5]. FGF-23 stimulates PTH production and defines a new hormonal cascade that protects the body from hyperphosphatemia in the early stages of CKD [6]. In the pre-dialysis stages, even a significant elevation in FGF-23 levels fails to prevent hyperphosphatemia and SHPT [7]. According to prospective studies an elevation in FGF-23 levels is associated with patient mortality and vascular calcification unrelated to the established risk factors [8]. FGF-23 levels have slowly decreased in dialysis patients who underwent parathyroidectomy, however its normal levels have not been reached. Kidney transplantation has not resulted in a complete return to FGF-23 normal levels and therefore hypophosphatemia cases have been reported. The kidney-produced Klotho protein is an obligate co-receptor for FGF-23 receptor binding and its hormonal action. FGF-23 cofactor-Klotho protein is produced and secreted by the proximal tubular cells and PTG cells. In the experimental study, the transmembrane Klotho protein was known as a co-receptor for FGF-23 involved in regulation of phosphorus, calcium and vitamin D metabolism [5]. Klotho protein expression is reduced in patients with CKD, thus this protein is an apparent renoprotective factor. Since elevated serum levels of FGF-23 in patients with CKD generally precede hyperphosphatemia, resistance to FGF-23 can be one of the earliest manifestations of phosphorus metabolism abnormality in CKD [6]. A decreased Klotho renal expression is considered to induce resistance to FGF-23. Therefore, a low level of Klotho renal expression can predict an unfavorable long-term prognosis in dialysis patients [8]. All the above-mentioned processes lead to SHPT mineral and bone disorders (MBD) which clinically manifest, on the one hand, with various bone lesions followed by osteitis fibrosa, osteomalacia and fractures, on the other hand, with vascular and valvular calcification and consequently, a high cardiovascular morbidity and mortality rates. MBD may be accompanied by myopathy, neuropathy, pruritus, skin manifestations associated with ectopic calcification and calciphylaxis. It also aggravates nephrogenic anemia [9,10].

TREATMENT OF CALCIUM AND PHOSPHORUS METABOLISM DISORDER IN SHPT AND ESRD

Various groups of drugs are currently aimed at hypocalcemia and hyperphosphatemia correction and PTH reduction to ultimately prevent or delay the development of fatal complications. Treatment options include administration of calcium-based and calcium-free phosphate binders; active metabolites of vitamin D and their analogues (calcitriol, alfacalcidol, paricalcitol) generally effective in mild to moderate SHPT, since disease progression and parathyroid gland hyperplasia are found resistant to therapy and associated with aggravated side effects. In 1993, EM Brown et al. made a significant breakthrough in understanding SHPT pathogenesis and then treatment, as they discovered calcium-sensing receptors (CaSR) also located in the PTG. Further comes understanding CaSR function and their abnormal regulation in SHPT, and the development of effective calcimimetics for treatment of SHPT in CKD [11-13].

Depending on the case, several forms of mineral metabolism disorders and abnormal bone remodeling can be defined. Table 1 summarizes the main therapeutic tactics available to the clinician [4,14] to tackle calcium and phosphorus metabolism disorders in SHPT.

Based on the above-mentioned table and cumulative clinical experience, a modern and successful pharmacological treatment for moderate to severe SHPT, except for hypocalcemia-related cases, seems unlikely without CaSR agonist (calcimimetic) cinacalcet (CCT). CaSR is a G-protein receptor expressed on the surface of parathyroid chief cells finely tuned to any slight fluctuations in the blood calcium levels. The main function of parathyroid CaSR consists in regulation of PTH secretion by maintaining mineral homeostasis in the blood and bone tissue. CaSR activation within normal physiological calcium level inhibits PTH production and secretion, while hypocalcemia leads to a decrease in CaSR activity and an elevation in PTH levels. [11]

One of the therapeutic options for SHPT treatment included creation of a drug targeted CaSR activation and reduced PTH production. The first of these drugs is cinacalcet. A candidate drug that acts on CaSR and can either lower the receptor activation threshold in response to extracellular calcium fluctuations, or directly activate the receptor by binding to the extracellular domain. Cinacalcet acts as a CaSR allosteric modulator, potentiates the extracellular calcium effect and lowers the receptor activation threshold that in turn leads to reduced PTH secretion [15].

To date, a great number of studies and clinical experience evidence the efficacy of cinacalcet in reducing PTH, calcium and phosphorus, and even FGF-23 levels, used as surrogate efficacy endpoints for SHPT treatment [16-18]. In large clinical studies, the drug product was shown to reduce the femoral fracture rate by 54% in dialysis patients, to reduce parathyroidectomy by 92% compared with the placebo group and to reduce hospitalizations related to cardiovascular morbidity by 39% [17,19,20].

Nevertheless, some patients develop resistance to cinacalcet therapy especially in severe SHPT. Its use is limited by the following side effects: nausea, vomiting, diarrhea and hypocalcemia. Both careful dose titration and regular once or twice daily dosing compromise significantly patient's compliance and chronic use of the drug product [21,22]. All this has evoked further search for calcimimetics, which are free from the above issues.

Etelcalcetide (ECC) is a new synthetic octapeptide calcimimetic composed of 7 D-amino acids instead of naturally occurring L-amino acids. It is an N-acetyl-D-arginamide disulfide bound to L-cysteine acting as the CaSR activator. Etelcalcetide and cinacalcet interact with CaSR at different sites. Although the acute pharmacodynamic

Table 1. Approaches to control calcium and phosphorus in SHPT

	Phosphorus higher than the desired levels (reference range)	Phosphorus within the desired levels	Phosphorus lower than the desired levels
Independent on calcium levels	Adequate dialysis.#Dietary restriction of phosphorus		Ensure that the patient eats adequately, avoid severe malnutrition
*High serum calcium levels	Withdraw calcium carbonate supplements.#Reduce the dose or withdraw active metabolites of vitamin D / vitamin D analogues (alfacalcidol, calcitriol, paricalcitol).#Prescribe phosphate binders: sevelamer hydrochloride, lanthanum carbonate.#If parathyroid hormone is high (more than 300-500 ng/mL) initiate or increase the dose of cinacalcet hydrochloride	Withdraw calcium carbonate	Reduce the dose or withdraw calcium carbonate supplements, reduce the dose or withdraw calcium-free phosphate binders (sevelamer hydrochloride, lanthanum carbonate).#Reduce the dose or withdraw vitamin D analogues / active metabolites
Normal serum calcium levels	Administration of calcium carbonate with each meal or immediately after meal (not more than 1500 mg).#Initiate or increase the dose of calcium-free phosphate binders: sevelamer hydrochloride, lanthanum carbonate.#Reduce the dose or withdraw analogues (paricalcitol) / active metabolites of vitamin D.#If PTH is high it is necessary to initiate or increase the dose of cinacalcet hydrochloride.		Reduce the dose or withdraw calcium carbonate supplements, calcium-free phosphate binders.#Initiate or increase the dose of active metabolites / analogues of vitamin D
*Low serum calcium levels	Increase the dose or initiate calcium carbonate supplements.#Initiate calcium-free phosphate binders: sevelamer hydrochloride, lanthanum carbonate.#Reduce the dose or withdraw cinacalcet hydrochloride		Reduce the dose or withdraw calcium-free phosphate binders: sevelamer hydrochloride, lanthanum carbonate. Increase the dose of active metabolites of vitamin D and/or add calcium carbonate supplements between meals.#Reduce the dose or withdraw cinacalcet hydrochloride

* High and low serum calcium levels can also be monitored by changing the dialysate composition. In some cases, surgical treatment of secondary hyperparathyroidism may be required if the elevated levels of parathyroid hormone, calcium and phosphorus is refractory to medical treatment.

effect of etelcalcetide is similar to that of cinacalcet, their pharmacokinetic profiles differ [23]. Table 2 summarizes the main properties of cinacalcet [24] and etelcalcetide [23,25,26].

To date, two large international multicenter studies on the efficacy of etelcalcetide in dialysis patients with SHPT and ESRD [9,10] and a Japanese double-blind, placebo-controlled, multicenter study have been conducted [27].

International multicenter registration studies were planned simultaneously and conducted in parallel. The first study was randomized, double-blind and placebo-controlled [10], while the second one was a comparative, randomized, double-blind study of cinacalcet vs etelcalcetide [9].

The study aimed at safety and efficacy evaluation of etelcalcetide in dialysis patients with CKD and uncontrolled SHPT based on the pooled results of two phase 3 parallel studies. All patients from any treatment group received standard treatment for SHPT: phosphate-binding drugs and calcitriol or active forms of vitamin D as prescribed by the investigator.

The study inclusion criteria were the following: adult patients ≥ 18 years old on hemodialysis 3 times a week for ≥ 3 months; PTH > 500 pg/mL and calcium corrected for albumin (cCa) ≥ 8.3 mg/mL measured in two consecutive tests on different days within 2 weeks before randomization; no significant change in the dose of calcium supplements, phosphate-binding drugs, dialysate calcium, or active form of vitamin D within 4 weeks prior to screening.

The placebo-controlled study enrolled 1023 patients of whom 509 patients received etelcalcetide and 514 patients received placebo. Patients were treated with etelcalcetide or placebo + phosphate-binding drugs and calcitriol or active forms of vitamin D as prescribed by the investigators. The initial dose of etelcalcetide or placebo was 5 mg and could be up-titrated by increments of 2.5 or 5 mg after 5, 9, 13 and 17 weeks to a maximum dose of 15 mg. Treatment duration was 27 weeks.

Clinical study endpoints: the primary endpoint was the proportion of patients who achieved > 30% decrease in mean PTH during the evaluation period (weeks 20–27). The secondary endpoint was the proportion of patients with mean PTH ≤ 300 pg/mL; relative decrease in PTH, cCa, phosphate and cCa x phosphate.

The study has shown a > 30% reduction in mean baseline PTH achieved in 74.7% of etelcalcetide patients, and in 8.9% of placebo patients ($P < 0.001$). The secondary endpoint, i.e. PTH decrease to less than 300 ng/mL, was

Table 2. Main properties of cinacalcet and etelcalcetide

Показатель	Цинакальцет	Этелкальцетид
Parameter	Cinacalcet	Etelcalcetide
Class	Calcimimetic	Calcimimetic
Description	Low molecular weight organic compound	Synthetic agonist containing 7 amino acid residues and bound to L-cysteine
Molecular weight	393.9 g/mol	1048.3 g/mol
Mechanism of action	Interacts with the transmembrane segment of CaSR and enhances signal transduction, thereby reducing PTH secretion	Reduces PTH secretion by activating CaSR
Method of administration	Oral daily	Intravenously after every hemodialysis session

achieved in 51.5% of etelcalcetide patients and in only 4.9% of placebo patients (P < 0.001).

Treatment with etelcalcetide was associated with a great decrease in calcium, phosphates and FGF-23, bone alkaline phosphatase (BAP) and C-terminal telopeptide of type 1 collagen (CTx) compared with placebo.

Table 2 presents data on adverse events (AEs).

According to Table 2, AEs were observed in 92% and 80% of patients receiving etelcalcetide and placebo, respectively. Nausea, vomiting, decrease in blood calcium levels and diarrhea were reported the most common AEs in the etelcalcetide group. The symptoms potentially associated with hypocalcemia included muscle cramps, headache and paresthesia. Significant but clinically asymptomatic prolonged QT interval potentially associated with calcium level change was observed in some patients of the etelcalcetide group. Hyperkalemia was more common in the etelcalcetide group; a thorough analysis of the events did not indicate any sound risk factors or associated AEs. The incidence of fatal outcomes, confirmed serious non-fatal cardiovascular AEs and cramps was comparable in both treatment groups.

Thus, the study showed a high efficacy of etelcalcetide in comparison with placebo in dialysis patients with moderate to severe SHPT. The efficacy was assessed according to all primary and secondary endpoints. Etelcalcetide therapy also demonstrated safety and satisfactory tolerance.

Another large multicenter international study [9] was dedicated to comparative efficacy and safety of two calcimimetics: intravenous etelcalcetide administered 3 times a week in hemodialysis and therefore assuming a good compliance, and oral cinacalcet taken daily at home.

- Study hypothesis: the efficacy of etelcalcetide in SHPT is not inferior to cinacalcet in terms of the number of patients with a > 30% decrease in pre-dialysis PTH levels during the period of efficacy evaluation.
- Purpose: to compare the efficacy and safety of oral cinacalcet with intravenous etelcalcetide in dialysis patients with SHPT.
- Study design: a phase 3 randomized, double-blind, double-dummy, active-controlled study.

683 patients were randomized into 2 groups: IV ECC 3 times/week + oral placebo daily (n = 340), the initial dose of etelcalcetide was 5 mg and could be up-titrated after 5, 9, 13 and 17 weeks to a maximum dose of 15 mg; oral CCT daily + IV placebo 3 times/week (n = 343), the initial dose of cinacalcet was 30 mg and could be up-titrated after 5, 9, 13 and 17 weeks to a maximum dose of 180 mg. Treatment duration was 26 weeks (16 weeks for dose titration, and 10 weeks for maintenance dose), and 30 days of follow-up.

Table 3. Safety review of ECC versus placebo

Parameters	Placebo, % (n = 513)	ECC, % (n = 503)
Reduction of serum calcium levels	10.1	63.8
Muscle cramps	6.6	11.5
Diarrhea	8.6	10.7
Nausea	6.2	10.7
Vomiting	5.1	8.9
Headache	6.0	7.6
Symptomatic hypocalcemia	0.2	7.0
Hyperkalemia/increased potassium levels	3.1	4.4
Death	2.9	2.2

Inclusion criteria: serum pre-dialysis PTH levels > 500 pg/mL and cCa ≥ 8.3 mg/dL based on the central laboratory tests at the screening (according to baseline, the actual mean PTH levels were 1092 pg/mL and 1139 pg/mL in the ECC and CCT groups, respectively, and their medians were 900 and 930 pg/mL, respectively); no cinacalcet therapy for 3 months; dialysate calcium concentration ≥ 2.5 μEq/L at least 4 weeks before screening; a stable dose of calcitriol, alfacalcidol or paricalcitol for 4 weeks, calcium supplements for 2 weeks and phosphate-binding drugs for 2 weeks before screening.

Primary endpoint: a > 30% decrease in mean baseline pre-dialysis PTH during the efficacy evaluation period (not less effective).

Main secondary endpoints: a > 50% decrease in mean baseline pre-dialysis PTH during the efficacy evaluation period (advantage); a > 30% decrease in mean baseline pre-dialysis PTH over the same time period (advantage). Average number of days a week with episodes of nausea or vomiting during the first 8 weeks.

Other secondary endpoints: relative change in mean baseline serum pre-dialysis cCa during the efficacy evaluation period; mean serum pre-dialysis P ≤ 4.5 mg/dL achieved. Moderate nausea during the first 8 weeks; an average number of vomiting episodes per week during the first 8 weeks.

Exploratory secondary endpoints: change from baseline serum concentrations of BAP, FGF-23 and CTx in 27 weeks.

Safety endpoints: less than 7.5, 8.0 or 8.3 mg/dL cCa reduction rate at any time point during the study; symptomatic hypocalcemia; nature, frequency, severity and attitude to adverse events (AEs).

The following data were obtained after the study:

- The efficacy of ECC was not inferior to CCT in terms of the patients with PTH declined by more than 30% (77.9% for ECC and 63.9% for CCT).
- The effect of ECC was superior to CCT in terms of the patient proportion who achieved a more than 50% PTH decline during the efficacy evaluation period (52% and 40%, respectively, $p < 0.001$) – Fig. 1.
- Treatment with ECC was associated with a more pronounced cCa decrease compared with CCT: hypocalcemia cases were observed in 68.9% of patients in the ECC group and in 59.8% of patients in the CCT group. In both groups, there was the need for either up-titrating the dose or prescribing calcium-containing drugs and/or active metabolites of vitamin D.

Table 4 summarizes the results for the other endpoints. According to the Table, a more pronounced decrease in calcium levels was observed in the ECC group, and there were no differences in the dynamics of phosphorus levels and nausea and vomiting cases.

This study also evaluated the effect of both drugs on bone markers and FGF-23. A more pronounced decrease in these markers was reported in the ECC group: bone alkaline phosphatase by 29%, C-terminal telopeptide by 36% and FGF-23 by 68%. In the CCT group, these values were 12%, 14% and 41%, respectively. The authors emphasized the FGF-23 decrease. There is evidence that a more marked increase in FGF-23 is associated with left ventricular hypertrophy and heart failure in patients on hemodialysis [28,29]. In the EVOLVE study [30] of the long-term CCT effect in SHPT with evaluation of clinical outcomes, including cardiovascular events, a 30% decrease in FGF-23 by week 20 of treatment was found to be associated with a significant reduction in heart failure and sudden death rates.

On the other hand, the comparative study of ECC and CCT has shown a quantitative disparity concerning heart failure (AE) in the etelcalcetide group (10 [3.0%]) compared with the cinacalcet group (2 [0.6%]). Heart failure was a serious AE in 5 patients (including 3 fatal AEs) from the ECC group and 1 patient (non-fatal AEs) from the CCT group. No cases of fatal or serious AE of heart failure were recorded in patients with hypocalcemia; 2 non-serious AEs in the etelcalcetide group were associated with low cCa values of 8.0 and 8.1 mg/dL. The investigator found no relation of

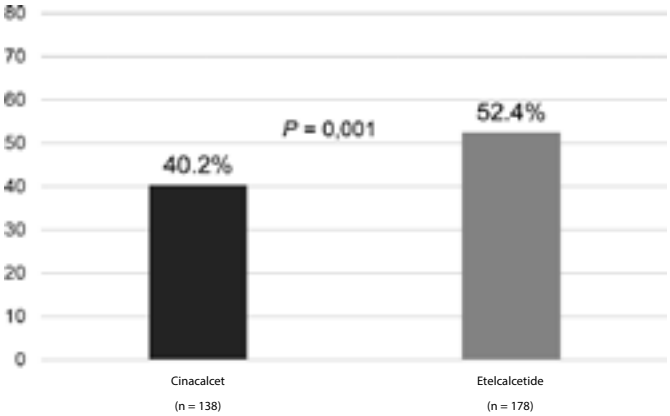

Figure 1. Figure 1. The proportion of patients with a decrease in PTH by more than 50%.

AEs to the study drug.

Thus, a comparative study on the efficacy and safety of ECC and CCT in SHPT has the following conclusions:

- Etelcalcetide showed a > 50% and > 30% decrease in PTH levels in a larger number of patients compared with cinacalcet, although the incidence of nausea and vomiting did not differ between the treatment groups.
- There was a quantitative disparity concerning AE of heart failure, however its causal relation to etelcalcetide has not been established.
- Hypocalcemia was more common in the etelcalcetide group.
- Intravenous administration of etelcalcetide is more effective than oral cinacalcet for SHPT treatment in dialysis patients.
- Increased efficacy of therapy apparently resulted from better adherence to the treatment due to less frequent dosing and method of administration of ECC in comparison with CCT.

The limitations of this study should be noted: it was conducted over a short period (26 weeks); efficacy was evaluated by surrogate criteria instead of final clinical outcomes; limited dialysis population regarding dialysis duration (on average 4 years) and age (mean age 55 years).

Nevertheless, intravenous method of ECC administration 3 times a week during dialysis is very important. A number of studies have demonstrated that dialysis patients are poorly compliant to the diet, fluid intake and daily administration of oral medications, which is potentially related to necessary administration of multiple oral tablets including antihypertensives, cholesterol-lowering drugs, vitamin D and calcium supplements, sevelamer, and finally, CCT. Each tablet formulation can cause some

Table 4. Results for other secondary endpoints

Parameters	Cinacalcet (n = 343) %	Etelcalcetide (n = 340) %	Nominal p-value
Relative change in mean baseline cCa concentration during the efficacy evaluation period, mean value (SE)	–6.28 (0.44)	–9.83 (0.49)	< 0.001
The proportion of patients with mean concentration of P ≤ 4.5 mg/dL during the efficacy evaluation period ,%	29.2	32.1	0.41
Moderate nausea during the first 8 weeks, adjusted mean (SE)	0.48 (0.06)	0.45 (0.06)	0.71
Mean number of vomiting episodes per week for the first 8 weeks, adjusted mean (SE)	0.1 (0.02)	0.2 (0.02)	0.26

adverse events, and their combination is fraught with a higher incidence of gastrointestinal complications [31]. The study on adherence of dialysis patients with SHPT to CCT administration has shown (totally 4923 patients enrolled) that after 12-month follow-up, only 28% of patients were fully compliant and continued treatment for a long time, 46% of patients stopped treatment and 23% were partially adhered to it. Better adherence to treatment was associated with significantly lower annual medical expenses for hospitalized patients ($ 8899 vs. $ 5858) [32].

CONCLUSION

Treatment of SHPT in ESRD is a serious issue, especially in severe SHPT. This is associated with multicomponent therapy, frequent development of side effects and drug therapy resistance. An important pathophysiological pathway in the complex treatment of SHPT is the use of CaSR agonists, calcimimetics. The development of intravenous calcimimetics represents a new stage in improving the treatment of SHPT and its efficacy.

The results from the published studies attest to a higher efficacy of etelcalcetide compared to cinacalcet. In addition, the posology of etelcalcetide and possible administration in the dialysis site can guarantee 100% compliance of patients and reduce limitations of drug administration.

Undoubtedly, further clinical studies on better biochemical parameters influencing clinical outcomes are required [33]. The questions are whether etelcalcetide can increase the life expectancy of patients and what are its effects on their quality of life; and whether there are any drug combinations that can increase etelcalcetide efficacy.

ADDITIONAL INFORMATION

Conflict of interests. Authors declare no explicit and potential conflicts of interests associated with the publication of this article.

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