Current therapeutic options for the treatment of secondary hyperparathyroidism in end-stage renal disease patients treated with hemodialysis: a 12-month comparative study

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A – research concept and design, B – data collection, C – data analysis and interpretation, D – article writing, E – critical review of the article, F – final approval of the article

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The aim *of the study was to investigate the effect of a new calcimimetic, Etelcalcetide, on secondary hyperparathyroidism and its effects in end-stage renal disease (ESRD) patients treated with hemodialysis (HD) compared with hemodialysis (HD) patients not treated with calcimimetics.*

Materials and methods. *The cohort study included 203 ESRD patients with secondary hyperparathyroidism (SHPT) who received HD treatment. Total number patients were randomly to two groups. The main group (n=71) included HD patients treated by new calcimimetic Etelcalcetide. The historical group (n=132) was evaluated retrospectively and included patients who had SHPT but did not receive calcimimetic treatment. Serum levels of phosphorus, calcium and parathyroid hormone were compared for 12 months. The primary endpoint of the study was death from any cause, surrogates – cases of fractures, parathyroidectomy, death from cardiovascular (CV) events.*

Results. *The dose of Etelcalcetide changed monthly and averaged 8.58±1.79 mg. The dynamics of parathormone (PTH) indicators showed that the decrease in PTH levels by 30% from basal occurred after 3 months of treatment in 39 (54.9%) and 12 (9.1%) patients of the main group and historical group, respectively (p<0.0001). At the end of the study, the target PTH level reached in 52 (73.2%) patients in the main group and only 14 (10.6%) in the comparison group (p<0.0001). In addition to the decrease in serum PTH content, in the main group of patients, there was also a decrease in serum calcium and phosphorus levels. During the time to be analyzed, 36 deaths were reported, 61.1% of which were fatal CV events. The proportion of CV events in the mortality structure is more than 70% higher in the historical group than in the group of patients treated with Etelcalcetide, and is 69,2% vs 40,0%, respectively. The frequency of fractures is almost three times higher in the historical than in the main group of patients. The proportion of patients who required parathyroidectomy was significantly more than three times higher in the historical group than in the main group (p<0,05).*

Conclusion. *In a prospective study, we demonstrated the high efficacy of Etelcalcetide in the treatment of SHPT in hemodialysis patients. Treatment of SHPT with the inclusion of Etelcalcetide is accompanied by improved clinical outcomes such as the incidence of bone fractures, cardiovascular morbidity and mortality.*

Key words: *chronic kidney disease, mineral and bone disorders (CKD-MBD), Etelcalcetide, treatment*

Pol Med J, 2022; L (299); 294–298

Aktualne opcje terapeutyczne leczenia wtórnej nadczynności przytarczyc u chorych ze schyłkową niewydolnością nerek leczonych hemodializą: 12-miesięczne badanie porównawcze

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Celem *pracy było zbadanie wpływu nowego kalcymimetyku, etelkalcetydu, na wtórną nadczynność przytarczyc i jego skutków u chorych ze schyłkową niewydolnością nerek (ESRD) leczonych hemodializą (HD) w porównaniu do chorych hemodializowanych (HD) nieleczonych kalcymimetykami.*

Materiały i metody*. Badanie kohortowe obejmowało 203 chorych z ESRD z wtórną nadczynnością przytarczyc (SHPT), którzy otrzymali leczenie HD. Całkowita liczba chorych została losowo podzielona na dwie grupy. Główną grupę (n=71) stanowili chorzy HD leczeni nowym kalcymimetykiem – etelkalcetydem. Grupa historyczna (n=132) została oceniona retrospektywnie i obejmowała chorych, którzy przeszli SHPT, ale nie otrzymali leczenia kalcymimetykiem. Porównywano stężenia fosforu, wapnia i parathormonu w surowicy przez 12 miesięcy. Pierwszorzędowym punktem końcowym badania był zgon z jakiejkolwiek przyczyny, zastępczymi – przypadki złamań, wycięcie przytarczyc, zgon z powodu zdarzeń sercowo-naczyniowych (CV).*

Wyniki. *Dawka etelkalcetydu zmieniała się co miesiąc i wynosiła średnio 8,58±1,79 mg. Dynamika wskaźników parathormonu (PTH) wykazała, że zmniejszenie stężenia PTH o 30% od wartości bazowej wystąpił po 3 miesiącach leczenia u 39 (54,9%) i 12 (9,1%) chorych odpowiednio z grupy głównej i historycznej (p <0,0001). Na koniec badania docelowe stężenie PTH osiągnęło 52 (73,2%) chorych w grupie głównej i tylko 14 (10,6%) w grupie porównawczej (p<0,0001). Oprócz obniżenia zawartości PTH w surowicy w głównej grupie chorych nastąpiło również zmniejszenie stężenia wapnia i fosforu w surowicy. W analizowanym okresie zgłoszono 36 zgonów, z których 61,1% stanowiły śmiertelne zdarzenia sercowo-naczyniowe. Odsetek zdarzeń sercowo-naczyniowych w strukturze śmiertelności jest o ponad 70% wyższy w grupie historycznej niż w grupie chorych leczonych etelkalcetydem i wynosi odpowiednio 69,2% vs 40,0%. Częstość złamań jest prawie trzykrotnie wyższa w grupie historycznej niż w głównej grupie chorych. Odsetek chorych wymagających paratyroidektomii był istotnie ponad trzykrotnie wyższy w grupie historycznej niż w grupie głównej (p<0,05).*

Wniosek. *W prospektywnym badaniu wykazaliśmy wysoką skuteczność etelkalcetydu w leczeniu SHPT u chorych hemodializowanych. Leczeniu SHPT z włączeniem etelkalcetydu towarzyszy poprawa wyników klinicznych, takich jak zmniejszenie częstości złamań kości, chorobowości i śmiertelności sercowo-naczyniowej.*

Słowa kluczowe*: przewlekła choroba nerek, zaburzenia mineralno-kostne (CKD-MBD), etelkalcetyd, leczenie*

Pol Merkur Lekarski, 2022; L (299); 294–298

Chronic kidney disease (CKD) is an important public health problem, as the incidence and prevalence of CKD continue to increase worldwide and today the incidence of CKD reaches 8-16% of the population [7,13]. In almost all patients with CKD develop disorders of calcium-phosphorus metabolism, which leads to a known condition "*Mineral and bone disorders associated with CKD*" (CKD-MBD) [8]. This condition develops due to phosphorus retention in the body due to poor renal excretion, which stimulates fibroblast growth factor 23 (FGF-23) and increased levels of parathyroid gland (PTG) hormone – parathormone (PTH). FGF-23, a peptide hormone produced primarily in osteocytes, is able to reduce phosphate levels in three ways: increase renal excretion, stimulate PTH synthesis, and inhibit calcitriol synthesis. The latter helps to reduce the gastrointestinal absorption of phosphorus and calcium, which leads to hypocalcemia. In turn, low levels of calcitriol and hypocalcemia also stimulate PTH secretion in the parathyroid glands and induce the development of parathyroid hyperplasia. Secondary hyperparathyroidism (SHPT) develops. SHPT is associated with increased bone regeneration, risk of fractures, vascular calcification and, most importantly, the risk of cardiovascular (CV) events and all-cause mortality [10]. Recent observational data suggest that PTH >600 pg/ml is associated with a higher risk of cardiovascular mortality, as well as with all causes of hospitalization [16]. It should be noted that adherence to recommended PTH levels is associated with better treatment outcomes, better bone metabolism, and better survival of hemodialysis (HD) patients [9,11]. Prior to the synthesis of calcimimetics, the classic treatment for SHPT was active vitamin D compounds and phosphate binders (for the binding of phosphates in the gastrointestinal tract) [11].

The key molecular regulators of parathyroid function, including PTH secretion, are the calcium-sensitive receptor (CaSR) on the cell surface and the nuclear vitamin D receptor (VDR). Reducing the concentration of ionized Ca in serum rapidly stimulates the secretion of pre-synthesized PTH. At the same time, prolonged hypocalcemia increases PTH synthesis, causing hyperplasia of PTG cells. VDR activation reduces PTH transcription, whereas a decrease in calcitriol stimulates PTH synthesis. The calcium receptor (CaSR) is needed to maintain systemic calcium homeostasis and is an excellent target for the treatment of bone and mineral disorders. 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), which bind to a site other than physiological ligand and increase the sensitivity of CaSR to ionized calcium, which leads to a decrease in the concentration of calcium for systemic calcium homeostasis (homeostasis is achieved at lower concentrations of ionized calcium) [15]. This reduces the level of PTH in the blood plasma and, consequently, the level of calcium. In addition, there are lower levels of phosphorus and calcium, a phosphorus product that demonstrates the ability of calcimimetics to improve four important biomarkers associated with SHPT (the effect of reducing phosphorus and calcium distinguishes calcimimetics from active vitamin D) [3].

Cinacalcet hydrochloride was the first type 2 calcimimetic approved for clinical use [1]. Cinacalcet treatment effectively reduces PTH, calcium, phosphorus and improves the biochemical control of CKD-MBD [2]. Etelcalcetide is a new second-generation calcimimetic. A new drug for intravenous administration with a pharmacokinetic profile, which allows you to administer the drug three times a week (during hemodialysis). Etelcalcetide has been developed to improve efficacy and adherence and to reduce gastrointestinal side effects. It has recently been approved in Europe and is seen as an effective way to improve the treatment outcomes of patients with CKD-MBD by optimizing SHPT treatment [4].

Aim of study was to investigate the effect of a new calcimimetic, Etelcalcetide, on secondary hyperparathyroidism and its effects in end-stage renal disease (ESRD) patients treated with hemodialysis (HD) compared with HD patients not treated with calcimimetics.

MATERIAL AND METHODS

The cohort included 203 patients with ESRD and SHPT who received HD treatment at the CNPE Kyiv City Center of Nephrology and Dialysis, which is the clinical base of the SI "Institute of Nephrology NAMS of Ukraine". Out of the total number of patients, 71 patients started treatment with SHPT with the calcimimetic Etelcalcetide and 132 patients started the course of SHPT retrospectively and did not receive calcimimetic therapy. All patients signed an Informed Consent to participate in the study.

The study protocol was approved by the local ethics commission SI Institute of Nephrology NAMS of Ukraine (Protocol, No1 of February 25, 2021). Criteria for inclusion of patients in the study were: age over 18 years, the presence of SHPT with serum PTH concentrations over 600 pg/ml, hemodialysis treatment >3 months, the ability to adequately cooperate in the study. Exclusion criteria were: patient refusal to participate in the study, age <18 years, duration of renal replacement therapy ≤3 months, history of acute cerebral and coronary circulatory disorders, chronic heart failure functional class III-IV (NYHA classification), hemoglobin level <70 g/l, acute infectious processes of any etiology, diagnosed during the last 3 months, cancer, history of kidney transplantation, acute and chronic liver failure, mental disorders, inability to cooperate adequately in the study.

Table 1. Characteristics of patients with ESRD in examined groups
Tabela 1. Charakterystyka chorych na ESRD w badanych grupach

Parameter	Main group (n=71)	Historical group (n=132)	p
Primary cause of ESRD, n/%			
Glomerulonephritis	32 / 45.1	56 / 42.4	0.7119
Diabetes mellitus	23 / 32.4	40 / 30.3	0.7583
Non-glomerular	9 / 12.7	21 / 15.9	0.5411
Other lesions	7 / 9.8	15 / 11.4	0.7272
Demographics			
Age, years (M ± SD)	51.2±10.1	50,6±9.4	0.6731
Men (n/%)	41 / 57.7	72 / 54.5	0.6624
Dialysis-associated indicators			
Duration of HD treatment, months (M ± SD)	21.3±6.7	19,3±7.2	0.0546
Anury, n/%	65 / 91.5%	117 / 88.6%	0.5194
eKt/V (M ± SD)	1.38 ± 0.11	1,35 ± 0.14	0.1194
Patients with eKt/V >1,2, n/%	70 / 98.6%	132 / 100%	0.1740

At the first stage of the study, all patients who started treatment with Etelcalcetide and formed the main group, when included in the study, conducted a laboratory examination to determine serum levels of calcium, phosphorus and parathyroid hormone. In addition, at this stage of the work, based on a retrospective analysis of medical records of dialysis patients, data were obtained on indicators that reflect the monthly course of SHPT in 132 HD patients who made up the historical group (comparison group). At the second stage, prospective monthly observation of patients of the main group was carried out, which included determination of biochemical parameters of mineral metabolism (calcium, phosphorus, parathyroid hormone), assessment of the dynamics of their changes and clinical observation. In the groups to be analyzed, a comparison of laboratory parameters reflecting the course of SHPT and endpoints was performed. Serum levels of phosphorus, calcium and parathyroid hormone were compared for 12 months. The primary endpoint of the study was death from any cause, surrogates – cases of fractures, parathyroidectomy, death from CV events. In the comparison groups there was no significant difference in age, sex, nosology of CKD, duration and adequacy of HD, residual renal function (Tab. 1).

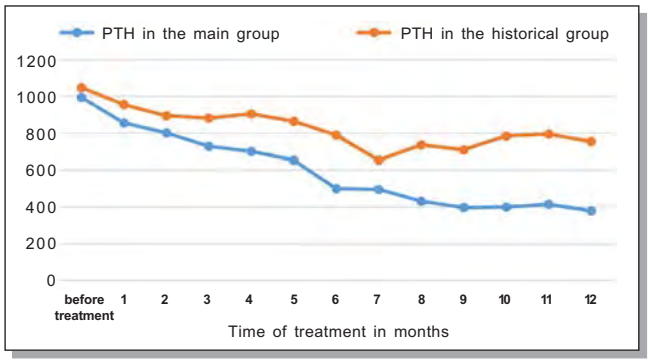

Figure 1. Dynamics of PTH in the main and historical groups
Rycina 1. Dynamika PPK w grupie głównej i historycznej

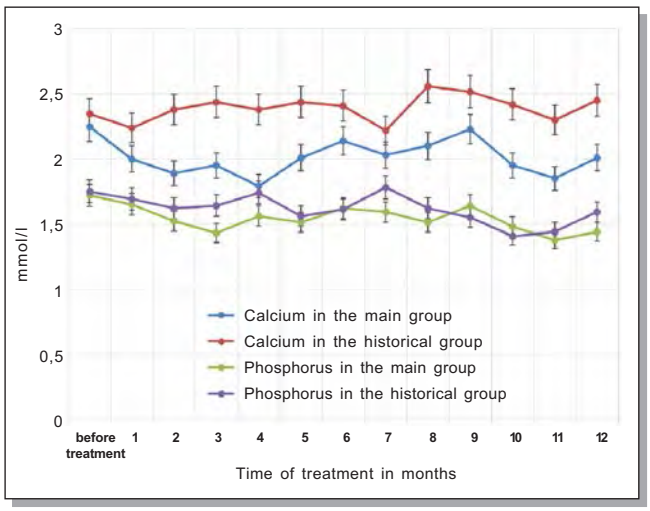

Figure 2. Dynamics of calcium and phosphorus levels during 12 months
Rycina 2. Dynamika stężeń wapnia i fosforu w ciągu 12 miesięcy

Baseline demographic characteristics (age, sex) and clinical data related to CKD (nosological basis, history of dialysis, adequacy of dialysis (eKt/V)) were collected during the inclusion of patients in the study. Venous blood samples were collected on an empty stomach to determine biochemical and laboratory parameters (after fasting overnight) before the start of the GD session. Patients in the main group for SHPT correction were administered Etelcalcetide intravenously at the end of the hemodialysis session. The dosage of the drug was changed according to the manufacturer's instructions. The starting point of observation in patients of the main group was the date of signing the informed consent.

Statistical processing and mathematical analysis of the results of the study was carried out by calculating the relative and average values, the criteria of their reliability. Determined the mean (M), standard deviation (SD). Significance of differences was assessed according to the generally accepted in Student's variation statistics, χ^2. The difference was considered significant at a significance level of $p<0.05$. All obtained digital data were processed using modern methods of variation statistics using the statistical software package STATISTIKA for Windows 10.0.

RESULTS

The dynamics of PTH in the main and historical group is shown in fig. 1.

Decrease in PTH level by 30% from basal was registered after 3 months of treatment in 39 (54.9%) and 12 (9.1%) patients of the main group and historical group, respectively ($p<0.0001$). After reaching the level of PTH 500 pg/ml – the dose of Etelcalcetide was not increased. PTH levels <500 pg/ml were reached in 44 (61.9%) patients at 5-6 months of treatment (20-24 weeks). After reaching the level of PTH 400 pg/ml – switched to a maintenance dose of Etelcalcetide – 2.5-5 mg. The dose of Etelcalcetide changed monthly and averaged 8.58±1.79 mg. At the end of the study, the target PTH level reached 52 (73.2%) patients in the main group and only 14 (10.6%) in the comparison group ($p<0.0001$).

It should be noted that in addition to reducing the serum content of parathyroid hormone, in the main group of patients, there was also a decrease in serum calcium and phosphorus levels (fig. 2).

The total follow-up was 65.76 and 112.22 patient-years in the main and historical groups, respectively. Analysis of the endpoints of the study revealed significant differences in the comparison groups (tab. 2).

During the time to be analyzed, 36 deaths were reported. The analysis, depending on the cause, shows the dominance of CV events, which in total caused 61.1% of fatal cases. At the same time, the share of CV events in the mortality structure of patients in the historical group is more than 70% higher than in the group of patients treated with Etelcalcetide in SHPT, and is 69.2% vs 40.0%, respectively.

Table 2. Clinical outcomes reported within 12 months in patients with ESRD depending on SHPT treatment tactics
Tabela 2. Wyniki kliniczne zgłaszane w ciągu 12 miesięcy u chorych na ESRD w zależności od taktyki leczenia SHPT

Clinical cases	Groups of patients				P_1	P_2
	Main group (n=71)		Historical group (n=132)			
	n / %	Level at 100 p/y	n / %	Level at 100 p/y		
Cases of death	10 / 14.1	15.21	26/ 19.7	23.2	0.3204	0.2541
CV death	4 / 5.6	6.1	18/ 13.6	16.0	0.0807	0.0682
Bone fractures	2 / 2.8	3.0	11 / 8.3	9.8	0.1271	0.1072
Parathyroidectomy	3 / 4.2	4.6	17/ 12.8	15.1	0.0498	0.0420

Notes: P_1 – statistical differences in the proportion of cases; P_2 – statistical differences of cases per 100 p/y

Similar data were obtained in the analysis of the proportion of bone fractures and parathyroidectomies in the comparison groups. Namely, the frequency of fractures is almost three times higher in the historical than in the main group of patients. The proportion of patients who required parathyroidectomy was significantly more than three times higher in the historical group than in the main group ($p<0.05$).

DISCUSSION

The presented work was conducted in Ukraine for the first time. Continuous improvement of nephroprotective strategy and methods of dialysis therapy has significantly improved the prognosis in CKD. However, the progression of complications of CKD – hypertension and related cardiovascular disease, anemia, MBD – impairs the quality of life and survival of patients [12,14]. MBD is common in patients with chronic kidney disease (CKD) and leads to a variety of clinical manifestations, including bone pain and fractures, which significantly affect medical and social rehabilitation, quality of life and survival of patients [5]. MBD often develops in patients with secondary hyperparathyroidism. Elevated parathyroid hormone levels are also associated with adverse clinical outcomes in hemodialysis patients. After the introduction of practical recommendations that provide higher levels of PTH than previously recommended, the situation has changed for the better. In the DOOPS study [16], in a large international sample of hemodialysis patients, PTH levels increased and SHPT treatment changed over time. Very low and very high levels of PTH have been associated with adverse effects. The use of intravenous vitamin D analogues and calcimimetics has increased, and parathyroidectomy has declined over time in all regions of the world. Etelcalcetide ("Parsabiv", "Amgen, Thousand Oaks", CA, USA), formerly known as AMG416 or velcalcetide, is a new second-generation calcimimetic approved for the treatment of SHPT in adult patients receiving D, in November 2016 in European countries, in December 2016 – in Japan and in February 2017 – in the United States. Etelcalcetide is a small peptide containing 8 amino acids with a molecular weight of 1,048. The protein leads to long-term allosteric activation of CaSR by forming covalent disulfide bonds between the D-cysteine of Etelcalcetide and cysteine 482 of the extracellular domain of CaSR [1]. We studied the effectiveness of Etelcalcetide in a prospective 12-month study. We have found that Etelcalcetide is an effective drug in the treatment of SHPT in patients with ESRD treated with hemodialysis. Decrease in PTH level by 30% from basal was registered after 3 months of treatment in 39 (54.9%). At the end of the study, the target PTH level was reached by 52 (73.2%) patients of the main group and only 14 (10.6%) of the comparison group ($p<0.0001$).

Our data resonate with other studies, such as *G. Bell et al.* [2] in the study of different doses of Etelcalcetide reported that all patients receiving Etelcalcetide, after 4 weeks, a significant reduction in PTH levels from baseline: 49.4% – at 10 mg and 33.0% – at a dose of 5 mg. Decrease in PTH level by 30% and more from basal was registered in 76.2% of cases with the use of Etelcalcetide, compared with placebo – 9.5% ($p<0.0001$). It should be noted that our study was longer (12 months compared with the 4-week study of *G. Bell et al*., and patients included in our study had more severe SHPT with a PTH level > 600 pg/ml, against PTH >350 pg/ml in a study by *G. Bell et al*.), but the positive results achieved in the treatment of SHPT were similar. In addition, we found a lower number of UP, namely in 23% of patients, taking into account that, unlike other studies – the concentration of calcium in dialysate in our patients did not change.

In studies by *G.A. Block et al*. criteria for inclusion in the study of dialysis patients with SHPT was a PTH level >400 pg/ml [4]. In addition to traditional SHPT therapy, participants received either Etelcalcetide or placebo for 26 weeks at the end of each HD session. The primary endpoint was the number of patients who achieved a 30% reduction in PTH levels. The initial dose was 5 mg and was adjusted during the study to a maximum of 15 mg according to PTH and Ca levels. It should be noted that the decrease in PTH levels in this study was slower than our results (from 20 to 27 weeks).

M. Fukagawa et al. reported the results of another multicenter randomized, double-blind, placebo-controlled, phase III study in parallel groups [6]. The study was conducted in Japan and included 155 HD of patients with SHPT who had a PTH level >300 pg/ml. The initial dose was 5 mg and could be titrated according to PTH and calcium levels once every 4 weeks, and ranged from 2.5 to 15 mg over 12 weeks. It was shown that patients randomized to the Etelcalcetide group were more likely to reach this primary endpoint (59.0% vs. 1.3%). Also in the Etelcalcetide group, 76.9% of participants achieved a reduction in PTH levels of 30% or more from baseline against 5.2% in the placebo group. Thus, many studies have demonstrated the high efficacy of calcimimetic – Etelcalcetide, all studies have shown a clinical and laboratory effect in most patients.

CONCLUSIONS

In a prospective study, we demonstrated the high efficacy of Etelcalcetide in the treatment of SHPT in hemodialysis patients. After 12 months of treatment, 52 (73.2%) patients reached the target PTH level at the end of the study. In main group also noted a decrease in calcium and phosphorus. The average dose of Etelcalcetide was 8.58±1.79 mg.

Treatment of SHPT with the inclusion of Etelcalcetide is accompanied by improved clinical outcomes and a reduction of more than 2.5 times the CV mortality rate and more than 3 times the incidence of bone fractures and parathyroidectomy. In our opinion, Etelcalcetide represents a significant advance in the treatment of SHPT by better monitoring PTH levels and improving adherence.

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Disclosure: The authors declare no conflict of interest

Received: 20.03.2022
Revised: 04.04.2022
Accepted: 29.04.2022

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