

Association between long-term efficacy of cinacalcet and parathyroid gland volume in haemodialysis patients with secondary hyperparathyroidism

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Abstract

Purpose. Secondary hyperparathyroidism with nodular hyperplasia is resistant to medical therapies. Cinacalcet is an effective treatment for severe secondary hyperparathyroidism. This multicentre retrospective study was designed to determine the long-term efficacy of cinacalcet in patients with nodular hyperplasia, the advanced type of parathyroid hyperplasia.

Subjects and methods. The study subjects were 20 haemodialysis patients with secondary hyperparathyroidism. Patients with ultrasonographically confirmed large parathyroid glands (volume >0.5 cm³) were considered to have nodular hyperplasia ($n = 8$). Cinacalcet was started at the dose of 25 mg/day and titrated up to 100 mg/day to achieve the target intact-parathyroid hormone (iPTH) level of <250 pg/ml. Serum iPTH, corrected calcium, serum phosphorus, calcium × phosphorus product were measured and compared over the 48-week period of treatment with cinacalcet in all 20 patients and over 120 weeks in 6 of the patients (2 with nodular hyperplasia and 4 with non-nodular hyperplasia). We also examined the achievement rate of K/DOQI guideline treatment targets. The dosages of vitamin D preparation, sevelamer hydrochloride and calcium-containing phosphate binder were adjusted for the above target values.

Results. iPTH levels were significantly lower at 48 weeks in both groups. However, corrected calcium levels, serum phosphorus levels and calcium phosphorus products were within the target values in the non-nodular hyperplasia group ($n = 12$), while the target value could not be achieved in the nodular hyperplasia group. In the long-term follow-up group, the levels of iPTH, corrected calcium, serum phosphorus and calcium × phosphorus products were significantly higher in nodular hyperplasia than in non-nodular hyperplasia.

Conclusion. Our study suggests that cinacalcet lacks long-term efficacy in nodular hyperplasia, especially for controlling serum calcium and phosphorus levels.

Keywords: cinacalcet; haemodialysis; nodular hyperplasia; secondary hyperparathyroidism; ultrasonography

Introduction

Nodular hyperplasia of the parathyroid glands is characterized by the presence of monoclonal proliferating cells [1,2], low density of calcitriol receptors [3] and calcium-sensing receptors [4]. Patients with this disorder are resistant to medical therapy, including calcitriol. The size of the gland is considered to be the best indicator of the presence of nodular hyperplasia. In fact, nodular hyperplasia is present in ≥90% of parathyroid glands larger than 1 cm in diameter or 0.5 cm³ in volume [5]. Moreover, Tominaga *et al.* [6] showed that in secondary hyperparathyroidism, enlarged parathyroid gland with a volume >300 could not be controlled by maxacalcitol therapy. When one or more parathyroid glands progress to the stage of nodular hyperplasia, it is usually difficult to control parathyroid hormone (PTH) secretion even by any vitamin D3 therapy. For such patients, parathyroid intervention therapy including selective percutaneous ethanol injection therapy (PEIT) or surgical parathyroidectomy (PTx) is indicated [7,8].

On the other hand, the recent introduction of cinacalcet, a novel class of therapeutic agents, has led to a change in the treatment strategy of secondary hyperparathyroidism in patients with end-stage renal disease [9–11]. Moreover, Colloton *et al.* [12] reported that cinacalcet inhibits the progression of parathyroid cell proliferation in rats. However, there are some serious cases that have not responded to cinacalcet and required PEIT or PTx [13]. There is little information on whether cinacalcet can reduce the size of enlarged parathyroid glands, or whether cinacalcet has long-term effects on haemodialysis patients with nodular hyperplasia.

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In the present study, we examined the association between long-term efficacy of cinacalcet and parathyroid gland volume in haemodialysis patients with secondary hyperparathyroidism.

Subjects and methods

In the present study, we retrospectively analysed a cohort of patients, included in a multicentre study on the long-term efficacy of cinacalcet in haemodialysis patients [11], with information on the development of nodular hyperplasia assessed by ultrasonography. In 2004, 20 subjects undergoing haemodialysis with secondary hyperparathyroidism were treated with cinacalcet hydrochloride. In this study, we established target values of serum intact-PTH (iPTH) level at <250 pg/ml, corrected calcium level at >8.4 but <10.0 mg/dl, serum phosphorus levels at >3.5 but <6.0 mg/dl, and calcium \times phosphorus products at <55. During the study period, the doses of vitamin D preparation, sevelamer hydrochloride and calcium-containing phosphate binder were adjusted for the above target values. Cinacalcet was started at the dose of 25 mg/day and titrated up to 100 mg/day to achieve the target iPTH level of <250 pg/ml. Before treatment with cinacalcet, the neck was examined by ultrasonography using an Aloka Pro Sound SSD-4000 Color Doppler Ultrasonography unit (Aloka Co., Tokyo, Japan) with 2.5–13 MHz transducers. The size of the enlarged parathyroid glands was estimated by three-dimensional measurement ($\pi/6 \times a \times b \times c$) [3]. Using the definition used in previous studies [5], parathyroid gland with a volume >0.5 cm³ was defined as nodular hyperplasia.

Based on the results of ultrasonography with regard to the volume of the enlarged glands, the subjects were divided into two groups: nodular hyperplasia group ($n = 8$) and non-nodular hyperplasia group ($n = 12$). Serum iPTH, corrected calcium, serum phosphorus, calcium \times phosphorus products were monitored over the 48-week treatment period in both groups. We also examined the achievement rate of K/DOQI guideline treatment targets. Among the 20 patients, we also followed up 6 cases (2 with nodular hyperplasia and 4 with non-nodular hyperplasia) for 120 weeks using the above protocol.

Statistical analysis

All data were expressed as mean \pm SD. Differences between groups were examined for statistical significance using Student's *t*-test. A *P*-value ≤ 0.05 denoted the presence of a statistically significant difference.

Results

As shown in Figure 1, serum iPTH levels were significantly reduced after a 48-week treatment period in both groups ($P < 0.01$), but the target value for iPTH levels of <250 pg/ml was not achieved in the nodular hyperplasia group. However, corrected calcium levels, serum phosphorus levels and calcium \times phosphorus products were within

the target values in the non-nodular hyperplasia group, while the target values were not achieved in the nodular hyperplasia group. Table 1 showed the achievement rate of K/DOQI guideline treatment targets. The achievement rate of K/DOQI guideline treatment targets was decreased in the nodular hyperplasia group, but increased in the non-nodular hyperplasia group.

In 6 of 20 subjects who were followed up for 120 weeks, 2 subjects with nodular hyperplasia showed significantly higher levels of iPTH, corrected calcium, serum phosphorus and calcium \times phosphorus products than the other 4 subjects with non-nodular hyperplasia (Figure 2).

Discussion

Elevated serum iPTH, calcium, phosphorus levels and calcium \times phosphorus products correlate with mortality in dialysis patients [14,15]. Therefore, treatment of secondary hyperparathyroidism with cinacalcet, which reduces PTH, serum calcium and phosphorus levels, has received much attention.

Cinacalcet hydrochloride was developed for the control of hyperparathyroidism in patients with chronic renal disease; these agents act by enhancing the sensitivity of the parathyroid calcium-sensing receptors, thereby reducing PTH, serum calcium and phosphorus and calcium-phosphorus product [9]. Previous studies demonstrated that treatment with cinacalcet in combination with conventional therapy resulted in improvement of K/DOQI to the recommended target range [16]. In Japan, a recent clinical study also demonstrated the efficacy and safety of cinacalcet therapy, even in patients with a longer average dialysis history [11]. With regard to the impact of cinacalcet treatment on the clinical outcome, several trials showed that this treatment significantly decreased the risks of parathyroidectomy, fracture and cardiovascular hospitalization [17]. However, it remains to be elucidated whether cinacalcet effectively controls hyperparathyroidism in patients with nodular hyperplasia, the advanced type of parathyroid hyperplasia [18].

The results of our study on PTH levels were similar to those reported by Fukagawa *et al.* [11], indicating that cinacalcet can effectively control PTH levels for ~ 3 months in severe secondary hyperparathyroidism. However, in the six patients who were observed for 120 weeks, cinacalcet was not effective in the long-term control of PTH values in the nodular hyperplasia group. In the non-nodular hyperplasia group, cinacalcet therapy resulted in the reduction of PTH levels as well as correction of calcium levels, serum phosphorus levels and calcium \times phosphorus products. Moreover, the proportion of patients with non-nodular hyperplasia who achieved the K/DOQI guideline was better than that of patients with nodular hyperplasia. On the other hand, in the nodular hyperplasia group, cinacalcet was not expected to be effective in the long-term control of PTH level. Specifically, in the nodular hyperplasia group, the long-term control of PTH levels, as well as corrected calcium, serum phosphorus levels and calcium \times phosphorus products was difficult to achieve during the observation period. Recent

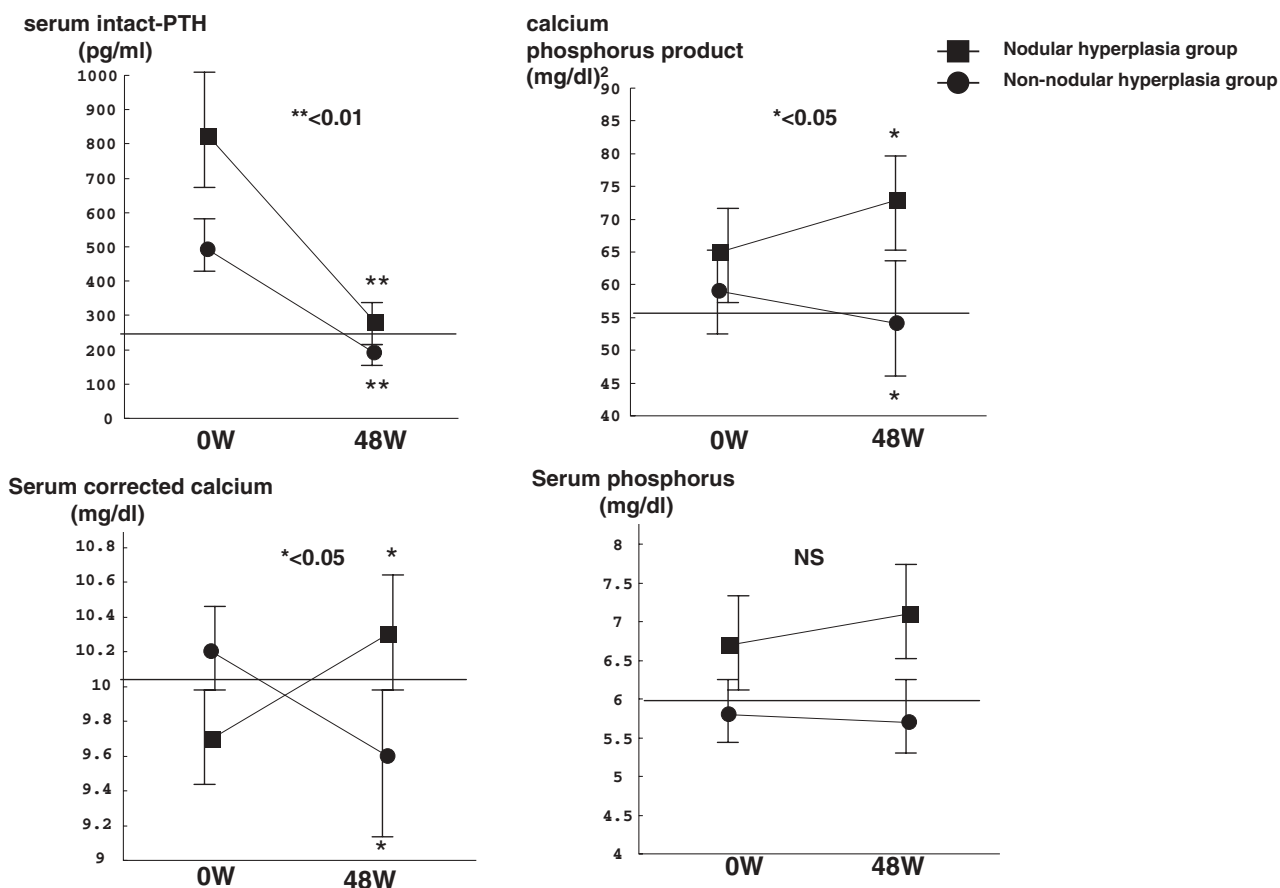


Fig. 1. Serum intact-PTH, corrected calcium, serum phosphorus levels and calcium × phosphorus products at baseline and 48-week treatment. Intact-PTH levels were significantly lower at 48 weeks in both groups, but the target value for intact-PTH levels of <250 pg/ml was not achieved in the nodular hyperplasia group. In the non-nodular hyperplasia group, serum corrected calcium, phosphorus levels and calcium × phosphorus products were significantly reduced to within the target values (horizontal line), while the target value was not achieved in the nodular hyperplasia group at the end of the 48-week treatment with cinacalcet.

Table 1. Achievement rate of K/DOQI guideline treatment targets after administration of cinacalcet

		Baseline (%)	48 weeks after administration of cinacalcet (%)
Serum intact-PTH levels	Nodular hyperplasia (+)	0	62.5
	Nodular hyperplasia (−)	8.3	75
Serum corrected calcium levels	Nodular hyperplasia (+)	50	12.5
	Nodular hyperplasia (−)	8.3	33.3
Serum phosphorus levels	Nodular hyperplasia (+)	25	12.5
	Nodular hyperplasia (−)	33.3	41.6
Calcium × phosphorus products	Nodular hyperplasia (+)	12.5	8.3
	Nodular hyperplasia (−)	25	50

studies have shown that cinacalcet is effective for patients with severe secondary hyperparathyroidism [9–11] and patients with prolonged secondary hyperparathyroidism after renal transplantation [19–21]. Considered together, these results suggest that cinacalcet can effectively control patients with nodular hyperplasia. In Japan, however, the highest dose of cinacalcet is 100 mg/day, while a dose of 180 mg/day was used in the above studies. The dose of cinacalcet is likely a significant factor that can influence its efficacy in severe secondary hyperparathyroidism. Fur-

ther examination in a large-scale trial is required to establish this evidence.

Although the effectiveness of cinacalcet on secondary hyperparathyroidism has been reported, the medical financial burden has been described as a setback [22,23]. To avoid such burden, overuse of cinacalcet should be abandoned, and parathyroid intervention such as PEIT or PTx should be done appropriately for haemodialysis patients with nodular hyperplasia detected by ultrasonography. Ultrasonographic examination might be useful to predict the

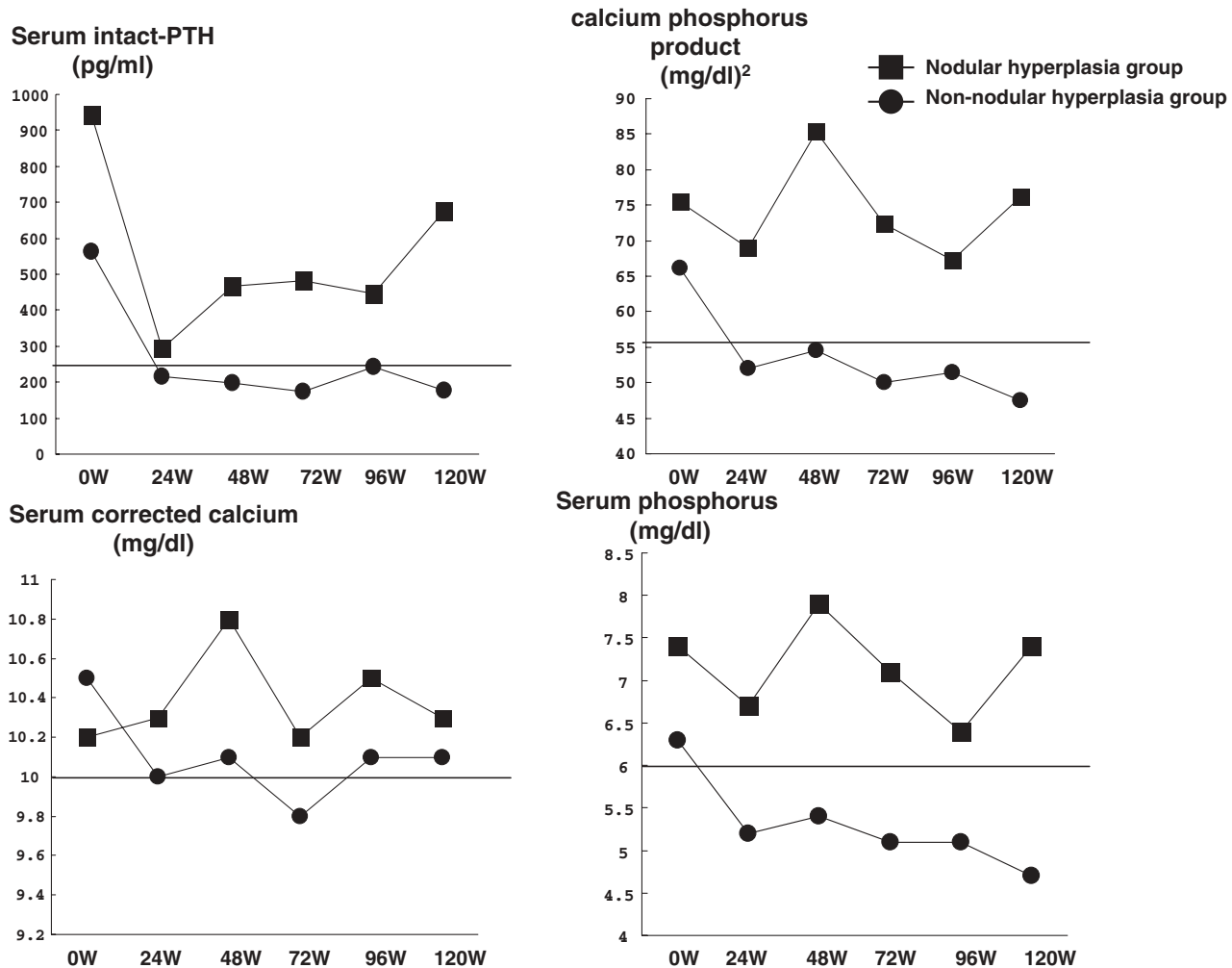


Fig. 2. Serum intact-PTH, corrected calcium, phosphorus levels and calcium \times phosphorus products after long-term treatment with cinacalcet. Intact-PTH levels were significantly lower at 24 weeks of treatment in both groups. However, after 48 weeks of treatment, the target value for intact-PTH levels of <250 pg/ml was not achieved in the nodular hyperplasia group. The levels of intact PTH, corrected calcium, serum phosphorus and calcium \times phosphorus products were significantly higher in the nodular hyperplasia group than in the non-nodular hyperplasia group.

long-term efficacy of cinacalcet for haemodialysis patients with secondary hyperparathyroidism.

In conclusion, our study suggests that cinacalcet lacks long-term efficacy in secondary hyperparathyroidism with nodular hyperplasia, especially in controlling serum calcium and phosphorus levels. However, it seems that the control of secondary hyperparathyroidism is possible by early treatment with cinacalcet, since a recent report showed that cinacalcet inhibits the progression of parathyroid cell proliferation in rats [12]. Further examination is necessary to clarify this effect of cinacalcet.

Conflict of interest statement. MF received a research grant from Kirin Pharma Co. Ltd., Japan. Others, none declared.

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