Clinical experience with cinacalcet HCl

Pablo Ureña Torres
Clinique de l’Orangerie, Aubervilliers, France

Abstract
Secondary hyperparathyroidism (SHPT) is associated with parathyroid gland hyperplasia, increased parathyroid hormone (PTH) production and secretion, disturbed bone and mineral metabolism, soft tissue calcification and an increased risk of death. The condition is an almost universal complication of end-stage renal disease (ESRD) and currently is managed by treatment with phosphate binders and vitamin D compounds, both of which are associated with significant side effects, including hypercalcaemia and hyperphosphataemia. Therapy with calcimimetics is a new approach to the treatment of SHPT. These agents act at the calcium-sensing receptor (CaR), where they increase the sensitivity of the receptor to ionized serum calcium. Activation of the CaR results in a rapid reduction in PTH secretion. The calcimimetic drug cinacalcet HCl currently is undergoing clinical trials in dialysis patients who have uncontrolled SHPT, despite treatment with vitamin D compounds and/or phosphate binders. Clinical trials have confirmed that the drug rapidly reduces plasma PTH, phosphorus and calcium–phosphorus product (Ca\(\times\)P) levels, and that levels of PTH, phosphorus and Ca\(\times\)P remain suppressed for up to 3 years. In clinical trials, cinacalcet HCl was a well-tolerated drug; only nausea and vomiting occurred more frequently in patients who took cinacalcet HCl than in those who took placebo, and the occurrence of hypocalcaemia was limited to the initial phase of the treatment. Cinacalcet HCl is therefore a potentially highly effective and well-tolerated treatment for SHPT in patients with ESRD.

Keywords: calcimimetic therapy; cinacalcet; clinical trials, secondary hyperparathyroidism

Introduction
Excess parathyroid hormone (PTH) secretion is triggered by low serum levels of calcium resulting from the failure of the kidney to clear phosphorus from the body and its inability to produce sufficient quantities of vitamin D. PTH, calcium and phosphorus levels are pathophysiologically inter-related, with the result that therapy aimed at optimizing one level frequently has a detrimental effect on another. Current therapy for secondary hyperparathyroidism (SHPT) is based principally on calcium salts, vitamin D compounds and phosphate-binding agents. Paradoxically, hyperphosphataemia and/or hypercalcaemia may occur as a result of these treatments, and thus prevent adequate reductions in PTH and calcium–phosphorus product (Ca\(\times\)P) levels [1].

Calcimimetic drugs offer a new approach to the treatment of SHPT. The parathyroid gland is extremely sensitive to small changes in extracellular calcium levels and releases PTH when calcium levels are reduced [2]. PTH acts on the kidneys and bone to increase levels of serum calcium, which in turn suppresses PTH secretion via the activation of the calcium-sensing receptor (CaR) on the parathyroid glands. Calcimimetics increase CaR sensitivity to extracellular calcium, thus enabling activation of the receptor at lower serum calcium levels than normal. As a result, in the presence of these agents, the low levels of endogenous calcium in patients with renal failure are able to exert a suppressive effect on PTH secretion. Clinical trials of cinacalcet HCl, the first agent in this new class of drugs to be developed at present, currently are ongoing and are reviewed briefly in this article.

Single- and multiple-dose studies
In a single-dose study, 52 haemodialysis patients with uncontrolled SHPT despite therapy each received single doses of cinacalcet HCl, ranging from 5 to 100 mg (n = 40), or placebo (n = 12) 3 h after their scheduled standard haemodialysis [3].
At baseline, PTH levels did not differ significantly between the groups, and ranged from 473 to 919 pg/ml. At doses of 5 and 10 mg, cinacalcet HCl failed to reduce PTH levels, but at doses of 25–100 mg, PTH levels decreased during the first hour after dosing compared with placebo. In the 25, 50 and 100 mg groups, PTH levels reached a nadir at ~4 h post-dose (72% reduction in the 100 mg group) and levels did not return to baseline during the 28 h study (Figure 1).

Parathyroid CaRs are often downregulated in patients with severe SHPT who have parathyroid gland hyperplasia, and this might be expected to compromise the efficacy of cinacalcet HCl. This is probably not the case, as demonstrated by patients in the 100 mg group who had severe SHPT (mean PTH level = 919 pg/ml) but still responded well to cinacalcet HCl. These data indicate that patients with varying degrees of severity of SHPT, and with a probably reduced parathyroid CaR expression, are likely to respond to calcimimetic treatment.

Reductions in serum calcium levels followed a similar pattern to those of PTH. Baseline calcium levels ranged from 9.5 to 10.4 mg/dl. At cinacalcet HCl doses of 75 and 100 mg, modest reductions in calcium levels occurred in the first 6–8 h after administration and remained below pre-treatment levels throughout the 28 h study. Despite this, however, no patient developed hypocalcaemia. At lower doses of cinacalcet HCl, calcium levels did not change, despite a reduction in PTH levels. At the two highest doses given, 75 and 100 mg, the maximal individual reductions in serum calcium levels were 1.0 and 0.9 mg/dl, respectively.

In the same study, single daily doses of cinacalcet HCl were administered for 8 days to 23 patients at doses of 10 mg/day (n = 8), 25 mg/day (n = 6) and 50 mg/day (n = 9); seven patients received placebo. Serum phosphorus and Ca × P levels were reduced in all active treatment groups, but did not change in the placebo group. Reductions of 20–30% in serum phosphorus levels contributed to reductions of 20–35% in the levels of Ca × P. However, the 50 mg dose was reduced to 25 mg in two patients on the second or third day of the study because their calcium levels fell transiently below 8.0 mg/dl. The dose was also reduced (from 50 to 25 mg) in a third patient because of nausea and a low serum calcium level (8.2 mg/dl). None of these patients experienced clinically significant hypocalcaemia and all patients completed the 8 day study.

Phase II studies

A placebo-controlled, double-blind, randomized, dose titration phase II study in haemodialysis patients was conducted in the USA [4]. All 71 patients had uncontrolled SHPT, despite treatment with phosphate binders or vitamin D compounds, or both.

Following a 12 week, dose titration phase, patients continued taking their final dose from the titration phase for a further 6 weeks. All patients had a baseline PTH level > 300 pg/ml, a serum calcium level of 8.8–11.0 mg/dl and a Ca × P value of < 70 mg²/dl². Thirty-six patients were randomized to receive cinacalcet HCl at a starting dose of 25 mg/day and 35 patients received placebo. Patients also continued taking phosphate binders and/or vitamin D compounds. The cinacalcet HCl and placebo doses were increased at 3 week intervals. Dose adjustments were made on the basis of changes in PTH and calcium levels. Three patients remained on the lowest dose of cinacalcet HCl throughout the study, six patients were administered 50 mg/day for 15 weeks, eight patients were administered 75 mg/day for 12 weeks, and 17 patients were administered 100 mg/day for 9 weeks.

At baseline, all patients had moderately severe SHPT, normal calcium levels and slightly elevated phosphorus levels (Table 1). Cinacalcet HCl treatment reduced PTH and Ca × P levels significantly compared
with placebo, with the mean reductions from baseline being 33 and 8%, respectively. A reduction in serum PTH levels was observed during the first 2 h post-cinacalcet administration. Serum phosphorus levels declined in the cinacalcet HCl group while they rose in the placebo group, although the difference between the groups did not reach statistical significance. There were no changes to concomitant therapy that would account for the improvements in PTH and Ca × P observed in the cinacalcet HCl group.

Serum calcium levels decreased by almost 5% in the cinacalcet HCl group and rose by 3% in the placebo group. The mechanisms underlying the observed reduction in serum calcium in response to cinacalcet HCl were not defined in the study. The effect of the calcimimetics may be similar to the ‘hungry bone syndrome’ that has been observed following parathyroidectomy, in which a rapid reduction in serum PTH is followed by increased bone mineralization; serum calcium and phosphorus fall as these minerals are incorporated into new bone [5]. Figure 2 shows that serum calcium levels decreased in the first few weeks of treatment and then stabilized.

Data were combined from three other phase II studies in which a total of 142 patients in the USA,

### Table 1. Mean (±SE) levels of PTH, serum calcium, serum phosphorus and Ca × P during the 6 week maintenance stage of a phase II, double-blind, randomized, placebo-controlled study

<table>
<thead>
<tr>
<th></th>
<th>Cinacalcet HCl (n = 36)*</th>
<th>Placebo (n = 35)*</th>
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<tbody>
<tr>
<td><strong>PTH (pg/ml)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>626 ± 53</td>
<td>583 ± 72</td>
</tr>
<tr>
<td>Maintenance</td>
<td>451 ± 74</td>
<td>552 ± 87</td>
</tr>
<tr>
<td>% change</td>
<td>-32.5 ± 7.6**</td>
<td>3.0 ± 8.5</td>
</tr>
<tr>
<td><strong>Serum calcium (mg/dl)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>9.6 ± 0.1</td>
<td>9.7 ± 0.1</td>
</tr>
<tr>
<td>Maintenance</td>
<td>9.2 ± 0.1</td>
<td>9.9 ± 0.1</td>
</tr>
<tr>
<td>% change</td>
<td>-4.6 ± 1.4**</td>
<td>2.6 ± 1.3</td>
</tr>
<tr>
<td><strong>Serum phosphorus (mg/dl)</strong></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>6.0 ± 0.2</td>
<td>5.5 ± 0.2</td>
</tr>
<tr>
<td>Maintenance</td>
<td>5.8 ± 0.2</td>
<td>5.7 ± 0.2</td>
</tr>
<tr>
<td>% change</td>
<td>-2.6 ± 3.4</td>
<td>7.0 ± 5.5</td>
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<tr>
<td><strong>Ca × P (mg²/dl²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>57.6 ± 1.6</td>
<td>53.4 ± 2.3</td>
</tr>
<tr>
<td>Maintenance</td>
<td>53.1 ± 1.8</td>
<td>56.6 ± 2.3</td>
</tr>
<tr>
<td>% change</td>
<td>-7.9 ± 2.9*</td>
<td>11.0 ± 6.5</td>
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</table>

*For the maintenance period, n = 34 in the cinacalcet HCl group and n = 31 in the placebo group.

*P = 0.013; **P < 0.001, compared with placebo.

Reproduced, with permission, from Quarles et al. [4].

**Fig. 2.** Mean (± SE) serum calcium levels during 18 weeks of treatment with cinacalcet HCl (25–100 mg/day) or placebo. Reproduced, with permission, from Quarles et al. [4].
Canada and Europe received cinacalcet HCl at doses of 50 or 100 mg/day for 12 weeks [6–8]. Mean reductions in PTH levels of 19 and 32% were observed in the 50 and 100 mg/day cinacalcet HCl groups, respectively, compared with an increase of ~20% in the placebo group. Overall, a reduction of 25% in PTH levels occurred in the patients who took cinacalcet HCl at a dose of either 50 or 100 mg/day. A reduction in the level of Ca × P of 8% also occurred in the cinacalcet HCl group, whereas both Ca × P and PTH levels increased in the placebo group by ~15% (Figure 3).

Block et al. administered placebo or cinacalcet HCl at doses titrated from 50 to 180 mg/day to 82 haemodialysis patients with SHPT not controlled by either phosphate binders or vitamin D compounds [9]. PTH levels were 300 pg/ml or higher at baseline and 98% of patients were taking phosphate binders; 61% of patients taking cinacalcet HCl and 54% of those taking placebo were also receiving vitamin D compounds. Patients continued taking these drugs throughout the study. The cinacalcet HCl dose was titrated at 2 week intervals over weeks 1–8 until the levels of PTH were ≤250 pg/ml, and the efficacy of the final dose was assessed over weeks 9–12.

During the efficacy assessment period, target PTH levels were achieved in 54% of patients administered cinacalcet HCl, compared with only 5% of those administered placebo. In 63% of patients receiving cinacalcet HCl, PTH levels were reduced by ≥30% (Table 2). As in other studies, Ca × P values were also reduced by cinacalcet HCl in the first 4–6 weeks of treatment and then stabilized. In contrast, there was a non-significant decrease from baseline in the placebo group.

**Phase III studies**

Three phase III, placebo-controlled, double-blind, randomized, dose titration studies have been completed at centres in North America, Europe and Australia. Over 1100 haemodialysis and peritoneal dialysis patients with uncontrolled SHPT participated in these 26 week studies. Patients included in the studies had intact PTH (iPTH) levels of ≥300 pg/ml and received cinacalcet HCl at 30–180 mg/day or placebo. The primary end-point was the proportion of patients who achieved a mean iPTH level of ≤250 pg/ml during the 14–16 week efficacy assessment period. The results of these studies recently were presented at a major meeting [10–12]. Cinacalcet HCl significantly reduced iPTH levels (P < 0.001) and significantly more cinacalcet HCl patients achieved an iPTH ≤250 pg/ml compared with the control group (P < 0.001). The reductions in iPTH were accompanied by significant reductions in serum Ca × P (P < 0.001), calcium (P < 0.001) and phosphorus (P < 0.001).

**Table 2.** PTH and Ca × P levels during the efficacy assessment phase of a 12 week, randomized, double-blind, placebo-controlled study of cinacalcet HCl at dosages of up to 180 mg/day.

<table>
<thead>
<tr>
<th></th>
<th>Cinacalcet HCl (n=41)</th>
<th>Placebo (n=41)</th>
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<tbody>
<tr>
<td>Baseline iPTH (pg/ml) (± SE)</td>
<td>556 (±46)</td>
<td>630 (±57)</td>
</tr>
<tr>
<td>% of patients with iPTH ≤250 pg/ml</td>
<td>54**</td>
<td>5</td>
</tr>
<tr>
<td>% of patients with iPTH reduced by ≥30%</td>
<td>63**</td>
<td>10</td>
</tr>
<tr>
<td>% change from baseline in mean Ca × P (± SE)</td>
<td>-13.1 (±4.1)</td>
<td>-5.6 (±3.2)</td>
</tr>
<tr>
<td>% of patients with iPTH reduced by ≥30% and no increase in Ca × P</td>
<td>51**</td>
<td>7</td>
</tr>
</tbody>
</table>

iPTH = intact PTH.

**P < 0.001.**

Reproduced, with permission, from Block et al. [9].
Long-term efficacy

Patients who took part in two separate, 1 year, phase II studies continued to take cinacalcet HCl 30–180 mg/day for another year in an extension study [13]. In addition, eligible patients who had taken placebo during the initial year of the phase II studies were switched to cinacalcet HCl at doses of up to 180 mg/day after a dose titration period. Interim data from 49 patients are shown in Figure 4. Patients who had been taking placebo in the previous studies and were then switched to cinacalcet HCl experienced a reduction in their PTH levels within a few weeks to the level of those in the patients who had been taking cinacalcet HCl throughout the studies. PTH levels remained suppressed for the remainder of the study, as did Ca × P values (data not shown).

At the Clinique de l’Orangerie, France, six haemodialysis patients with SHPT took cinacalcet HCl in both a phase II study and the open-label extension study. Four of the patients have now been treated for >3 years and, at baseline, the mean PTH level for these patients was 842 pg/ml. At 166 weeks on cinacalcet HCl, the mean PTH level was 264 pg/ml. Thus, cinacalcet HCl sustained reduced PTH levels in long-term treatment. In addition, alkaline phosphatase levels, a reliable marker of bone remodelling and bone formation, normalized in these patients (Figure 5).

Bone mineral density measurements at three sites, including the femoral neck, in the six patients who received cinacalcet HCl increased by ~10% after 3 years of treatment. This is in marked contrast to findings in 10 patients who received conventional SHPT treatment in the clinic. These patients lost 3% of bone mass at the femoral neck each year. After 3 years, they had lost ~10% of femoral neck bone mineral density. Such results are consistent with those in other clinics, but remain to be confirmed in a large-scale clinical trial.

Tolerability

Combined results from phase III studies suggest that cinacalcet HCl is a well-tolerated drug [14–16]. Most side effects were reported by similar proportions of the cinacalcet HCl and placebo groups, with the exception of nausea and vomiting. In the largest phase III study, which included >400 patients, nausea occurred in 33% of cinacalcet HCl patients and in 19% of those who took placebo [11]. However, the number of patients withdrawing from the study was similar in both groups. Serious adverse events and deaths were similar between treatment groups. Transient hypocalcaemia may be observed during the first weeks of cinacalcet HCl treatment. However, once steady-state cinacalcet HCl levels are reached within 4 days, calcium levels remain constant over the 24 h dosing interval [17].
Conclusion

In conclusion, clinical studies have indicated that cinacalcet HCl reduces plasma PTH and Ca × P levels efficiently in study patients with SHPT without causing significant adverse events. In study patients, the benefits of treatment are sustained in the long term and may include normalization of bone metabolism with a concomitant recovery of bone density. Cinacalcet HCl therefore represents a novel and exciting approach to the control and prevention of SHPT in patients with chronic kidney disease.

Conflict of interest statement. None declared.

References

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Fig. 5. Bone-specific alkaline phosphatase levels in patients on cinacalcet HCl over time (normal range = 3.7–20.9 ng/ml).

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