Cinacalcet (KRN1493) effectively decreases the serum intact PTH level with favorable control of the serum phosphorus and calcium levels in Japanese dialysis patients

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Abstract
Background. Cinacalcet hydrochloride (KRN1493) acts on the parathyroid calcium receptors to suppress parathyroid hormone (PTH) secretion, and is already in wide use in the United States and the European countries. In this study, we examined the efficacy and safety of cinacalcet in Japanese patients on maintenance haemodialysis.

Methods. One hundred forty-four patients with serum intact PTH (iPTH) levels \( \geq 300 \text{ pg/ml} \) were enrolled and randomly allocated to two groups assigned to receive either cinacalcet or placebo for 14 weeks. 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.

Results. Cinacalcet significantly decreased the median iPTH level from 606.5 pg/ml to 241.0 pg/ml, despite the mean dialysis vintage being 2.4 times longer (14.3 ± 7.1 years) and the proportion of patients receiving vitamin D sterols being higher, than in the phase 3 studies conducted in the US/EU. The target iPTH level was achieved in 51.4% of the patients in the cinacalcet group, in sharp contrast to only 2.8% in the placebo group. Furthermore, the percentage of patients with both the serum calcium and phosphorus levels within the target range in the K/DOQI guidelines increased from 4.2% to 26.4% by cinacalcet.

Conclusions. These results suggest that lower dose levels of cinacalcet, as compared to those in US/EU studies, may be sufficient effectively suppress the serum iPTH levels and allow favourable management of the serum calcium and phosphorus levels in Japanese patients, having a longer average dialysis vintage.

Keywords: calcimimetics; calcium; calcium-sensing receptor; cinacalcet; PTH; phosphorus; secondary hyperparathyroidism

Introduction

Secondary hyperparathyroidism (SHPT) is a major complication of end-stage renal disease (ESRD), characterized by persistent elevation of the serum levels of intact parathyroid hormone (iPTH) and is frequently complicated by disturbed mineral metabolism [1,2].

Excessive serum levels of iPTH are known to cause high-turnover bone disease, i.e. osteitis fibrosa, and have also been reported to increase the mortality risk in patients undergoing haemodialysis [3–5]. It was also reported that bone marrow fibrosis was observed when intact PTH levels were >250 pg/ml [1].

The medical therapeutic options available for SHPT are oral or intravenously administered vitamin D sterols and phosphate binders. Although vitamin D sterols have been shown to be effective in suppressing elevation of the serum PTH levels, they also enhance the intestinal absorption of calcium and phosphorus to cause deranged mineral metabolism in patients with ESRD [6]. Furthermore, combined use of vitamin D sterols with calcium-containing phosphate binders increases the risk of hypercalcemia and elevation of serum calcium phosphorus product (\( \text{Ca} \times \text{P} \)). Studies by Ganesh et al. [3] and Block et al. [4] have reported that elevated serum levels of calcium, phosphorus and \( \text{Ca} \times \text{P} \) are strongly correlated with increased risk of
cardiovascular diseases and mortality in haemodialysis patients. Based on such evidence, the K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Renal Disease were published in 2003, in which the target ranges for the serum concentrations of calcium (8.4–9.5 mg/dl), phosphorus (3.5–5.5 mg/dl) and iPTH (150–300 pg/ml) in patients undergoing dialysis are indicated [7].

Two medical approaches, namely, the use of new vitamin D analogues and that of non-calcemic phosphate binders, have been adopted to suppress the development of SHPT. However, their availability in Japan, as compared with that in the US/EU, is still limited, as 19-nor-1,25-(OH)2D2 has not yet been launched in the market and lanthanum carbonate has not yet been approved in Japan. Another noteworthy feature in Japan is the longer mean dialysis vintage in the patients. The average duration of haemodialysis in Japan is 7.4 years, while it is only 3.4 years and 5.1 years, on average, in the United States and EU, respectively [8]. As SHPT is a progressive disease, the severity of SHPT has been shown to be correlated with the dialysis vintage. Thus, this study was prompted based on the consideration that these unique clinical circumstances in Japan may affect the efficacy and safety of newly developed therapies for the treatment of SHPT in patients of ESRD undergoing haemodialysis.

Calcimimetic agents, such as cinacalcet HCl (KRN1493), have been developed for controlling PTH secretion; these agents act by enhancing the sensitivity of the parathyroid calcium receptors to extracellular calcium ion levels [9,10], without increasing the serum levels of calcium, phosphorus or Ca × P [11–14]. In this article, we report the results of a phase 3 trial of cinacalcet in Japanese haemodialysis patients with SHPT.

Methods

Study participants

Patients with ESRD and SHPT who were undergoing haemodialysis three times a week for at least 16 weeks and were in a medically stable condition were enrolled as the candidates in this study. The main eligibility criteria were serum iPTH level ≥300 pg/ml both at 1 and 2 weeks prior to the cinacalcet administration; serum calcium level ≥9.0 mg/dl at 1 week prior to the cinacalcet administration and age ≥20 years. The main exclusion criteria were parathyroidectomy within 24 weeks prior to the treatment; percutaneous ethanol injection therapy into the parathyroid gland (PEIT) during the 4 weeks’ screening period; severe impairment of hepatic function; severe hypertension; uncontrolled diabetes mellitus; cancer; severe infection and severe cardiac failure. During the screening period of 4 weeks, the use of vitamin D sterols and phosphate binders, the dialysate calcium concentration and the type of dialyzer were kept unchanged in all the patients. During the study, all patients included in this study were receiving regular haemodialysis, three times a week. Generally, Japanese patients were receiving haemodialysis for 4 h at one dialysis session. In general, blood flow volume is 200 ml/min and dialysate volume is 500 ml/min.

Twenty-nine dialysis centers in Japan participated in this study. This study was conducted in conformity with ICH-GCP and the Declaration of Helsinki. The protocol and informed consent forms were approved by each institution’s Research Ethics Committee. All the patients gave written consent prior to their participation in the study. This study was registered as CGR030600060 in COCHRANE.

Study design

This placebo-controlled, double blind, randomized, multi-centre study was conducted in Japan from April through December 2004. The study period consisted of a screening period of 4 weeks followed by a treatment period of 14 weeks. The primary endpoint was the percentage of patients with serum iPTH levels ≥250 pg/ml at the end of the dosing. One hundred and forty-four patients who fulfilled the eligibility criteria were randomly allocated to either cinacalcet or placebo by a central computerized system. For the randomization, it was considered to stratify the patients according to the serum iPTH (<800, 800–1000 or >1000 pg/ml) and calcium (<10.5, >10.5 or ≥10.5 mg/dl) levels measured at 1 week prior to the start of the treatment. Furthermore, to minimize allocation bias, the difference in the number of patients between the two groups at each centre was limited to less than two. Not only the investigators, but also all the members involved in the study from the sponsor’s side were blinded to the respective patients’ allocation. The study medication was administered immediately before the start of dialysis on the first day, and then daily, at approximately the same time of the day.

Each patient’s compliance with the treatment was checked weekly from diary entries made by the patients. Cinacalcet was started at the dose of 25 mg daily (free base equivalent, one tablet). Both the cinacalcet and placebo tablets were manufactured by Kirin Brewery Co., Ltd (Tokyo, Japan). The dose of cinacalcet was increased sequentially by 25 mg/day up to 100 mg/day with at least a 3-week interval. Dose increases were undertaken only in patients with (i) serum iPTH levels over 250 pg/ml, (ii) serum calcium levels ≥8.4 mg/dl, (iii) no adverse events precluding the dose increase. The dose could be reduced at the investigator’s discretion in the case of adverse events or excessive decrease of the serum iPTH level. In addition, the study drug administration was necessarily withheld if the serum calcium decreased to less than 7.5 mg/dl.

The serum levels of iPTH, calcium, albumin, phosphorus, bone alkaline phosphatase, osteocalcin, tartrate-resistant acid phosphatase (TRAP) and other blood chemistry parameters were measured at a central laboratory (Mitsubishi Kagaku Bio-Clinical Laboratories, Inc., Tokyo, Japan). The serum levels of iPTH, calcium, albumin and phosphorus were measured weekly. The serum iPTH level was determined by immunometric assay (Allegro PTH, Nichols Institute Diagnostics, CA). Serum samples were collected just before the dialysis and study drug administration, 3 days after the previous dialysis, in most cases, on the first dialysis day of the week. The serum calcium values were corrected for the albumin concentration using modified Payne’s method [15]. For each 0.1 g/dl decrease in the serum
albumin level below 4.0 g/dl, the serum calcium was increased by 0.1 mg/dl. The safety of the treatment was assessed by monitoring adverse events, laboratory variables and vital signs.

Concomitant therapy

During the treatment phase, increases in the dose of vitamin D sterols were permitted only if the serum iPTH level exceeded the baseline value by 50% or more on three consecutive visits, the serum calcium level remained below 8.4 mg/dl or hypocalcemic symptoms persisted despite increase in the dose of calcium-containing phosphate binders. Reductions in the doses of vitamin D sterols were permitted in cases where the serum calcium levels were over 11.0 mg/dl. No restrictions were imposed on the dose or type of phosphate binders used. From the 2 weeks prior to the cinacalcet treatment through the end of dosing, the dialysate calcium concentration was kept fixed for each patient. Because cinacalcet inhibits cytochrome P450 2D6, drugs metabolized by this enzyme and having a narrow therapeutic index, such as flecainide, thioridazine, haloperidol and tricyclic antidepressants, were prohibited throughout the study period. Drugs affecting bone metabolism, such as bisphosphonates, calciiton, estrogen or its analogues, selective estrogen receptor modulators and parathyroidectomy or percutaneous injection of ethanol, acetate or vitamin D sterols into the parathyroid gland were also prohibited.

Statistical analyses

Balance in demographic factors and baseline variables among the treatment groups were examined by the chi-square test and one-way ANOVA, and two-sided $P$ values <0.15 were considered statistically significant. The full analysis set (FAS) was used to analyse all the efficacy endpoints. The percentage of patients with serum iPTH levels $\leq 250$ pg/ml at the end of the dosing in the two treatment groups was compared by the chi-square test and two-sided $P$ values <0.05 were considered statistically significant. The percentage of patients in whom the serum iPTH levels decreased by $\geq 30\%$ by the end of the dosing in the two groups was compared by chi-square test and two-sided $P$ values <0.05 were considered statistically significant. Serum levels of iPTH, phosphorus, $\text{Ca} \times \text{P}$, bone alkaline phosphatase, osteocalcin and tartrate-resistant acid phosphatase at the end of the dosing period in the two treatment groups were compared by a non-paired $t$-test and two-sided $P$ values <0.05 were considered statistically significant. All statistical analyses were performed using the SAS software package (version 8.02; SAS Inc, Cary, NC). The percentage of patients with serum calcium and phosphorus levels within the target ranges specified in the K/DOQI guidelines was calculated for each treatment group at baseline and at the end of the dosing period. The data on the serum iPTH level were expressed as median with 25% and 75% quartiles, and the other serum chemistry data were expressed as mean $\pm$ SD. All the patients who received at least one dose of the study drug were included for the safety analysis.

Estimation of sample size was based on a chi-square test of equal proportions of patients with iPTH level $\leq 250$ pg/ml at the end of dosing, with a statistical significance level of 0.05 (two-sided). The placebo response was predicted on the basis of the previous cinacalcet study in Japan to be 10%. With a cinacalcet response rate of 35% assumed for the purpose of sample size considerations, a sample size of 140 patients (70 cinacalcet, 70 placebo) yielded 90% of power.

Results

Patient demographics and distribution

Of the total 144 patients enrolled, one patient dropped out of the study prior to the start of the treatment. Of the remaining 143, 72 received cinacalcet and 71 received placebo. Two cinacalcet-treated patients withdrew from the study because of the development of adverse events and two placebo-treated patients withdrew their consent. Thus, the study was completed in 70 cinacalcet-treated patients and 69 placebo-treated patients. Table 1 shows the baseline demographics of the study patients. The mean age of the patients was around 55 years and the average duration of dialysis was 171.8 months. There were no statistically significant differences in the baseline demographic characteristics between the two treatment groups.

Table 2 shows the biochemical parameters in the two groups. The median serum iPTH levels at baseline were 606.5 pg/ml and 552.0 pg/ml in the cinacalcet and placebo group, respectively (difference not significant, NS). The percentage of patients with serum iPTH $\geq 800$ pg/ml was 27.8% in the cinacalcet and 26.8% in the placebo group (difference NS). No significant differences between the two groups were observed in relation to any other biochemical parameters either. The percentage of patients with high serum calcium levels ($\geq 10.5$ mg/dl) was 36.1% in the cinacalcet and 31.0% in the placebo group (difference NS).

### Table 1. Baseline demographics of the study patients

<table>
<thead>
<tr>
<th></th>
<th>Cinacalcet $(N = 72)$</th>
<th>Placebo $(N = 71)$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean $\pm$ SD</td>
<td>54.7 $\pm$ 11.0</td>
<td>55.7 $\pm$ 11.7</td>
<td>0.620</td>
</tr>
<tr>
<td>Duration of dialysis (months)</td>
<td>170.4 $\pm$ 93.7</td>
<td>173.3 $\pm$ 76.0</td>
<td>0.839</td>
</tr>
<tr>
<td>Gender $N$ (%)</td>
<td>Female $(32 (44.4))$</td>
<td>34 (47.9)</td>
<td>0.679</td>
</tr>
<tr>
<td></td>
<td>Male $(40 (55.6))$</td>
<td>37 (52.1)</td>
<td></td>
</tr>
<tr>
<td>Primary diagnosis $N$ (%)</td>
<td>Chronic glomerulonephritis $(46 (63.9))$</td>
<td>51 (71.8)</td>
<td>0.318</td>
</tr>
<tr>
<td></td>
<td>Diabetic nephritis $(3 (4.2))$</td>
<td>4 (5.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cystic kidney disease $(2 (2.8))$</td>
<td>4 (5.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others $(21 (29.2))$</td>
<td>12 (16.9)</td>
<td></td>
</tr>
<tr>
<td>Vitamin D use $N$ (%)</td>
<td>No $(9 (12.5))$</td>
<td>8 (11.3)</td>
<td>0.819</td>
</tr>
<tr>
<td></td>
<td>Yes $(63 (87.5))$</td>
<td>63 (88.7)</td>
<td></td>
</tr>
<tr>
<td>Phosphate binder use $N$</td>
<td>No $(5 (6.9))$</td>
<td>3 (4.2)</td>
<td>0.479</td>
</tr>
<tr>
<td></td>
<td>Yes $(67 (93.1))$</td>
<td>68 (95.8)</td>
<td></td>
</tr>
</tbody>
</table>
The mean cinacalcet dose at the end of the dosing period was 63.9 mg/day. Mean dose at the end of study in the patients with baseline PTH level < 800 pg/ml was 60.6 mg/day, while 85.0 mg/day in the others. In the cinacalcet group, 44.4% of patients were using dialysate with calcium level less than 3.0 mEq/l, while 47.9% of patients in the placebo group. For the use of phosphate binders at baseline, the proportional pattern of patients using calcium containing drug, sevelamer and both of them were similar between the cinacalcet group and the placebo group. There was no change of the phosphate binders in most of patients in the placebo group throughout the study. On the other hand, about 30% of patients in the cinacalcet group increased the dose of calcium containing phosphate binders. In addition, 15% of patients who had been using only sevelamer at baseline started additional use of calcium salt after the start of cinacalcet treatment. No modification was taken for vitamin D use in all the patients through the study period.

**PTH results**

Significant decrease of the serum median iPTH level was noted at the end of the dosing (606.5–241.0 pg/ml) in the cinacalcet group, while no significant change was observed in the placebo group (552.0–544.0 pg/ml) (Table 2, Figure 1). The target iPTH level (≤250 pg/ml) was achieved in 51.4% (37/72) of the patients in the cinacalcet group at the end of the dosing, in sharp contrast to only 2.8% (2/71) in the placebo group (P < 0.001, Figure 2). The mean percent reduction in the serum iPTH level at the end of the dosing relative to that at baseline was 54.4% in the cinacalcet group, while it was as low as −0.4% in the placebo group (Table 2). The percentage of patients in whom the serum iPTH levels decreased at ≥30% by the end of the dosing relative to the value at baseline was higher in the cinacalcet group than in the placebo group (P < 0.001, Figure 2).

In the cinacalcet group, the percentage of patients in whom the target iPTH level was achieved decreased as the baseline serum iPTH level increased; 81.0, 48 and 25% in the patients with baseline iPTH levels below 500 pg/ml, 500–800 pg/ml and over 800 pg/ml, respectively.

**Efficacy of cinacalcet stratified by the disease severity, concomitant use of vitamin D sterols and the serum calcium levels**

There were no significant differences in the percentage of patients using vitamin D sterols before the start of the study period and the baseline serum PTH or

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**Table 2. Biochemical parameters at baseline and at the end of the dosing period**

<table>
<thead>
<tr>
<th></th>
<th>Cinacalcet (N = 72)</th>
<th>Placebo (N = 71)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact PTH (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>606.5 (439.0, 848.5)</td>
<td>552.0 (420.0, 864.0)</td>
<td></td>
</tr>
<tr>
<td>End of dosing</td>
<td>241.0 (169.5, 355.5)</td>
<td>544.0 (365.0, 858.0)</td>
<td></td>
</tr>
<tr>
<td>Percent change from baseline</td>
<td>54.36 ± 20.13</td>
<td>0.38 ± 36.40</td>
<td></td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10.22 ± 0.61</td>
<td>10.15 ± 0.62</td>
<td>0.516</td>
</tr>
<tr>
<td>End of dosing</td>
<td>9.29 ± 0.82</td>
<td>10.24 ± 0.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.18 ± 1.33</td>
<td>6.06 ± 1.39</td>
<td>0.594</td>
</tr>
<tr>
<td>End of dosing</td>
<td>5.55 ± 1.48</td>
<td>6.05 ± 1.49</td>
<td>0.042</td>
</tr>
<tr>
<td>Calcium-phosphorus product (mg/dl)²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>63.05 ± 13.41</td>
<td>61.34 ± 13.60</td>
<td>0.449</td>
</tr>
<tr>
<td>End of dosing</td>
<td>51.62 ± 14.71</td>
<td>61.83 ± 14.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bone alkaline phosphatase (U/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>42.16 ± 29.89</td>
<td>41.79 ± 31.77</td>
<td>0.942</td>
</tr>
<tr>
<td>End of dosing</td>
<td>46.60 ± 51.98</td>
<td>43.86 ± 25.95</td>
<td>0.691</td>
</tr>
<tr>
<td>Serum osteocalcin (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>172.3 ± 105.1</td>
<td>166.3 ± 95.6</td>
<td>0.718</td>
</tr>
<tr>
<td>End of dosing</td>
<td>107.9 ± 66.9</td>
<td>169.5 ± 90.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tartrate-resistant acid phosphatase (IU/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>9.51 ± 3.26</td>
<td>9.29 ± 2.84</td>
<td>0.670</td>
</tr>
<tr>
<td>End of dosing</td>
<td>8.02 ± 2.37</td>
<td>9.59 ± 2.92</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data on intact PTH are expressed as median (Q1, Q3), while the other parameters are expressed as Mean ± SD.
calcium levels between the cinacalcet and the placebo group.

The effect of cinacalcet on the percent changes of the serum iPTH level at week 14 of the study relative to that at baseline did not differ significantly between patients receiving/not receiving vitamin D sterols at baseline (−55.3 ± 20.5% vs −51.3 ± 17.3%). Also, the percent change in the serum iPTH level following treatment with cinacalcet was similar (−57.2 ± 22.6% vs −53.8 ± 19.1%) in patients with higher (≥800 pg/ml) and lower (<800 pg/ml) serum iPTH levels at baseline. In addition, the baseline serum calcium levels did not affect the percent change of the serum iPTH level induced by cinacalcet (−55.1 ± 19.3% vs −54.6 ± 20.7%, respectively, in patients with higher (≥10.5 mg/dl) baseline serum calcium levels and lower (<10.5 mg/dl) baseline serum calcium levels.

Effects on the serum levels of calcium, phosphorus and the calcium-phosphorus product

Significant decreases of the serum levels of calcium, phosphorus and Ca × P were observed in the cinacalcet group as compared with that in the placebo group (Table 2, Figure 3).

The percentage of patients in whom the serum levels of both calcium and phosphorus were over the respective target ranges proposed by the K/DOQI guidelines decreased dramatically from 58.3% at baseline to 22.2% at the end of the dosing period in the cinacalcet group, while no significant change was observed in the placebo group (54.9% vs 52.1%). Furthermore, the percentage of patients in whom the serum levels of both calcium and phosphorus were controlled to within the respective target ranges specified in the K/DOQI guidelines increased from 4.2% at baseline to 26.4% at the end of the dosing period in the cinacalcet group, while no significant change was observed in the placebo group (Table 3). In addition, the mean Ca × P decreased significantly from 63.1 (mg/dl)² at baseline to 51.6 (mg/dl)² following treatment in the cinacalcet group.

Effects on the bone metabolism markers

A decrease in the mean serum level of osteocalcin by 32.7% was observed in the cinacalcet group, whereas no significant change was observed in the placebo group (P < 0.001). In addition, a decrease in the mean serum level of TRAP by 13.3% was also observed in the cinacalcet group, whereas the serum bone alkaline phosphatase level was slightly increased in this group (Table 2).

Safety results

At least one adverse event was reported in 97.2% (70 of 72) of the patients in the cinacalcet group and 94.4% (67 of 71) of the patients in the placebo group. Two cinacalcet-treated patients withdrew from the study because of adverse events (‘pneumonia’ and ‘gastrointestinal haemorrhage’). Both events were judged to be not related to the study drug by the investigator. No patient withdrew from the study because of drug-related adverse events. No serious adverse event related to cinacalcet was reported. The most frequent adverse event in the cinacalcet group was ‘nausea’ (36.1%), which occurred significantly less frequently in the placebo group (19.7%). Other adverse events that occurred more frequently in the
cinacalcet group than in the placebo group were ‘stomach discomfort’ (25% vs 11.3% in the placebo group), and ‘vomiting’ (22.2% vs 5.6% in the placebo group). Most of the gastrointestinal events were generally mild to moderate in severity. In the cinacalcet group, the numbers of events for nausea, vomiting, stomach discomfort and appetite loss were 32, 21, 20 and 4, respectively (total 77 events). Of those, the number of events which needed medical treatment was 36 (47%). Dose reduction was also needed for 16 events (21%), and dose stopping was conducted for six events (8%) in which re-exposure to cinacalcet enabled the patients to complete the study.

‘Blood calcium decreased’ and ‘hypocalcemia’ developed in two (2.8%) and four (5.6%) of cinacalcet-treated patients, respectively, while no such event was observed in the placebo group. In the cinacalcet group, mean serum calcium level remained lower in the patients not using vitamin D, although in whom no case of hypocalcemia was observed, than the patients using vitamin D. All of these hypocalcemic events could be managed by increasing the dose of calcium carbonate and/or vitamin D sterols received by the patients, or adjustment of the cinacalcet dose. In the cinacalcet group, mean QTc interval was prolong (27) by 6.3, 10.8, 10.7, 7.5 and 8.1 ms at study week 3, 6, 9, 12 and 14, respectively, while placebo did not prolong (27) QTc interval. These prolongations (28) by cinacalcet were considered to be related to (29) the reduction in serum calcium level. However, there was no significant difference in the incidence of cardiac events between the two treatment groups.

Discussion

Notwithstanding the differences in the availability of some clinical drugs used in haemodialysis patients and the demographic characteristics of these patients between Japan and the US/EU, the efficacy and safety profile of cinacalcet in this study was similar to that reported from the United States and European countries [11].

The primary endpoint of this study was the percentage of patients with serum iPTH levels ≤250 pg/ml at the end of the dosing period. While it was achieved in 51.4% (n = 37) of the patients in the cinacalcet group, 48.6% (n = 35) of the patients failed to reach it. Comparison of the baseline demographic characteristics between the two groups revealed no statistically significant differences, except in the mean baseline iPTH level, which was 554.5 pg/ml in the patients in whom the primary endpoint was achieved, and 836.7 pg/ml in those in whom it was not (P < 0.001). Actually, the percentage of patients in whom the target iPTH level was achieved decreased significantly as the baseline serum iPTH level increased (P < 0.001 by Cochran-Armitage test); 81%, 48% and 25% in the patients with baseline iPTH levels below 500 pg/ml, 500–800 pg/ml and over 800 pg/ml, respectively.

The K/DOQI guidelines recommend parathyroidectomy in patients with severe SHPT (serum levels of iPTH >800 pg/ml) associated with hypercalcemia and/or hyperphosphatemia refractory to medical therapy [7]. Tominaga et al. [16] showed that patients with intact PTH levels >500 pg/ml were likely to have at least one nodular hyperplastic parathyroid gland and refractory to maxacalcitol therapy, and also described that total gland weight correlated well with PTH levels in patients. Therefore, patients with intact PTH levels >800 pg/ml were deduced to have further progression in hyperplastic nodularity or severity. In this study, cinacalcet enabled 25% of the patients with baseline iPTH levels >800 pg/ml to achieve the target iPTH level. This result suggests that cinacalcet may be a promising and potent medical therapeutic alternative for some haemodialysis patients with elevated serum iPTH levels.

Patients with SHPT frequently exhibit hypercalcemia and/or hyperphosphatemia; the finding in this study that 38.3% and 54.9% of patients in the cinacalcet and placebo groups, respectively, had serum levels of both calcium and phosphorus over the target ranges specified in the K/DOQI guidelines at baseline was consistent with this clinical observation. While control of the serum levels of calcium and phosphorus was not a primary endpoint in our study, simultaneous reduction of the serum calcium and phosphorus levels along with that of the serum iPTH was observed in the cinacalcet group, with an increase in the number of patients with serum calcium and phosphorus levels within the target ranges specified in the K/DOQI guidelines. These results are similar to those reported from the United States, however, the two-dimensional method showing the distribution of the patients in each matrix is very suggestive and important to understand the simultaneous changes in the serum calcium and phosphorus levels observed with the use of cinacalcet; it provides us with a direction on how to use or
combine cinacalcet therapy and other treatments, such as vitamin D and/or phosphate binders, for better managing SHPT in patients with ESRD.

The efficacy and safety profile of cinacalcet in this study was similar to that reported from the United States and European countries [11]. However, a clear difference was observed in the percentage of patients receiving vitamin D sterols at baseline (87.5% and 66%), despite the absence of any significant difference in the mean baseline iPTH levels, between our study and the studies reported from the US/EU. In addition, the mean baseline serum calcium level in this study was equal or higher than that in the US/EU studies (10.2 mg/dl vs 9.9 mg/dl). These demographic characteristics suggest the possibility that the patients in our study were more refractory to vitamin D therapy.

In general, SHPT is known to be a progressive disease. The longer the duration of haemodialysis, the greater the proliferation of the parathyroid cells, with the formation of nodules in the parathyroid glands and greater the resistance to conventional medical treatment. An increase in the frequency of surgical PTx has been reported with increasing dialysis vintage [17]. The mean dialysis vintage in the patients of this study was 14.3 ± 7.1 years, not only longer than the average vintage in Japanese dialysis patients (7.4 years) [8], but also 2.4 times longer than that in the patients of the phase 3 studies in the US/EU [11]. Therefore, it is assumed that the Japanese patients enrolled in this study had more severe SHPT.

Recently, Arenas et al. reported the efficacy of cinacalcet in Spanish patients that presented SHPT with hypercalcemia and hyperphosphatemia [18], and their results were comparable to our results, in that cinacalcet was effective even in patients with high serum calcium levels. There are several reports indicating that cinacalcet is effective for reducing the serum levels of iPTH and calcium in patients with persistent hyperparathyroidism and hypercalcemia after kidney transplantation [19–21]. Our data and these findings suggest the potential usefulness of cinacalcet in cases with severe SHPT and high serum calcium and/or phosphorus levels with diminished regulation of parathyroid function by vitamin D.

One the other hand, the dose range of cinacalcet in this study was lower than that used in the United States and European studies. The maximum dose in the United States and European studies was 180 mg/day, while it was only 100 mg/day in this study. One possible explanation for the higher potency of cinacalcet in Japanese patients is a plausible difference in the pharmacokinetics of the drug between the two geographical regions. However, there appear to be no significant ethnicity-related differences in the pharmacokinetics of cinacalcet, because similar results of single-dose pharmacokinetic studies have been reported from the United States and Japan [22,23].

Another possibility is a difference in the genetic properties of the calcium receptors between the two geographic populations. Recently, one genetic polymorphism of the calcium receptor was reported to affect the response of the parathyroid glands to extracellular calcium [24] and cinacalcet [25] concentrations. This polymorphism may also be the reason for the difference in the efficacy of cinacalcet between the Japanese and western populations. However, the incidence of this polymorphism in Japanese and western populations still remains to be clearly determined. Further long-term studies and further clinical experience will be needed to elucidate whether cinacalcet is indeed effective at lower doses in Japanese patients as compared with those in patients from the United States and European countries.

In conclusion, cinacalcet appears to be a safe and effective therapy for SHPT, even in haemodialysis patients with a relatively long dialysis vintage. Because of its unique mechanism of action and also its effect of lowering the serum calcium and phosphorus levels, cinacalcet may represent a promising new medical therapeutic alternative for SHPT in Japanese haemodialysis patients as in Western populations.

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**Appendix**

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