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Safety and efficiency of treatment with cinacalcet of haemodialysed patients with chronic kidney disease and secondary hyperparathyroidism

Bezpieczeństwo i skuteczność leczenia preparatem cynakalcet hemodializowanych chorych na przewlekłą chorobę nerek z wtórną nadczynnością przytarczyc

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Abstract

Introduction: Secondary hyperparathyroidism (sHPT) is a common disorder in haemodialysed patients with chronic kidney disease (CKD). Cinacalcet increases the sensitivity of calcium receptor to the serum calcium, thus reducing serum parathormone (PTH) concentration. The aim of this study was to assess the safety and efficacy of six-month treatment with cinacalcet in haemodialysed CKD patients with sHPT in upper Silesia.

Material and methods: 71 haemodialysed CKD patients with sHPT (PTH > 300 pg/mL) were enrolled in this study. The target was to decrease PTH concentration below 300 pg/mL. PTH (ECL; Roche, Mannheim, Germany), calcium and phosphate concentration was assessed before the first dose of cinacalcet and then after three and six months of treatment, before haemodialysis session. The results are shown as means and 95% confidence index.

Results: 58 patients completed the study. There was a significant decrease in serum PTH concentration from 1,138 pg/mL (931–1,345 pg/mL) to 772 pg/mL (551–992 pg/mL) after three months of treatment ($p < 0.0001$) and to 635 pg/mL (430-839 pg/mL; $p < 0.0001$) after six months. The target PTH concentration was reached in 25% of the patients after three months and in 45% after six months of treatment. Cinacalcet was ineffective in decreasing serum PTH in 16 (28%) patients. There were no significant differences in serum calcium and phosphate concentration during the observation period.

Conclusions:

1. Cinacalcet decreases serum PTH concentration in most haemodialysed CKD patients with sHPT.
2. In 28% of patients, resistance to treatment with cinacalcet was observed. 3. Cinacalcet treatment was well tolerated and caused only a few side effects. **(Endokrynol Pol 2013; 64 (2): 176–181)**

Key words: *cinacalcet, end stage kidney disease, haemodialysis, secondary hyperparathyroidism*

Streszczenie

Wstęp: U hemodializowanych chorych na przewlekłą chorobą nerek (PChN) często występuje wtórna nadczynność przytarczyc. Cynakalcet zwiększa wrażliwość receptora wapniowego na wapń w surowicy krwi i powoduje obniżenie stężenia parathormonu (PTH) w surowicy. Celem badania była ocena bezpieczeństwa i skuteczności sześciomiesięcznego leczenia preparatem cynakalcet hemodializowanych chorych na PChN z sHPT w województwie śląskim.

Materiał i metody: Badaniem objęto 71 hemodializowanych chorych na PChN z sHPT. Celem leczenia było zmniejszenie stężenia PTH w surowicy do wartości poniżej 300 pg/ml. U wszystkich chorych na początku badania, jak również po 3 i 6 miesiącach oznaczono stężenia PTH (ECL; Roche, Mannheim, Niemcy), wapnia i fosforanów w surowicy przed zabiegiem hemodializy. Wyniki przedstawiono jako średnie i 95% przedział ufności.

Wyniki: Badanie ukończyło 58 osób. Leczenie cynakalcetem doprowadziło do znamiennego obniżenia stężenia PTH z 1138 pg/ml (931–1345 pg/ml) na początku badania do 772 pg/ml (551–992 pg/ml) po 3 miesiącach leczenia ($p < 0, 0001$), a po 6 miesiącach do 635 pg/ml (430–839 pg/ml; $p < 0, 0001$). Docelowe stężenie PTH w surowicy osiągnięto u 25% chorych po 3 miesiącach leczenia i u 45% chorych po 6 miesiącach leczenia. U 16 (28%) chorych leczenie cynakalcetem nie spowodowało zmniejszenia stężenia PTH w surowicy. Podczas leczenia preparatem cynakalcet nie obserwowano znamiennych zmian stężenia wapnia i fosforanów w surowicy.

Wnioski:

1. Cynakalcet obniża stężenie PTH w surowicy u większości hemodializowanych chorych na PChN z wtórną nadczynnością przytarczyc.
2. U 28% chorych obserwuje się oporność na leczenie preparatem cynakalcet. 3. Leczenie preparatem cynakalcet było u większości chorych dobrze tolerowane i powodowało niewiele działań niepożądanych. **(Endokrynol Pol 2013; 64 (2): 176–181)**

Słowa kluczowe: *cynakalcet, przewlekła niewydolność nerek, hemodializa, wtórna nadczynność przytarczyc*

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Introduction

Mineral and bone disorders caused by secondary hyperparathyroidism (sHPT) are one of the most common abnormalities in haemodialysed patients with chronic kidney disease (CKD). This results in increased general and cardiovascular mortality in these patients [1–4].

Recently published data from clinical trials suggests that current sHPT pharmacotherapy might not be sufficient to achieve KDIGO Guidelines for Chronic Kidney Disease-Mineral and Bone Disorders (CKD-MBD) [5, 10].

Cinacalcet is a type II calcimimetic [6, 7]. Such compounds bind to the calcium receptor (CaR), leading to its positive allosteric modulation, which results in increased sensitivity of CaR to serum calcium. This leads to decreased parathormone (PTH) production by the parathyroid glands [6, 8, 9]. Cinacalcet is mostly used in stage 5 CKD patients who require renal replacement therapy.

Recent clinical trials suggest that cinacalcet (alone, or in addition to active vitamin D analogues) is effective in treating secondary hyperparathyroidism in haemodialysed CKD patients [11–14]. In the multicentre randomised ACHIEVE trial, the increased effectiveness of cinacalcet was confirmed with small doses of active vitamin D_3 analogues vs. vitamin D alone in sHPT treatment. Also, in the ACHIEVE study such a treatment showed greater reduction in the progression of cardiovascular and heart valve calcification compared to vitamin D alone [15, 16]. In other clinical trials, not only decreased PTH concentration, but also a tendency to decreased parathyroid gland volume, has been described as a consequence of cinacalcet treatment [17–21]. Long term efficiency of cinacalcet has also been confirmed — the target plasma PTH and ionised calcium concentrations, along with the decreased concentration of markers of bone metabolism (alkaline phosphatase, tartrate resistant acid phosphatase, N-terminal type-1 collagen telopeptide), was sustained during a three-year observation in haemodialysed CKD patients [22, 23].

Cinacalcet is also effective in the treatment of primary hyperparathyroidism relapses after parathyroidectomy [24]. Some authors suggest that in selected patients with primary hyperparathyroidism, cinacalcet treatment may be an alternative to surgical treatment [25]. Nevertheless, cinacalcet treatment does not cause permanent parathyroid gland involution, nor permanently suppress PTH secretion. In most cases, sHPT recurrence after cinacalcet withdrawal is observed.

Despite the fact that in Poland cinacalcet has by now been used in sHPT treatment for several years, the clinical experience with this drug seems to be limited.

This paper for the first time describes the results of cinacalcet therapy in a large cohort of haemodialysed patients in Poland.

The aim of this study was to assess the efficacy and safety of six-month cinacalcet treatment in haemodialysed CKD patients with sHPT in the Silesia region of Poland.

Material and methods

71 haemodialysed CKD patients (40 males, 31 females) with sHPT from nine different haemodialysis centres in Silesia were enrolled in this prospective, multicentre study. Mean age of patients was 53.3 ± 14.8 years, median time of renal replacement therapy was 32 months [interquartile range (IQR) — 28 months]. We included adult (> 18 years of age) haemodialysed CKD patients with sHPT (defined as serum PTH concentration > 300 pg/mL) resistant to conventional treatment. Exclusion criteria were: age below 18 years, severe liver insufficiency, oversensitivity to any of the drug compounds, high probability of non-compliance and suspected short life expectancy on renal replacement therapy.

Secondary hyperparathyroidism was treated with cinacalcet. Initial dose was 30 mg once daily and was modified if needed every four weeks depending on the serum intact-PTH concentration. The target was to decrease serum PTH concentration to 150–300 pg/mL. Maximal allowed dose of cinacalcet was 120 mg daily.

In every patient, serum concentration of PTH, calcium and phosphate, as well as the parameters of peripheral blood morphology, were assessed before the first dose of cinacalcet and then after three and six months of treatment. The blood samples were collected before haemodialysis procedure in the middle of the week. After collection, blood samples were centrifuged, serum was aliquoted in 1ml test-tubes and then rapidly frozen at –70°C. Serum PTH concentration was assessed using the electrochemiluminescence (ECL) technique (Roche, Mannheim, Germany).

Statistical analyses were performed using the Statistica 10.0 PL software (StatSoft Polska, Krakow, Poland). Shapiro-Wilk test was used to test the variables distribution, Wilcoxon matched pairs test was used to assess the longitudinal (in-time) changes of variables. Mann-Whitney U-test was used to assess the differences between responders and non-responders and the correlation coefficients were calculated using Spearman's rank correlation.

Results are shown as means with 95% confidence index (CI) in brackets, or as means with standard deviation in brackets, alternatively as median values with interquartile range (IQR) for variables with skewed distribution. Differences between measured parameters were considered significant when $p < 0.05$. The study protocol was accepted by the Medical University of Silesia Ethics Committee (KNW/0022/KB1/56/I/10 —

Table I. *The influence of cinacalcet treatment on serum PTH, calcium and phosphate concentrations in haemodialysed patients with secondary hyperparathyroidism*

Tabela I. *Wpływ leczenia cynakalcetem na stężenie PTH, wapnia i fosforanów w surowicy u hemodializowanych chorych z wtórną nadczynnością przytarczyc*

	Before treatment	After three months of treatment	After six months of treatment	*p* 0–3 months	*p* 3–6 months	*p* 0–6 months
Serum PTH concentration [pg/mL]	1,138 (931–1,345)	772 (551–992)	635 (430–839)	< 0.0001	0.013	< 0.0001
Serum calcium concentration [mmol/L]	2.15 (2.07–2.22)	2.11 (2.04–2.17)	2.08 (2–2.15)	0.23	0.38	0.12
Serum phosphate concentration [mmol/L]	2.02 (1.87–2.18)	1.97 (1.81–2.14)	1.90 (1.74–2.05)	0.27	0.38	0.20

PTH — parathormone

21.09.2010) and all patients gave informed consent to participate in the study.

Results

From 71 enrolled patients, 58 (35 males, 23 females, mean age 53.8 ± 14.9 years) finished the study. Of the 13 patients who were ruled out of the study, four died, two received kidney allograft, two patients discontinued the study because of permanent decrease of serum PTH concentration below 150 pg/mL, two underwent parathyroidectomy, one patient refused to continue the study reporting paresthesia, one patient withdrew consent for the study, and one moved away from Silesia.

The mean doses of cinacalcet after three and six months of treatment were 41.6 ± 16.8mg and 51.3 ± 22.8 mg respectively.

In patients who finished the study, cinacalcet treatment caused a significant decrease of serum PTH from 1,138 pg/mL (931–1,345 pg/mL) at the baseline, to 772 pg/mL (551–992 pg/mL) after three months of treatment ($p < 0.0001$), and to 635 pg/mL (430–839 pg/mL; $p < 0.0001$) after six months of treatment (Table I). The mean decrease of serum PTH concentration after three and six months of treatment was 32.2% and 44.2% respectively.

The target PTH concentration was achieved in 25% of patients after three months of treatment and in 45% of patients after six months of treatment. It is important to stress the heterogeneous response to the cinacalcet treatment (Fig. 1). During the half-year observation in 42 patients (72%), serum PTH concentration decreased, while in 16 cases (28%) there was an increase of serum PTH (n = 6), or serum PTH concentration was stable (n = 10; Δ PTH < 10%). The responders were significantly older than the non-responders [56.5 (52.0–61.1) v. 47.8 (40.4–55.2) years of age, $p = 0.04$]. Moreover, there was a significant positive correlation between the magnitude of serum PTH decrease and patients' age after three and six months of treatment ($R = 0.35$; $p = 0.01$ and $R = 0.28$; $p = 0.03$ respectively). There were no significant differences in the patients' gender, length of renal replacement therapy, nor the serum PTH, calcium and phosphate concentrations at the baseline (Table II).

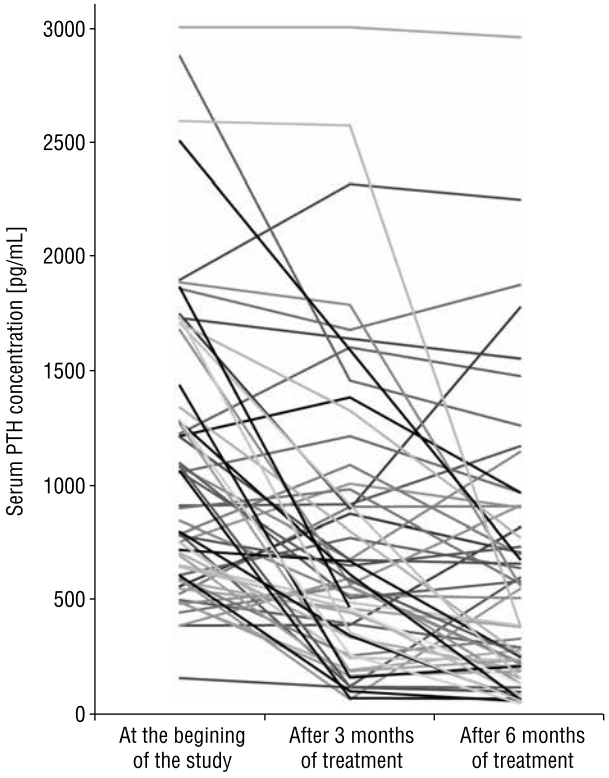

Figure 1. *Serum PTH changes during cinacalcet treatment in individual patients who finished the observation*

Rycina 1. *Zmiany stężenia PTH w surowicy podczas leczenia cynakalcetem u poszczególnych chorych, którzy ukończyli badanie*

Serum calcium and phosphate concentrations were stable during the six months of cinacalcet treatment. Nevertheless, the mean daily dose of active vitamin D_3 analogue (alfacalcidol) was increased from 0.26 μg (0.17–0.36 μg) at the baseline, to 0.39 μg (0.25–0.52 μg);

Table II. *Comparison between patients in whom serum PTH concentration decreased (> 10% PTH decrease), and those in whom serum PTH did not decrease (serum PTH concentration increase or ∆ PTH < 10%)*

Tabela II. *Porównanie chorych, u których doszło do obniżenia stężenia PTH w surowicy (spadek > 10%), z tymi u których stężenie PTH nie obniżyło się (wzrost stężenia PTH w surowicy, lub ∆ PTH < 10%)*

	Patients with serum PTH decrease after treatment (n = 42)	Patients without serum PTH decrease after treatment (n = 16)	p
Mean age (years)	56.5 (52.0–61.1)	47.8 (40.4–55.2)	0.04
Sex — male/female (%)	27m/16f (63%m)	9m/7f (56%m)	0.56
Median of haemodialysis vintage (months)	31 (IQR:42)	32 (IQR:71)	0.33
Mean PTH concentration [pg/mL]	1,075 (878–1,271)	1,058 (771–1,334)	0.82
Mean calcium concentration [mmol/L]	2.14 (2.05–2.22)	2.17 (1.99–2.36)	0.64
Mean phosphate concentration [mmol/L]	1.97 (1.82–2.11)	2.17 (1.72–2.63)	0.50

PTH — parathormone; f — female; m — male

Table III. *Doses of alfacalcidol, intestinal phosphate binders and the number of patients using those drugs during cinacalcet treatment*

Tabela III. *Dawki alfakalcydolu i leków wiążących fosforany w jelicie oraz liczba chorych je stosujących podczas leczenia cynakalcetem*

	Before treatment	After three months of treatment	After six months of treatment	p 0–3 months	p 3–6 months	p 0–6 months
Dose of alfacalcidol [μg/24 h]	0.26 (0.17–0.36)	0.32 (0.2–0.44)	0.39 (0.25–0.52)	0.16	0.16	0.04
Number of patients treated with alfacalcidol	30 (52%)	34 (59%)	40 (69%)			
Dose of $CaCO_3$ [g/24 h]	3.49 (2.68–4.30)	3.84 (2.95–4.72)	3.88 (3.04–4.72)	0.052	0.68	0.07
Number of patients treated with $CaCO_3$	53 (91%)	55 (95%)	54 (93%)			
Dose of aluminium hydroxide [mg/24 h]	385 (170–605)	310 (80–540)	180 (15–350)	0.44	0.11	0.02
Number of patients treated with aluminium hydroxide	12 (21%)	8 (14%)	5 (9%)			

(p = 0.04) after six months, also the percentage of patients treated with alfacalcidol increased (Table III). Moreover, there was a significant (p = 0.02) decrease in the mean dose of aluminium hydroxide (Alusal) from 385 mg/day (170–410 mg/day) at the baseline, to 180 mg/day (15–350 mg/day) after six months of treatment; also the percentage of patients treated with Alusal decreased. Conversely, the mean dose of calcium carbonate and the number of patients treated with this drug remained stable (Table III).

Discussion

Cinacalcet was introduced to the treatment of secondary hyperparathyroidism in 2004. Many observational and randomised clinical trials (RCTs) with cinacalcet have been conducted so far [12–16, 26, 27]. This paper for the first time summarises the experience in cinacalcet treatment in such a large cohort of patients in the Upper Silesia region.

As mentioned above, there was a decrease in serum PTH concentration of 32.2% after three months of treatment and 44.2% after six months of treatment. These results are similar to those published in the most important recent trials concerning cinacalcet (Table IV). Cinacalcet treatment was generally well tolerated.

The main enrollment criterion in our study was serum PTH concentration exceeding 300 pg/mL and the target was to decrease the PTH concentration just below 300 pg/mL; however, the recent KDIGO guidelines suggest maintaining serum PTH concentration in haemodialysed patients in the range between 2–9 times higher than the 'normal' upper limit (i.e. ~150–600 pg/mL). The reason for such a wide accepted range of serum PTH concentration in these patients is that: "there are no RCTs showing that treatment to achieve a specific PTH level results in improved outcomes". In addition, "there are no interventional RCTs that establish a 'cause and effect' relationship between the observed outcomes

Table IV. *Comparison of the results of cinacalcet treatment in haemodialysed CKD patients with secondary hyperparathyroidism in selected clinical trials*

Tabela IV. *Wyniki leczenia cynakalcetem hemodializowanych chorych na PChN z wtórną nadczynnością przytarczyc w wybranych badaniach klinicznych*

Study	Number of patients treated with cinacalcet	Observation length [months]	PTH concentrationat the beginning of the study [pg/mL]	Mean decrease of PTH concentration (%)	Mean dose of cinacalcet [mg]
Lindberg et al. [13]	294	6	526	40	60
OPTIMA [12]	224	6	505	46	56
ECHO [14]	1,865	12	605–954	38–58	44–54
ACHIEVE [15]	87	6	597	46	69
ADVANCE [16]	180	12	417	32	29
IMPACT p.o. [26]	72	6	510	43	32
Frazão J.M. et al. [27]	654	6	418	47	55
Current study	71	6	1,138	44	52

p.o. — the branch of IMPACT study with oral administration of cinacalcet

and the measured biochemical variables" [5]. However, in some patients with secondary hyperparathyroidisms (sHPT) the complex pharmacotherapy consisting of intestinal phosphate binders, vitamin D_3 analogues and calcimimetics may lead to oversuppression of PTH secretion, which significantly increases the danger of development of the adynamic bone disease (in our study, despite the enrollment criterion, this happened in two patients — serum PTH dropped below 150 pg/mL). Adynamic bone disease may lead to increased fragility of the skeleton (the bones are prone to fractures) and accumulation of calcium in the organism. The excess amount of calcium may be responsible for increased calcifications in the soft tissue and vascular wall.

In many of the abovementioned studies, hypocalcaemia and hypophosphatemia related to cinacalcet treatment have been described. In this study, serum calcium and phosphate concentrations remained stable during the whole half-year observation period. It is plausible to assume that this was caused by the fact that the study protocol, contrary to the majority of cinacalcet trials, presumed flexible dosing of the intestinal phosphate binders (e.g. calcium carbonate) and active vitamin D_3 analogues. Probably when a tendency to hypocalcaemia occurred, patients were administered higher (borderline significance — Table II) doses of calcium carbonate and active vitamin D_3 analogues. Lower phosphate concentrations were also the cause of a more liberal manner of treatment with vitamin D_3 analogues (significant dose increase — Table II) and significant aluminium hydroxide dose decrease (Table II).

Similarly, in one of the few studies with flexible doses of intestinal phosphate binders (calcium carbonate, sevelemer, aluminium hydroxide) and vitamin D_3 analogues, there were no significant differences in serum calcium nor phosphate concentration during a three-year observation period. Moreover, similarly to our study, there was a significant decrease in aluminium hydroxide dose in the study population [11].

So far there has been little published data concerning the resistance to cinacalcet treatment in haemodialysed patients with chronic kidney disease. Our study showed that the patients in whom cinacalcet was ineffective were considerably younger. One of the few documented factors potentially associated with cinacalcet resistance is nodular parathyroid hyperplasia (particularly if the volume of one or more hyperplasic glands exceeds 0.5 cm^3 [28, 29]), or there is a multiplicity of enlarged glands [30]. It is difficult to establish how many of our patients had such enlarged parathyroid glands, as the ultrasonographic examination was not a routine procedure in patients enrolled in our study.

The duration of renal replacement therapy also seems to be a factor predicting cinacalcet therapy resistance. Yamamoto et al. [30] showed longer haemodialysis treatment in patients who did not reach target criteria for sHPT management (according to Japanese Society of Nephrology — serum PTH concentration below 180 pg/mL). In our study, such a profound decrease in serum PTH secretion was not desired. Also serum PTH concentration was much higher (498–656.6 pg/mL — Yamamoto et al. [30] *v.* 1,138 pg/mL — this study), which may explain the differences between these studies. Of course, there is a possibility of non-compliance, during a part or the whole study, as a potential factor causing cinacalcet resistance in some of our patients.

Nevertheless, the patients were given their next packet of cinacalcet only after returning an emptied previous packet which, at least up to a point, should diminish the prevalence of such cases.

Conclusions

1. Cinacalcet decreases serum PTH concentration in most haemodialysed CKD patients with secondary hyperparathyroidism.
2. In 28% of patients, resistance to cinacalcet treatment was diagnosed.
3. Cinacalcet treatment was well tolerated and caused only a few side-effects.

References

1. Torres PA, De Broe M. Calcium-sensing receptor, calcimimetics, and cardio-vascular calcifications in chronic kidney disease. Kidney Int 2012; 82: 19–25.
2. Malindretos P, Sarafidis P, Lazaridis A et al. A study of the association of higher parathormone levels with health-related quality of life in hemodialysis patients. Clin Nephrol 2012; 77: 196–203.
3. Young EW, Akiba T, Albert JM et al. Magnitude and impact of abnormal mineral metabolism in hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 2004; 44: 34–38.
4. Block GA. Therapeutic interventions for chronic kidney disease-mineral and bone disorders: focus on mortality. Curr Opin Nephrol Hypertens 2011; 20: 376–381.
5. Moe SM, Drüeke TB, Block GA et al. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl 2009; 113: S1–S130.
6. Nagano N. Pharmacological and clinical properties of calcimimetics: calcium receptor activators that afford an innovative approach to controlling hyperparathyroidism. Pharmacol Ther 2006; 109: 339–365.
7. Koleganova N, Piecha G, Ritz E. Vasculotropic effects of calcimimetics. Curr Opin Nephrol Hypertens 2010; 19: 32–36.
8. Harrington PE, Fotsch C. Calcium sensing receptor activators: calcimimetics. Curr Med Chem, 2007; 14: 3027–3034.
9. Steddon SJ, Cunningham J. Calcimimetics and calcilytics-fooling the calcium receptor. Lancet 2005; 365: 2237–2239.
10. London G, Coyne D, Hruska K et al. The new kidney disease: improving global outcomes (KDIGO) guidelines — expert clinical focus on bone and vascular calcification. Clin Nephrol 2010; 74: 423–432.
11. Lucchi L, Carboni C, Stipo L et al. Early initiation of cinacalcet for the treatment of secondary hyperparathyroidism in hemodialysis patients: a three-year clinical experience. Artif Organs 2011; 35: 1186–1193.
12. Messa P, Macário F, Yaqoob M et al. The OPTIMA study: assessing a new cinacalcet (Sensipar/Mimpara) treatment algorithm for secondary hyperparathyroidism. Clin J Am Soc Nephrol 2008; 3: 36–45.
13. Lindberg JS, Culleton B, Wong G et al. Cinacalcet HCl, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: a randomized, double-blind, multicenter study. J Am Soc Nephrol 2005; 16: 800–807.
14. Ryba M, Fouque D, Dehmel B, Petavy F et al. "Real-World" use of cinacalcet for managing SHPT in different European countries: analysis of data from the ECHO observational study. Clin Nephrol 2010; 74: 198–208.
15. Fishbane S, Shapiro WB, Corry DB et al. Cinacalcet HCl and concurrent low-dose vitamin D improves treatment of secondary hyperparathyroidism in dialysis patients compared with vitamin D alone: the ACHIEVE study results. Clin J Am Soc Nephrol 2008; 3: 1718–1725
16. Raggi P, Chertow GM, Torres PU et al. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. Nephrol Dial Transplant 2011; 26: 1327–1339.
17. Meola M, Petrucci I, Barsotti G. Long-term treatment with cinacalcet and conventional therapy reduces parathyroid hyperplasia in severe secondary hyperparathyroidism. Nephrol Dial Transplant 2009; 24: 982–989.
18. Ichii M, Ishimura E, Okuno S et al. Decreases in parathyroid gland volume after cinacalcet treatment in hemodialysis patients with secondary hyperparathyroidism. Nephron Clin Pract 2010; 115: 195–202
19. Komaba H, Nakanishi S, Fujimori A et al. Cinacalcet effectively reduces parathyroid hormone secretion and gland volume regardless of pretreatment gland size in patients with secondary hyperparathyroidism. Clin J Am Soc Nephrol 2010; 5: 2305–2314.
20. Miller G, Davis J, Shatzen E et al. Cinacalcet HCl prevents development of parathyroid gland hyperplasia and reverses established parathyroid gland hyperplasia in a rodent model of CKD. Nephrol Dial Transplant 2012; 27: 2198–2205.
21. Komaba H, Fukagawa M. Regression of parathyroid hyperplasia by calcimimetics - fact or illusion? Nephrol Dial Transplant 2009; 24: 707–709.
22. Sprague SM, Evenepoel P, Curzi MP et al. Simultaneous control of PTH and CaxP is sustained over three years of treatment with cinacalcet HCl. Clin J Am Soc Nephrol 2009; 4: 1465–1476.
23. Shigematsu T, Akizawa T, Uchida E et al. Long-term cinacalcet HCl treatment improved bone metabolism in Japanese hemodialysis patients with secondary hyperparathyroidism Am J Nephrol 2009; 29: 230–236.
24. Lomonte C, Antonelli M, Losurdo N et al. Cinacalcet is effective in relapses of secondary hyperparathyroidism after parathyroidectomy. Nephrol Dial Transplant 2007; 22: 2056–2062
25. Kakuta T, Tanaka R, Kanai G et al. Can cinacalcet replace parathyroid intervention in severe secondary hyperparathyroidism? Ther Apher Dial 2009; 13: 20–27.
26. Ketteler M, Martin KJ, Wolf M et al. Paricalcitol versus cinacalcet plus low-dose vitamin D therapy for the treatment of secondary hyperparathyroidism in patients receiving haemodialysis: results of the IMPACT SHPT study. Nephrol Dial Transplant 2012; 27: 3270–3278.
27. Frazão JM, Messa P, Mellotte GJ et al. Cinacalcet reduces plasma intact parathyroid hormone, serum phosphate and calcium levels in patients with secondary hyperparathyroidism irrespective of its severity. Clin Nephrol 2011; 76: 233–243.
28. Tanaka M, Nakanishi S, Komaba H et al. Association between long-term efficacy of cinacalcet and parathyroid gland volume in haemodialysis patients with secondary hyperparathyroidism. NDT Plus 2008; (Suppl. 3): iii49–iii53.
29. Hirai T, Nakashima A, Takasugi N et al. Association of nodularhyperplasia with resistance to cinacalcet therapy for secondary hyperparathyroidism in hemodialysis patients. Ther Apher Dial 2010; 14: 577–582.
30. Yamamoto M, Ogata H, Mizobuchi M et al. Number of enlarged parathyroid glands might be a predictor of cinacalcet response in advanced secondary hyperparathyroidism Clin Exp Nephrol 2012; 16: 292–299.