Long-Term Cinacalcet HCl Treatment Improved Bone Metabolism in Japanese Hemodialysis Patients with Secondary Hyperparathyroidism

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Key Words

Osteodystrophy • Bone disease • Hyperparathyroidism • Parathyroid hormone • Calcium

Abstract

Background/Aims: Few clinical trials conducted with cinacalcet have thoroughly addressed its effects of on bone metabolism. We assessed the effects of cinacalcet on bone markers in Japanese hemodialysis (HD) patients with secondary hyperparathyroidism (SHPT). **Methods:** 200 Japanese HD patients with intact PTH (iPTH) levels ≥ 300 pg/ml were enrolled. The dose of cinacalcet was titrated from 25 up to 100 mg/day to achieve iPTH levels ≤ 250 pg/ml for 52 weeks. **Results:** At the end of the study visit, 57.8% of patients (115/199) had achieved iPTH levels ≤ 250 pg/ml. Serum Ca, phosphorus (P) and $\text{Ca} \times \text{P}$ levels decreased rapidly and were maintained throughout the study. At week 52, all bone metabolic markers levels had decreased significantly from baseline. Although bone resorption markers gradually decreased throughout the study period, bone alkaline phosphatase significantly increased during the first 4 weeks and then gradually decreased. **Conclusions:** The time courses of changes in bone markers after cinacalcet treatment resem-

bled those observed after surgical parathyroidectomy (PTx), sometimes described as the hungry bone syndrome, indicating that cinacalcet treatment induces a rapid recovery in bone response to calcium. In addition, long-term efficacy and safety of cinacalcet were also observed in Japanese patients undertaking long-term hemodialysis (167.0 ± 81.4 months).

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Introduction

Secondary hyperparathyroidism (SHPT) is a serious complication in patients undergoing hemodialysis (HD), and is characterized by progressive hyperplasia of the parathyroid glands and excessive parathyroid hormone (PTH) secretion [1]. Elevated levels of PTH cause high bone turnover characterized by increased bone formation with abnormally high rates of bone resorption. Cinacalcet HCl, a calcimimetic agent, acts as a positive allo-

Disclosure/Conflict of Interest: Funding for this study was provided by Kirin Pharma Co., Ltd. Drs Akizawa, Uchida, Tsukamoto, Iwasaki and Koshikawa are scientific advisors of Kirin Pharma Co., Ltd.

steric modulator of the Ca receptor (CaR) [2, 3] by increasing the sensitivity of the receptor to extracellular Ca, thereby reducing the secretion of PTH without increasing the serum levels of calcium (Ca), phosphorus (P) or $\text{Ca} \times \text{P}$ [4]. A previous study indicated that cinacalcet treatment reduced the PTH-driven Ca and P efflux from bone [5]. However, few studies have evaluated the effects of cinacalcet on bone metabolism in patients with SHPT. Lien et al. [6] reported that cinacalcet treatment reversed bone loss in the proximal femur but did not improve the BMD of the lumbar spine. Jean et al. [7] demonstrated improvement in bone turnover markers with cinacalcet; however, the number of patients was limited, and there were only two observation points at 6 and 12 months after commencing treatment. In this study, we investigated the therapeutic advantages and safety of cinacalcet and its effect on bone metabolism using time-lapse analysis in Japanese patients on long-term HD.

Methods

This study was an open-label multicenter study of 52 weeks' duration conducted at 39 centers in Japan. HD patients were eligible if intact PTH (iPTH) levels were ≥ 300 pg/ml and serum Ca levels, corrected by serum albumin, were ≥ 9.0 mg/dl. Major exclusion criteria were a history of PTx within the past 24 weeks, pregnancy or lactation, severe hepatic and cardiac diseases, and uncontrollable hypertension or diabetes. Patients received cinacalcet once daily and the dose was titrated from 25 mg to a maximum of 100 mg in order to achieve iPTH levels ≤ 250 pg/ml. If serum Ca levels decreased to 8.4 mg/dl or less, dose titration was restricted and if serum Ca levels decreased to 7.5 mg/dl or less, cinacalcet was temporarily discontinued until the serum Ca level recovered to 8.4 mg/ml or greater. No restrictions were imposed on the use of active vitamin D or its analogs and on the use of phosphate binders. PTx or other intervention (e.g. percutaneous ethanol or calcitriol direct injection therapy) was restricted during the study period. iPTH, serum Ca and serum P levels were assessed weekly (weeks 0–24) or biweekly (weeks 26–52) and biochemical markers of bone metabolism were assessed every 4 weeks. Serum Ca values were corrected for the albumin concentration as follows. For each 0.1 g/dl decrease in albumin below 4.0 g/dl, the serum Ca was increased by 0.1 mg/dl. The efficacy population consisted of patients with at least one efficacy measurement. The safety population included all patients who received at least one dose of cinacalcet. To confirm the efficacy results, 95% CIs were calculated. The population of patients who received concomitant medication at week 52 was compared with the population at baseline using McNemar's test. The mean dose of concomitant medication at week 52 was compared with the dose at baseline using a paired t test. $p < 0.05$ is considered statistically significant. All statistical analyses were performed using the SAS software package (version 8.02; SAS Inc., Cary, N.C., USA).

Table 1. Baseline demographics and clinical characteristics

Characteristic	Efficacy population (n = 199)
Gender, n (%)	
Male	128 (64.3)
Female	71 (35.7)
Age, years	54.4 $\pm$ 11.8
Dry weight, kg	54.6 $\pm$ 10.7
Duration of dialysis, months	167.0 $\pm$ 81.4
0–1 year, n (%)	3 (1.5)
1–5 years, n (%)	10 (5.0)
5–10 years, n (%)	54 (27.1)
10–20 years, n (%)	92 (46.2)
20 years, n (%)	39 (19.6)
Unknown, n (%)	1 (0.5)
Active vitamin D sterols, n (%)	150 (75.4)
Maxacalcitol (i.v.) use	94 (47.2)
Calcitriol (i.v.) use	28 (14.1)
Falecalcitriol (oral) use	7 (3.5)
Calcitriol (oral) use	6 (3.0)
Alfacalcidol (oral) use	16 (8.0)
Phosphate binder use, n (%)	193 (97.0)
CaCO ₃ use	114 (57.3)
Sevelamer use	113 (56.8)
Dialysate Ca concentration, n (%)	
<3.0 mEq/l	76 (38.2)
≥ 3.0 mEq/l	123 (61.8)
Serum intact PTH, pg/ml	640.5 $\pm$ 297.2
Serum Ca, mg/dl	10.01 $\pm$ 0.60
Serum P, mg/dl	6.35 $\pm$ 1.18
Ca $\times$ P, mg ² /dl ²	63.54 $\pm$ 12.09

Results

A total of 200 SHPT patients were enrolled and all of them were evaluated for safety. One patient was eliminated from the efficacy population due to no measured efficacy parameters, and baseline demographics and laboratory values for the remaining 199 patients are shown in table 1. Thirty patients discontinued the study (14 adverse events, 9 withdrawal of consent, 6 inappropriate administration, and 1 kidney transplantation). After administration of cinacalcet, serum iPTH levels (mean $\pm$ SD) decreased gradually from 640.5 $\pm$ 297.2 pg/ml (baseline) to 281.8 $\pm$ 226.3 pg/ml (week 20), and then remained stable through the study period (fig. 1a). Cinacalcet treatment achieved a 52.38 $\pm$ 33.34% (mean $\pm$ SD) reduction in average iPTH levels at the end of the study visit. The target iPTH level of ≤ 250 pg/ml was achieved in 57.8% (95% CI: 50.6–64.7) of patients (115/199) at the

Fig. 1. Effect of cinacalcet treatment on serum levels of **a** intact PTH, and **b** Ca (●), P (■) and Ca × P (△) in HD patients with SHPT. Values are mean ± SD. HD = Hemodialysis; PTH = parathyroid hormone; SHPT = secondary hyperparathyroidism.

end of the study visit. The proportion of patients whose iPTH levels were reduced by 30% or more at the end of the study was 85.9% (95% CI: 80.3–90.4; 171/199). In contrast to the gradual suppression of iPTH levels, serum levels of Ca and P and the Ca × P product decreased rapidly after initiation of cinacalcet treatment, reached stable levels within a week, and maintained thereafter throughout the study period (fig. 1b). The typical differences in the acute and continued changes induced by cinacalcet treatment are depicted in figure 3 by comparing the percentage changes of these parameters from the baseline at weeks 4 and 52. Tartrate-resistant acid phosphatase (TRAP) and the amino-terminal telopeptide of type I collagen (NTx) levels decreased gradually through the study period. In contrast, bone-alkaline phosphatase (BSAP) levels started increasing just after commencement of cinacalcet treatment and then declined between weeks 4 and 8. The gradual decrease after week 8 ceased at week 36 and levels remained stable thereafter (fig. 2). As shown in figure 3, cinacalcet treatment preferentially suppressed the osteoclastic bone resorption markers, TRAP and NTx, rather than BSAP that reflects osteoblastic function.

The mean dose of cinacalcet was 44.50 mg/day at 12 weeks and remained stable during the rest of the study (table 2). Of the 169 remaining participants at week 52, 68 (40.2%) were maintained on 25 mg/day, 60 (35.5%) on 50 mg/day, 23 (13.6%) on 75 mg/day and 15 patients (8.9%) on 100 mg/day. Three patients (1.8%) temporarily discontinued cinacalcet treatment. The percentage of patients receiving intravenous active vitamin D sterols (maxacalcitol or calcitriol) and the mean equivalent calcitriol dose (conversion formula 1.5 µg calcitriol = 10 µg maxacalcitol) remained almost unchanged through the study period. In contrast, the percentage of patients receiving a Ca-containing phosphate binder increased significantly at week 52 and the mean dose also showed a slight but significant increase at week 52 compared with baseline (table 2). Cinacalcet was generally well tolerated at once-daily doses ranging from 25 to 100 mg daily. Adverse events considered related to treatment occurred in 72.5% of patients (145/200), with most mild-to-moderate in severity. Abdominal discomfort, nausea and vomiting were the most common treatment-related adverse events (21.5, 14.0 and 9.5% of patients, respectively).

Discussion

This is the first report of long-term cinacalcet treatment with ad libitum medications of active vitamin D sterols and phosphate binders in Japanese HD patients with SHPT. It is well known that many Japanese dialysis patients have a long dialysis vintage compared to patients in the US and EU [8], and the patients in this study were similar in mean dialysis duration (167 ± 81.4 months) to those in our previous report (170.4 ± 93.7 months), who were assumed to have a high severity of SHPT [9]. Serum levels of iPTH, Ca, P and Ca $\times$ P were successfully decreased, and the outcomes of this study are comparable to those of previous studies conducted in the US or EU with shorter dialysis durations [4], indicating that cinacalcet provides effective therapeutic outcomes even for patients with a long dialysis duration. In the first week of treatment, serum Ca, P and Ca $\times$ P product quickly decreased prior to adequate suppression of iPTH. This finding suggests that cinacalcet would be very useful in achieving the Japanese guidelines for the management of SHPT in chronic dialysis patients, in whom the achievement of phosphorus and calcium control are accorded higher priority for survival than PTH control [10]. In the next phase around week 4, we observed an increase in

Table 2. Treatment of SHPT with cinacalcet and concomitant medication for SHPT

	Baseline (n = 199)	Week 4 (n = 197)	Week 12 (n = 192)	Week 24 (n = 182)	Week 52 (n = 169)
Cinacalcet, mg/day	0 ± 0	32.87 ± 11.84	44.50 ± 21.86	46.55 ± 23.68	46.85 ± 24.43
<i>Active vitamin D derivative</i>					
<i>Maxacalcitol</i>					
On maxacalcitol, n (%)	94 (47.2)	94 (47.7)	93 (48.4)	81 (44.5)	78 (46.2)
Maxacalcitol dosage, µg/week*	15.80 ± 10.56	16.80 ± 11.65	18.87 ± 11.02	18.25 ± 12.79	15.83 ± 11.35
<i>Calcitriol</i>					
On calcitriol, n (%)	28 (14.1)	28 (14.2)	30 (15.6)	29 (15.9)	28 (16.6)
Calcitriol dosage, µg/week*	2.07 ± 0.87	2.29 ± 1.05	2.35 ± 0.91	2.12 ± 0.92	2.14 ± 0.96
<i>Equivalent calcitriol[†]</i>					
On maxacalcitol and/or calcitriol, n (%)	122 (61.3)	122 (61.9)	122 (63.5)	110 (60.4)	106 (62.7)
Equivalent calcitriol dosage, µg/week*	2.30 ± 1.45	2.47 ± 1.61	2.74 ± 1.54	2.58 ± 1.73	2.31 ± 1.54
<i>Phosphate binder</i>					
<i>CaCO₃</i>					
On CaCO ₃ , n (%)	114 (57.3)	127 (64.5)	128 (66.7)	133 (73.1)	123 (72.8) [‡]
CaCO ₃ dosage, mg/day*	2,748 ± 1,573	2,821 ± 1,753	3,105 ± 1,799	2,927 ± 1,940	2,940 ± 1,770 [§]
<i>Sevelamer</i>					
On sevelamer, n (%)	113 (56.8)	111 (56.3)	99 (51.6)	92 (50.5)	90 (53.3)
Sevelamar dosage, mg/day*	3,305 ± 1,696	3,192 ± 1,662	3,117 ± 1,731	3,250 ± 1,744	3,365 ± 1,832

* Dosages were calculated for patients administered concomitant medication.

[†] 1.5 µg calcitriol = 10 µg maxacalcitol.

[‡] p < 0.001 compared to baseline for 169 patients still in the study at week 52.

[§] p < 0.001 compared to baseline for 92 patients who were on CaCO₃ at baseline and at week 52.

BSAP, whereas the osteoclastic reabsorption markers, TRAP and NTx, decreased. These changes suggest the alteration of bone metabolism from preexisting pathophysiological settings under SHPT, probably due to amelioration of PTH hyperactivity. It is of interest to note that a similar temporal increase in BSAP is also observed after PTx. This condition is sometimes referred to as the hungry bone syndrome, and is characterized by a temporary increase in BSAP and prolonged hypocalcemia [11, 12]. The suggested causative mechanism is that a sudden disappearance of PTH leads to suppression of osteoclast activity [13], a subsequent increase in calcium influx into bone, and accelerated osteoblast-mediated bone formation [14]. Cinacalcet regulates the moment-to-moment secretion of PTH [15] via activation of CaR, and can lower serum levels of PTH within 1 h after an oral dose, with maximum reduction around 2–4 h after administration [16]. Since our measurements of iPTH were performed approximately 24 h after administration of cinacalcet, the magnitude of changes in PTH levels induced by treatment with cinacalcet in this study may have been underestimated. A drastic reduction in PTH levels within a few

hours might work as a transient chemical PTx, inducing a hungry bone-like response as with real surgical PTx. After 36 weeks, when the hungry bone syndrome had dissipated, TRAP and NTx continued to decrease, whereas BSAP and PTH levels stayed stable. At week 52, BSAP was below the baseline level, but its reduction was less significant than that of either TRAP or NTx. In other words, long-term cinacalcet treatment appeared to preferentially suppress osteoclastic bone resorption rather than osteoblast-mediated bone formation in the late phase of this study. These findings suggest that cinacalcet may not only correct PTH levels, but also lead to a preferable outcome in bone metabolism. The effect of cinacalcet on bone metabolism in patients with SHPT has also been studied elsewhere, and Lien et al. [6] reported that cinacalcet treatment reversed bone loss in the proximal femur but did not improve the BMD of lumbar spine. However, BMD was measured after 26 weeks of treatment in that study, and did not address the effects of cinacalcet on bone metabolism in the later stages that this study has shed light on. Flexible use of active vitamin D sterols and phosphate binders also probably contributed to the mod-

ulation of bone metabolism in our study. Management of serum Ca and P levels is important for better outcomes in SHPT treatment, and it is well known that conventional therapeutic regimens such as active vitamin D sterols and Ca-containing phosphate binders can cause hypercalcemia and hyperphosphatemia [17]. The dosage of concomitant medication in this study reflects that a typical Japanese therapeutic pattern was different from those in the US and EU judging from the previous studies which were conducted with almost the same criteria as our study [18, 19]. In brief, the lower dosage of vitamin D sterols and Ca-containing phosphate binders were observed in this study than those of other two studies (vitamin D sterols; 2.3, 4.7 and 3.3 µg/week, Ca-containing phosphate binders; 1,099, 1,903 and 2,200 mg/day as of elemental calcium intake, in Japan, US and EU, respectively). The mean serum calcium level in a Japanese patient population was higher than those in the US and EU (10.01 vs. 9.6 and 9.7 mg/dl), which might be caused by longer vintage of dialysis. This characteristic might be one reason for the lower dosage of vitamin D sterols and Ca-containing phosphate binders. The mean sevelamer dosage was also lower in our population (3,305 vs. 5,094 and 4,500 mg/day) probably due to the higher sensitivity to the gastrointestinal side effects of Japanese patients [20]. Few studies have demonstrated the impact of cinacalcet on conventional treatment regimens allowing flexible dosing of active vitamin D sterols and phosphate binders. As shown in table 2, dosages of intravenous active vitamin D sterols and sevelamer HCl remained almost unchanged, although both were reduced in a previous study in which cinacalcet treatment was fixed by protocol [21]. It is worthy of note that significant increases in the mean dosage and the percentage of patients on a Ca-containing phosphate binder were observed both in the earlier study and this one. The appropriate dosing of active vitamin D sterols and sevelamer are still contro-

versial, but it is evident that cinacalcet treatment extends the use of Ca-containing phosphate-binder. In conclusion, we demonstrated in this 52-week study that cinacalcet is effective and safe in Japanese patients undertaking long-term hemodialysis, and behaves like surgical PTx. Cinacalcet can improve bone metabolism, although further studies are needed to clarify its effect on bone metabolism and long-term outcomes in clinical practice.

Acknowledgements

Funding for this study was provided by Kirin Pharma Co., Ltd. The authors wish to thank the following investigators who participated in this study: Yoshio Taguma (Sendai Shakaihoken Hospital), Masayuki Suzuki (Yamagata Prefectural Central Hospital), Hiroshi Kawaguchi (Iwaki Urology), Kenjiro Kumakawa (Jusendo Clinic), Takashi Sato (Sumiyoshi Clinic Hospital), Ryoichi Nakazawa (Tokatsu Clinic Matsudo), Takehiko Sakai (Mihama Hospital), Takashi Kono (Mihama Narita Clinic), Fukuji Takeda (Bousei Anesaki Clinic), Takashi Akiba (Tokyo Women's Medical University), Toshiaki Suzuki (Asagaya Suzuki Clinic), Aiji Yajima (Towa Hospital), Yoshindo Kawaguchi (Kanagawa Prefectural Hospital Affiliated with Nurses Training School), Kanji Shishido (Kawasaki Clinic), Masashi Suzuki (Shinrakuen Hospital), Hisao Muto (Kanazawa Social Insurance Hospital), Ryoichi Miyazaki (Fujita Memorial Hospital), Masanori Wakabayashi (Bousei Dai-ichi Clinic), Fumi Kato (Masuko Memorial Hospital), Chikao Yamazaki (Masuko Memorial Hospital Noritake Clinic), Tomohiko Naruse (Kasugai Municipal Hospital), Hiroshi Ogawa (Shinseikai Dai-ichi Hospital), Noriyuki Iwamoto (Kyoto First Red Cross Hospital), Tadashi Aoki (Nishijin Hospital), Yoshihiro Ikeda (Sakae Building Ikeda Clinic), Senji Okuno (Shirasagi Hospital), Yoshihiro Tsujimoto (Inoue Hospital), Akira Fujimori (Konan Hospital), Masato Nishioka (Sumiyoshigawa Hospital), Yoshihiro Motomiya (Suiyukai Clinic), Masaki Fukushima (Kurashiki Central Hospital), Misaki Moriishi (Nakajima Tsuchiya Clinic), Seiichi Obayashi (Kinashi Obayashi Hospital), Shigeaki Hayashida (Tokuyama Central Hospital), Satoru Fujimi (Fukuoka Renal Clinic), Satoshi Funakoshi (Sakuramachi Clinic), Toru Ikeda (Ikeda Hospital), and Kiyoyuki Tokuyama (Tokuyama Clinic).

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