Saudi J Kidney Dis Transpl 2016;27(1):15-22

Saudi Journal of Kidney Diseases and Transplantation

Original Article

The Effects of Cinacalcet Treatment on Bone Mineral Metabolism, Anemia Parameters, Left Ventricular Mass Index and Parathyroid Gland Volume in Hemodialysis Patients with Severe Secondary Hyperparathyroidism

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ABSTRACT. The aim of this study was to investigate the effects of cinacalcet therapy on anemia parameters, bone mineral metabolism, left ventricular mass index (LVMI) and parathyroid gland volume in hemodialysis (HD) patients with secondary hyperparathyroidism. Twenty-five HD patients (M/F: 11/14, mean age: 45.2 ± 17.9 years, mean HD duration: 96.4 ± 32.7 months) were included in this prospective pilot study. The indication to start calcimimetic therapy was persistent serum levels of parathyroid hormone (PTH) >1000 pg/mL, refractory to intravenous (i.v.) vitamin D and phosphate-binding therapy. The initial and one-year results of adjusted serum calcium (Ca^{+2}), phosphate (P), Ca × P product, PTH, hemoglobin (Hb) and ferritin levels, transferrin saturation index (TSAT), median weekly erythropoietin (EPO) dose, LVMI, and parathyroid volume by parathyroid ultrasonography were determined. There were no differences between pre- and post-treatment levels of serum Ca^{+2} (P = 0.853), P (P = 0.447), Ca × P product (P = 0.587), PTH (P = 0.273), ferritin (P = 0.153) and TSAT (P = 0.104). After 1 year of calcimimetic therapy, the Hb levels were significantly higher than the initial levels (P = 0.048). The weekly dose of EPO decreased with no statistical significance. The dose of cinacalcet was increased from 32.4 ± 12.0 to 60.0 ± 24.4 mg/day (P = 0.01). There were no differences between the pre- and post-treatment results regarding weekly vitamin D dose, parenteral iron dose, LVMI and parathyroid volume. The results of our study suggest that cinacalcet therapy might have an additional benefit in the control anemia in HD patients.

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Introduction

Secondary hyperparathyroidism (sHPT) is a common complication in patients with chronic kidney disease (CKD). It is associated with increased synthesis and secretion of parathyroid hormone (PTH) along with hyperplasia of the parathyroid glands. Vitamin D deficiency, hyper-

phosphatemia and hypocalcemia play an important role in the etiopathogenesis of sHPT in CKD. Vitamin D compounds and phosphate-binding agents are used commonly to treat sHPT in these patients. Treatment with vitamin D can cause hypercalcemia and hyperphosphatemia, which are associated with increased calcification and also cardiovascular risk.[1]

Parathyroid gland volume plays an essential role in the severity of sHPT and increased PTH secretion. Development of parathyroid hyperplasia is associated with down-regulation of calcium-sensing receptors (CaSR). Both reduction in receptor number and decreased sensitivity to vitamin D are seen. Cinacalcet is a calcimimetic that has a role in the regulation of CaSR existing on the cell surface of parathyroid glands. Cinacalcet increases the sensitivity of CaSR to extracellular calcium and decreases both calcium (Ca^{+2}) and phosphate (P) levels in addition to a reduction of PTH.[2] The combination of cinacalcet and vitamin D treatment has demonstrated a more effective control of serum Ca^{+2}, P, PTH and Ca × P product than monotherapy in CKD patients with sHPT.[3-6]

In addition to the detrimental effects on bone-mineral metabolism, sHPT is also associated with increased cardiovascular mortality and morbidity and reduced response to erythropoietin (EPO) therapy. Uremic toxins such as PTH are proposed to contribute to the anemia by suppressing bone marrow and also by causing left ventricular hypertrophy (LVH).[7-10] The aim of this study is to investigate the effects of cinacalcet therapy on anemia parameters, bone mineral metabolism, left ventricular mass index (LVMI) and parathyroid gland volume in hemodialysis (HD) patients with sHPT.

Materials and Methods

Twenty-five adult patients (11 males and 14 females; mean age 45.2 ± 17.9 years; mean HD duration 96.4 ± 32.7 months) with severe sHPT were included in this study. All the patients were followed-up for >1 year in a three-times-weekly HD program.

Patients having previously known bone marrow disease and active malignancy and having had acute inflammatory disease in the previous one month, having acute blood loss and having iron deficiency anemia and receiving iron therapy (transferrin saturation TSAT <%20, ferritin <100 ng/dL) were excluded.

The indication for cinacalcet therapy was determined based on the mean serum PTH ≥1000 pg/mL, Ca^{+2} ≥8.4 mg/dL and Ca × P product >55 in the last three months before the study, despite management with phosphate binders and i.v. vitamin D. None of the patients had a history of parathyroidectomy.

The cause of end-stage renal disease in the study group was hypertensive nephrosclerosis (seven patients, 28%), chronic pyelonephritis (seven patients, 28%), chronic glomerulonephritis (five patients, 20%) and diabetic nephropathy (three patients, 12%). The cause was unknown in three cases (12%).

All the patients were undergoing bicarbonate-based HD, including 1.25 mg/dL Ca^{+2} three-times weekly with hemophan membrane. Each session was 4–5 h long and the blood flow rates ranged from 300 to 350 mL/min. The mean Kt/V value was 1.59 ± 0.2.

Before and during dialysis treatment, the patients' management protocol included phosphate binder (phosphate binder with or without calcium), active vitamin D (i.v. calcitriol) and EPO (weekly), their doses were retrieved from the HD treatment records.

Cinacalcet treatment was begun in a dose of 30 mg/day to all the patients. Dose titration was made according to the Ca^{+2} and PTH levels. The maximum dose of cinacalcet was 60 mg/day. Dose augmentation was not performed in patients with serum Ca^{+2} ≤8.4 mg/dL.

The Ca^{+2}, P and hemoglobin (Hb) levels were measured once a month. The transferrin saturation (TSAT), ferritin and PTH levels were measured every three-months during the study period.

Serum levels of Ca^{+2} and P were assessed using standard laboratory methods (Roche Hitachi analyzer 902; Roche, Indianapolis, IN, USA). The Hb levels were determined by a

spectrophotometric method (Cell DYN 3700; Abbott, Indianapolis, IN, USA) and the serum PTH levels were determined by an electrochemiluminescence immunoassay (Roche Diagnostics Corporation, Indianapolis, IN, USA). The normal level of PTH was 12–72 pg/mL.

Doses of cinacalcet, EPO, vitamin D and i.v. iron and phosphate binders were adjusted according to the biochemical results. Side-effects occurring during the study period were reported.

LVMI was evaluated by a cardiologist unaware of the patients' clinical status using M mode echo-cardiography at the beginning and in the 12th month of the treatment period. The thickness of the interventricular septum, posterior wall and left ventricular internal diastolic diameter were measured. The LVMI was calculated by dividing the left ventricular mass by the body mass index.[11]

Parathyroid ultrasonography examination was performed by a nuclear medicine specialist before treatment and in the 12th month of treatment with a 7-MHz linear array probe. Image analysis studied its echotexture, configuration and location in relation to the thyroid gland. A relatively hypoechoic or anechoic, homogeneous or heterogeneous ovoid mass adjacent to the thyroid lobes was considered as an abnormal parathyroid gland. Parathyroid gland volume was calculated according to the ellipsoid formula at the start of the study and in the 12th month of treatment as below.

Ellipsoid formula: 4/3 Π × 1/2 anteroposterior diameter × 1/2 latero-lateral diameter × 1/2 craniocaudal diameter.

Statistical Analysis

SPSS for Windows 16 was used for statistical evaluation of the data. Descriptive statistics (number, percentage and mean ± SD) was given as the statistical method. A paired samples *T* test was used for comparing the variables between repeated measurements. P <0.05 was accepted as statistically significant.

Results

Pre-treatment demographic features, laboratory values and treatment information of patients are shown in Table 1.

In the 3rd, 6th and 9th months of cinacalcet treatment, there was a decrease in the serum Ca^{+2} levels while a slight increase was observed in the 12th month. Cinacalcet treatment had no effect on the serum P level (P >0.05). There was a decrease in the serum PTH values and the

Table 1. Pre-treatment demographic, laboratory data and treatment information of patients.

Pre-treatment	**Patient (N = 25)**
Age (years)	45.2 ± 17.9
Sex (M/F)	11/14
Hemodialysis duration (months)	96.4 ± 32.7
Kt/V	1.59 ± 0.2
Basal laboratory values	
Hemoglobin (g/dL)	10.4 ± 1.2
Calcium (mg/dL)	9. 3 ± 0.6
Phosphorus (mg/dL)	6.7 ± 1.5
Ca × P product	62.7 ± 15.6
Parathormone (pg/mL)	1505.6 ± 444.4
Transferrin saturation (%)	29.6 ± 14.8
Ferritin (ng/mL)	1505.6 ± 444.4
Treatments administered	
Not using phosphate binder	1 (4%)
Calcium carbonate ($CaCO_3$)	2 (8%)
Sevelamer	22 (88%)
Intravenous calcitriol	10 (40%)

Table 2. Anemia parameters before treatment and during 1 year of treatment.

	Hb (g/dL)	Ferritin (mg/dL)	TSAT (%)
Basal	10.4 ± 1.2	712.0 ± 320.9	29.6 ± 14.8
3rd month	10.6 ± 1.3	731.1 ± 298.2	28.8 ± 12.6
6th month	10.7 ± 2.3	821.3 ± 425.2	26.4 ± 17.5
9th month	10.7 ± 1.6	899.1 ± 510.4	32.5 ± 17.1
12th month	11.2 ± 1.7*	844.9 ± 441.1	37.1 ± 17.7

*P <0.05, Hb: Hemoglobin, TSAT: Transferrin saturation.

Table 3. Calcium, phosphate, calcium x phosphate product and parathyroid hormone before treatment and during one-year of treatment.

	Ca^{+2} (mg/dL)	P (mg/dL)	Ca × P	PTH (pg/mL)
Basal	9.3 ± 0.6	6.7 ± 1.5	62.7 ± 15.6	1505.6 ± 444.4
3rd month	8.9 ± 0.7*	6.5 ± 1.2	58.2 ± 13.2	1351.1 ± 650.8
6th month	8.8 ± 0.7*	5.8 ± 1.6	51.8 ± 17.0	1420.2 ± 663.9
9th month	8.8 ± 0.6*	6.5 ± 1.6	58.2 ± 16.0	1489.2 ± 665.0
12th month	9.1 ± 0.8	6.5 ± 2.0	59.9 ± 18.9	1237.1 ± 581.3

*P < 0.05, Ca: Calcium, P: Phosphorus, PTH: Parathormone.

Ca × P product, which was not statistically significant (P >0.05).

No difference was found regarding serum Hb, ferritin, TSAT, Ca^{+2}, P and PTH levels and Ca × P product before and after cinacalcet treatment (P > 0.05) (Tables 2 and 3).

Initially, 88% of the patients were using non-calcium-containing phosphate binder (sevelamer). During the study, the frequency of use of calcium-containing phosphate binder was increased, but there was no change regarding the frequency of use of sevelamer treatment (8% vs.16%, P <0.05). At the beginning of cinacalcet treatment, vitamin D was being used in 40% of the patients; this increased to 52% in the 12th month of cinacalcet treatment (Table 4).

The dose of cinecalcet increased from 32.4 ± 12.0 mg/day to 60.0 ± 24.4 mg/day. Elemental calcium consumption was found to be much higher during cinacalcet treatment. No change was observed in the dose of sevelamer in the follow-up period. The weekly dose of i.v. calcitriol was higher in the 9th and 12th months of treatment. The monthly dose of i.v. iron was similar before and after treatment. The weekly dose of EPO decreased during the study period, but no statistically significant difference was found (5800 ± 3041 vs. 4416 ± 3775 IU/week) (Tables 4 and 5).

On parathyroid gland ultrasonography, no parathyroid pathology was found in nine patients. However, hyperplasia or nodule in one or more parathyroid glands was detected in 16 patients. Although there was a post-treatment decrease in the parathyroid gland volume, it was not statistically significant (1196.1 ± 862.631 vs. 1000.4 ± 734.74 mm^3, P >0.05).

Furthermore, the LVMI decreased after cina-

Table 4. The use of phosphate binder and vitamin D by the study patients before treatment and during 1 year of treatment.

	Not using P binder No. (%)	Phosphate binder		Vitamin D
		$CaCO_3$ No. (%)	Sevelamer No. (%)	Calcitriol No. (%)
Basal	1 (4)	2 (8)	22 (88)	10 (40)
3rd month	1 (4)	5 (20)	19 (76)	10 (40)
6th month	4 (16)	2 (8)	19 (76)	10 (40)
9th month	1 (4)	5 (20)	19 (76)	12 (48)
12th month	0 (0)	4 (16)	21 (84)	13 (52)

P: Phosphorus, $CaCO_3$: Calcium carbonate.

Table 5. Treatment doses that patients used before treatment and during 1 year of treatment.

	Basal	3rd month	6th month	9th month	12th month
Cinacalcet (mg/day)	32.4 ± 12.0	40.0 ± 14.4	47.7 ± 15.0	55.2 ± 20.6	60.0 ± 24.4
E.Ca^{+2} (g/day)	0.79 ± 0.99	2.1 ± 0.82	2.2 ± 0.10	2.2 ± 0.11	2.2 ± 0.86
Sevelamer (g/day)	4.83 ± 1.22	4.8 ± 0.80	4.6 ± 0.55	4.6 ± 0.55	4.8 ± 0.52
Calcitriol (μ/week)	6.46 ± 2.9	4.5 ± 1.5	5.9 ± 2.6	7.5 ± 2.7	6.8 ± 3.0
EPO (IU/week)	5800 ± 3041	4920 ± 3604	4640 ± 3806	4041 ± 3012	4416 ± 3775

Ca: Calcium, EPO: Erythropoietin.

calcet treatment, but it was not statistically significant (174.2 ± 49.7 vs. 161.9 ± 42.9 g/m^2, P >0.05).

The following side-effects were noted during cinacalcet treatment: nausea in 15 patients, vomiting in ten patients, diarrhea in five patients, dyspepsia in eight patients and asymptomatic hypocalcemia in six patients. Severe symptomatic hypocalcemia was not observed.

Discussion

sHPT, a common complication of end-stage renal disease, is a clinical condition associated with pain, bone fractures, anemia, pruritus, hypertension, vascular calcification and sexual dysfunction.[1] It has been shown that bone and mineral disorder is associated with cardio-vascular morbidity and mortality.[12-14] Active vitamin D and phosphate binders, including calcium, that are commonly used in treatment are effective in the control of high PTH levels. Nevertheless, they may cause some side-effects such as hyperphosphatemia and hypercalcemia by increasing the absorption of calcium and phosphate from the gastrointestinal tract.[15]

The most important advantage of calcimimetics in the treatment of sHPT is lack of adverse affects on calcium and phosphate metabolism observed in vitamin D treatment. It was shown that cinacalcet treatment together with low doses of vitamin D was more effective in achieving target goals of Ca^{+2}, P, PTH levels and Ca × P product than the use of either drug alone.[3] Likewise, the Optima study showed that the percentage of patients reaching the targets of the KDOQI guidelines increased when cinacalcet was added to conventional therapy in HD patients with uncontrolled sHPT. Additionally, there was a 22% decrease in the required dose of vitamin D.[5] In this study, cinacalcet treatment did not show any significant improvement in the serum levels of Ca^{+2}, P, and PTH levels and Ca × P product in HD patients with serious sHPT. Possible explanations could be the small subject number, selection of patients with severe sHPT (PTH >1000 pg/mL) and late beginning of treatment. In general, the cinacalcet dose is titrated to a maximum of 90 mg/day for effective control of high PTH. This dose was not reached in our patients because of the side-effects, especially related to the gastrointestinal tract.

Because of the presence of hyperphosphatemia, the percentage of patients receiving cinacalcet together with active vitamin D was 40% at the beginning. The lack of initial dual treatment might explain the failure to achieve target goals.

Cinacalcet treatment has not only improved the bone mineral metabolism but it has also been thought to have some positive effects on anemia, LVH and parathyroid gland volume.[7-10,16-19]

Hyperparathyroidism is an important cause of EPO resistance in patients with CKD. A possible cause of anemia due to sHPT is the direct or indirect effects of PTH on EPO release. In a few studies carried out on a limited number of patients, it was asserted that control of anemia was provided with low-dose EPO after cinacalcet treatment. This positive effect was attributed to a decrease in the serum PTH levels.[8,9] In accordance with the literature, we found higher levels of Hb with a lower dose of EPO treatment after the beginning of cinacalcet treatment. However, unlike the literature, this positive effect was independent of the PTH levels.

The pleiotropic effect of cinacalcet treatment is not known well, like vitamin D. The study conducted by Mpio showed a decrease in serum C-reactive protein levels after cinacalcet treatment. The control of anemia with low-dose EPO after cinacalcet treatment could be linked to the decrease of inflammation. We did not investigate the anti-inflammatory effect of cinacalcet treatment on anemia control. Therefore, we could only speculate the reason behind achieving higher Hb levels with a lower dose of EPO. Despite ensuring effective control of laboratory parameters related to bone mineral metabolism disorders, improvement was not observed in the frequency of cardiovascular and all-cause mortality with cinacalcet treatment.[20,21] Left ventricular hypertrophy is an important cardiovascular risk factor and anemia, volume overload, arterio-venous fistula and bone mineral metabolism disorders contribute to high prevalance in dialysis patients. In dialysis patients with sHPT, a significant association was found between PTH and LVH and PTH and LVMI.[22] Additionally, a 22% decrease has been observed in LVMI after parathyroidectomy.[23] In animal studies and small uncontrolled clinical trials, i.v. calcitriol in dialysis patients has been shown to reduce LVH.[24,25] Besides this, the calcimimetic effects on LVH are not known. In our patients, a significant reduction was not observed in the LVMI after one year of cinacalcet treatment.

Despite the positive effects of cinacalcet treatment on bone mineral metabolism, the effect on the parathyroid glands is not fully known. Meola et al, in their study on nine patients with sHPT, showed that cinacalcet treatment reduced the parathyroid volume, in particular in small glands. Also, it has been suggested that early initiation of therapy may be more effective on the parathyroid gland.[26] We observed a partial but not significant reduction in parathyroid volume after one year of cinacalcet treatment, suggesting the need for a longer treatment duration with a sufficient number of patients. The dose and frequency of calcium-containing phosphate binder was increased after cinacalcet treatment. Increased calcium load due to the use of calcium-containing phosphate binders in dialysis patients is associated with excess vascular calcification.[26,27] In comparison with sevelamer, there has been an increased progression of vascular calcification with calcium-containing phosphate binders.[28,29] The possible adverse effects of calcium-containing phosphate binders to normalize or increase serum Ca^{+2} levels were not known during the cinacalcet treatment. There was no relationship between calcimimetics and vascular calcification in some studies.[18]

The limitations of the current study were small subject number and absence of initial dual therapy (cinacalcet and vitamin D) because of hyperphosphatemia. Further studies with a larger patient population are needed to show the possible effects of cinacalcet together with the calcium-containing phosphate binder usage.

Conclusion

Cinacalcet treatment did not provide a significant improvement on the biochemical parameters of bone mineral disorders, LVH and parathyroid volume. Nevertheless, it allowed achieving higher Hb levels with a lower dose of EPO. The management of sHPT with cinacalcet therapy might have an additional benefit to control anemia in those patients.

Conflict of interest

The authors declare that the article is original, does not infringe upon any copyright, is not under consideration by another journal, and has not been published previously. All data collected during the study is presented in this manuscript. Each author believes that the manuscript represents honest work. Also, there is no conflict of interest.

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