Paricalcitol- or cinacalcet-centred therapy affects markers of bone mineral disease in patients with secondary hyperparathyroidism receiving haemodialysis: results of the IMPACT-SHPT study

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ABSTRACT

Background. In this Phase 4 international study, efficacy and safety of paricalcitol-centred therapy were compared with that of cinacalcet-centred therapy for the treatment of chronic kidney disease (CKD)-associated secondary hyperparathyroidism (SHPT) in patients undergoing haemodialysis (ClinicalTrials.gov identifier NCT00977080).

Methods. Patients ≥18 years of age with Stage 5 CKD and SHPT [intact parathyroid hormone (iPTH) level of 300–800 pg/mL, calcium level of 8.4–10.0 mg/dL and phosphate concentration of ≤6.5 mg/dL] who were undergoing haemodialysis were included. Patients were randomized by mode of paricalcitol administration [i.e. intravenous (IV) or oral strata] to receive paricalcitol- or cinacalcet-centred therapy for ≤28 weeks. Changes in metabolic markers [total alkaline phosphatase (AP), bone-specific AP and fibroblast growth factor-23 (FGF-23)] and the proportion of patients in each treatment group who achieved an iPTH level of 150–300 pg/mL during Weeks 8, 16 and 28 as a composite value were evaluated.

Results. Compared with cinacalcet-centred therapy, levels of both bone turnover markers were significantly reduced from baseline with IV and oral paricalcitol-centred treatment (P < 0.05 for both dosing strata) at Weeks 8, 16 and 28. Levels of FGF-23 were increased with paricalcitol versus cinacalcet-centred treatment. A greater proportion of patients receiving paricalcitol-centred therapy achieved target iPTH levels (i.e. 150–300 pg/mL) throughout the study in the IV and oral dosing strata compared with patients receiving cinacalcet-centred treatment.

Conclusions. In patients with CKD and SHPT undergoing haemodialysis, paricalcitol-centred therapy reduced circulating bone turnover markers and iPTH levels and increased FGF-23 levels compared with cinacalcet-centred treatment.

Trial registration. ClinicalTrials.gov identifier NCT00977080.

Keywords: bone turnover marker, chronic kidney disease, cinacalcet, paricalcitol, secondary hyperparathyroidism

INTRODUCTION

Chronic kidney disease (CKD; defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m2 or an albumin/creatinine ratio of ≥30 mg/day) is a growing public health concern. According to the National Health and Nutrition Examination Survey, ~13% of the US population has CKD [1], and its prevalence has been increasing in recent years [2]. In addition, CKD is associated with increased morbidity and mortality [3] even after adjusting for other health concerns, such as diabetes [4] and hypertension [2], and is linked with bone disease [5] and vascular calcification [6, 7] as a consequence of a disruption in mineral (i.e. phosphate, calcium) homeostasis. Patients with CKD also often experience secondary hyperparathyroidism (SHPT) attributable to altered calcium and phosphate homeostases, vitamin D deficiency and elevated levels of fibroblast growth factor-23 (FGF-23) [8].
Patients with CKD-associated SHPT have an elevated risk of mortality [9], perhaps as a consequence of the conditions underlying the disease (e.g., alterations in calcium [10], hyperphosphatemia [10], elevated parathyroid hormone [PTH] [10] and FGF-23 levels [11]). Thus, a major therapeutic goal for treatment of SHPT is the normalization of metabolism and mineral homeostasis.

Current treatment options for CKD-associated SHPT include non-selective calcimimetic agents (e.g., cinacalcet), vitamin D, and non-selective (e.g., alfacalcidol, calcitriol) and selective (e.g., paricalcitol) vitamin D analogues [5]. However, high doses of calcitriol may cause hypercalcemia [12], potentially increasing the risk of extraskeletal calcification, and cinacalcet has been associated with hypocalcemia and, consequently, is only indicated for treatment of severe Stage 5 CKD [5]. In contrast, the selective vitamin D analogue, paricalcitol, significantly reduced intact parathyroid hormone (iPTH) levels and maintained serum calcium levels within the range of normal with no alteration of phosphate levels in patients with advanced kidney disease [13]. In addition, top-line results from the IMPACT-SHPT study demonstrated that paricalcitol-centred treatment was more effective than cinacalcet-centred treatment in achieving Kidney Disease Outcomes Quality Initiative (KDOQI)-recommended iPTH target levels [14]. The present report from the IMPACT-SHPT study describes the effect of paricalcitol-centred therapy on bone turnover markers [total alkaline phosphatase (AP) and bone-specific alkaline phosphatase (BSAP)] and FGF-23 in patients with SHPT receiving haemodialysis.

**Subjects and methods**

**Study design and participants**

The IMPACT-SHPT study was a 28-week, randomized, open-label Phase 4 study (ClinicalTrials.gov identifier NCT00977080) that compared the efficacy of paricalcitol-centred treatment with cinacalcet-centred treatment in patients with SHPT receiving haemodialysis [15]. This multinational study was conducted at 89 sites in 12 countries in accordance with the study protocol, International Conference on Harmonization guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles established in the Declaration of Helsinki [14]. All participants provided written informed consent before beginning the study [15]. The study design, population and inclusion/exclusion criteria have been previously described in detail in Ketteler et al. [15].

In brief, patients ≥18 years of age with Stage 5 CKD who were receiving maintenance haemodialysis three times a week for ≥3 months before screening and were to continue haemodialysis throughout the designated study period were enrolled between November 2009 and May 2011. Eligible patients were required to have a serum iPTH level 130–300 pg/mL, a phosphorus level of ≤6.5 mg/dL at randomization. Patients with an allergic reaction or significant sensitivity to any study drug, an expected daily requirement of >2.0 g of oral elemental calcium, or previous parathyroidectomy, chronic gastrointestinal disorders, clinically significant liver disease and use of known inhibitors or inducers of cytochrome P450 3A or of drugs metabolized by cytochrome P450 2D6 within 2 weeks before administration of the study drug were excluded from the study.

Patients were stratified according to the mode of paricalcitol administration including IV stratum (in US and Russian sites) or oral stratum (at all other study sites); however, the cinacalcet treatment group received oral cinacalcet treatment in both the IV and oral strata. After stratification, patients were randomized (1:1) to receive either paricalcitol-centred therapy (initial IV paricalcitol dose 0.07 µg/kg or initial oral paricalcitol dose iPTH/60) or cinacalcet-centred therapy (initial oral cinacalcet dose of 30 mg concomitant with fixed-dose IV doxercalciferol 1.0 µg three times a week or initial oral cinacalcet dose 30 mg concomitant with fixed-dose oral alfacalcidol 0.25 µg/day) for 28 weeks [15]. Cinacalcet was only used as supplemental therapy in patients who experienced hypercalcemia [defined as serum calcium levels of ≥10.5 mg/dL on at least two consecutive blood tests in the presence of high iPTH levels (≥150 pg/mL)] in the paricalcitol-centred IV or oral strata. Dose adjustments of paricalcitol were based on iPTH, calcium and Ca × P levels, and adjustments for cinacalcet were based on calcium and iPTH levels.

**Laboratory assessments**

Serum calcium, phosphorus and iPTH levels were assessed at baseline, every 2 weeks from Weeks 2 through 25 of the study, and at Week 28. KDOQI iPTH target levels were within the range of 150–300 pg/mL [16]. Serum FGF-23 levels were evaluated at baseline and at Weeks 5, 15 and 28. Serum AP and BSAP levels were determined at baseline and at Weeks 5, 15 and 28. Normal values for the parameters assessed are as follows: iPTH, 10–55 pg/mL; Ca++, 9–10.5 mg/dL (2.2–2.6 mmol/L); AP, 20–140 IU/L; BSAP for adult males aged 30–39 years, 7.7–21.3 µg/L and for adult females aged 30–39 years, 5.3–18.8 µg/L; intact FGF-23, 10–50 pg/mL.

iPTH was measured by IMMULITE® chemiluminescent assay system (Siemens, Deerfield, IL) with a linear range of 3–2500 pg/mL. FGF-23 was measured by an enzyme-linked immunosorbent assay for human intact FGF-23 (Immutopics, Inc, San Clemente, CA). Total AP levels were determined by enzymatic assay using p-nitrophenyl phosphate hydrolysis (Roche Diagnostics, Indianapolis, IN). Bone-specific AP was assayed after immune capture with selective high-affinity antibodies (Microvue™ BAP EIA kit; Quidel Corporation, San Diego, CA) [14].

**Statistical methods**

Quantitative baseline demographic and disease characteristics were summarized by mean and standard deviation within stratum and treatment arm. Treatment group comparability was assessed by analysis of variance. Categorical demographic variables were compared between groups using the
Fisher exact test. Mean changes in iPTH, calcium, phosphorus, AP and BSAP levels from baseline to Week 28 were analysed by stratum using an analysis of covariance model that included baseline value as a covariate. Negative binomial regression analysis was used to compare the number of doses held between treatment groups by stratum.

RESULTS

Study participants

As previously described [15], of the 746 patients who underwent screening, 168 patients did not meet the study inclusion criteria. Following a subsequent washout period, an additional 306 patients failed to meet the eligibility criteria. Of the 272 patients randomized to treatment, 268 patients received ≥1 dose of the study drug and were included in the intent-to-treat population. Thus, the IV and oral strata included 126 and 142 patients, respectively. Within the IV stratum, 62 and 64 patients received paricalcitol- and cinacalcet-centred therapy, respectively, and within the oral stratum, 72 and 70 patients received paricalcitol- and cinacalcet-centred treatment, respectively. In the paricalcitol-centred IV stratum, only four patients (8%) developed hypercalcaemia, exhibiting serum calcium of ≥10.5 mg/dL on two consecutive blood tests, in the presence of high iPTH levels and these patients received supplementary cinacalcet; no patient developed hypercalcaemia in the paricalcitol-centred oral stratum [14]. As previously reported [14, 15], baseline demographics and disease characteristics of the study participants were similar for both treatment arms within each stratum (Table 1).

Effects of treatment on bone turnover and other metabolic markers

Mean AP levels decreased from baseline to Week 28 in the paricalcitol-centred groups in both the IV [109.2 to 91.7 IU/L; mean change, −19.1 IU/L (standard error (SE), 6.6)] and oral [95.6 IU/L to 81.2 IU/L; mean change, −15.7 IU/L (SE, 5.1)] strata (Figure 1). In contrast, AP levels increased from baseline to the end of the study in the cinacalcet-centred IV [124.0 to 153.0 IU/L; mean change, 30.5 IU/L (SE, 6.5)] and oral [104.5 to 108.9 IU/L; mean change, 5.4 IU/L (SE, 4.6)] strata. Similarly, BSAP levels decreased from baseline to Week 28 in the paricalcitol-centred IV [53.9 to 27.4 U/L; mean change, −9.3 U/L (SE, 3.6)] and oral [39.2 to 27.3 U/L; mean change, −13.9 U/L (SE, 2.6)] strata (Figure 1). However, BSAP levels increased from baseline to Week 28 in the cinacalcet-centred IV [41.9 to 62.3 U/L; mean change, 21.2 U/L (SE, 3.6)] and oral [47.6 to 48.3 U/L; mean change, 2.5 U/L (SE, 2.5)] strata. IV (Figure 2A) and oral (Figure 2B) administration of paricalcitol-centred therapy led to an increase in levels of FGF-23 compared with baseline at Weeks 5, 15 and 28. At Week 28, FGF-23 levels increased from 5.3 log pg/mL in both paricalcitol-centred groups to 6.1 log pg/mL in the IV (mean change, 0.9 log pg/mL; SE, 0.1) and 6.4 log pg/mL in the oral strata (mean change, 1.2 log pg/mL; SE, 0.1). In comparison, minimal reductions in FGF-23 were observed in the cinacalcet-centred IV and oral strata. In the IV stratum, cinacalcet-centred treatment decreased mean FGF-23 levels from 5 log pg/mL at baseline to 4.6 log pg/mL at Week 28 (mean change, −0.5 log pg/mL; SE, 0.1), which corresponds to an absolute reduction of 60.1 pg/mL from baseline. In the cinacalcet-centred oral stratum, the FGF-23 levels increased from 5.1 log pg/mL at baseline to 5.4 log pg/mL at Week 28 (mean change, 0.3 log pg/mL; SE, 0.1), which corresponds to an absolute reduction of 8.1 pg/mL from baseline.

Table 1. Baseline demographics [14, 15]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IV stratum</th>
<th>Oral stratum</th>
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<tbody>
<tr>
<td></td>
<td>Paricalcitol-centred (n = 62)</td>
<td>Cinacalcet-centred (n = 64)</td>
</tr>
<tr>
<td>Age, mean ± SD (years)</td>
<td>61.2 ± 12.7</td>
<td>59.9 ± 12.0</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>38 (61.3)</td>
<td>38 (59.4)</td>
</tr>
<tr>
<td>Laboratory values (mean ± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum iPTH (pg/mL)</td>
<td>526.3 ± 153.1</td>
<td>521.1 ± 149.2</td>
</tr>
<tr>
<td>Corrected Ca (mg/dL)</td>
<td>9.0 ± 0.6</td>
<td>9.0 ± 0.7</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>4.9 ± 1.1</td>
<td>4.9 ± 1.1</td>
</tr>
<tr>
<td>Total AP (U/L)</td>
<td>111.2 ± 49.4</td>
<td>123.8 ± 51.2</td>
</tr>
<tr>
<td>BSAP (U/L)</td>
<td>36.6 ± 15.8</td>
<td>41.3 ± 25.4</td>
</tr>
<tr>
<td>25-Hydroxyvitamin D (ng/mL)</td>
<td>22.1 ± 13.3</td>
<td>23.2 ± 10.9</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>8.2 ± 2.4</td>
<td>8.6 ± 2.5</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.0 ± 0.3</td>
<td>4.0 ± 0.3</td>
</tr>
</tbody>
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AP, alkaline phosphatase; BSAP, bone-specific alkaline phosphatase; Ca, calcium; iPTH, intact parathyroid hormone; IV, intravenous; SD, standard deviation.
centred oral stratum, FGF-23 levels decreased from 4.9 log pg/mL at baseline to 4.6 log pg/mL at Week 28 (mean change, −0.4 log pg/mL; SE, 0.1), for an absolute reduction of 90.1 pg/mL compared with baseline. Overall, FGF-23 levels were significantly different in the paricalcitol-centred group compared with the cinacalcet-centred group (P < 0.001 for both IV and oral strata). Phosphorus levels peaked at Week 5 and decreased at Weeks 15 and 28 with IV and oral paricalcitol-centred therapy (Figure 2A and B). Whereas phosphorus levels slightly decreased from weeks 5–28 in the cinacalcet-centred IV stratum (Figure 2A), but decreased at Week 5 and increased at Week 28 in the oral stratum (Figure 2B).

**Effects of treatment on iPTH, calcium and phosphate levels**

A greater proportion of patients receiving paricalcitol-centred treatment achieved target iPTH levels (i.e. 150–300 pg/mL) in both the IV (P = 0.016) and oral strata (P = 0.260; data not shown) [14]. Additional analyses demonstrated a continuous increase in the proportion of patients achieving KDOQI iPTH target levels throughout the duration of the study with paricalcitol-centred therapy despite a reduction in the overall dose of paricalcitol administered (Figure 3). In addition, levels of iPTH decreased from baseline and reached KDOQI-defined targets more frequently after treatment with paricalcitol-centred than with cinacalcet-centred therapy, whereas calcium and phosphate levels remained relatively constant with both treatments in both strata (Figure 4).

**Safety**

Hypocalcaemia (calcium <8.4 mg/dL) was more common with cinacalcet-centred therapy (47 and 55% for the IV and oral strata, respectively) than hypercalcaemia (calcium >10.5 mg/dL) with paricalcitol-centred therapy (8 and 0% for the IV and oral strata, respectively) [14]. Significantly, more doses were withheld for patients receiving cinacalcet-centred therapy in the IV and oral strata compared with those receiving paricalcitol-centred therapy. Most of the dose holds in patients receiving paricalcitol-centred treatment resulted from hypercalcaemia, high Ca × P and/or low iPTH levels, whereas most of the dose holds in patients receiving cinacalcet-centred treatment were due to low calcium or iPTH levels (Table 2).

**DISCUSSION**

The benefit of paricalcitol-centred therapy compared with cinacalcet-centred therapy for the reduction of iPTH in patients with SHPT undergoing haemodialysis was previously reported [14]. However, given the diverse set of consequences associated with SHPT in patients undergoing haemodialysis (e.g. bone and mineral disorders), the effects of these two therapies on overall bone and mineral metabolic markers warranted investigation.

SHPT is associated with a diffuse set of skeletal and extraskeletal manifestations, including bone disease and vascular calcification [5]. Multiple factors impact bone formation and resorption [17] and increase bone fragility, which predisposes patients to fractures, joint stiffness and proximal muscle weakness [18]. Use of paricalcitol had beneficial effects on circulating levels of surrogate bone turnover markers (i.e. AP and BSAP) from baseline compared with use of cinacalcet. Thus, the normalization of bone turnover (i.e. reduction in AP and BSAP levels) with paricalcitol-centred treatment may reduce fracture risk and possibly even overall mortality given that increased AP levels have been associated with higher risk of death [19]. However, as bone biopsies with bone histomorphometry were not performed in this study, further research using such evaluations is needed to provide evidence for this potentially beneficial effect.
Levels of FGF-23, a key regulator of phosphate and calcium metabolism [20], were elevated from baseline with paricalcitol-centred therapy and were reduced with cinacalcet-centred therapy. The contrast in FGF-23 levels between the two types of treatment may reflect the differences between the mechanisms of action of the two drugs: cinacalcet antagonizes the calcium-sensing receptor, thereby diminishing PTH release [5] and FGF-23 levels [21], whereas paricalcitol activates vitamin D receptors, potentially promoting the production of FGF-23 through the vitamin D-responsive elements located within the FGF-23 promotor [22]. Given that levels of FGF-23 are predictive of mortality [11], treatment response [23] and cardiovascular calcification [24] in patients receiving dialysis, the increased concentration of FGF-23 associated with paricalcitol-centred therapy may suggest that patients who received paricalcitol-centred therapy might have a worse
prognosis than patients who received cinacalcet-centred therapy. However, the risk of mortality in patients undergoing chronic haemodialysis has been shown to be significantly decreased with paricalcitol treatment [19, 25, 26] compared with no vitamin D analog use and compared with calcitriol [26]. Thus, further insight into the association between increased FGF-23 levels and mortality risk is needed.

As previously reported [14], paricalcitol-centred therapy significantly lowered iPTH levels throughout the 28-week study with minimal alterations in serum calcium or phosphate levels. Similar results have been reported in patients with calcitriol-resistant SHPT undergoing dialysis [27] and in patients with CKD-associated SHPT not receiving dialysis [28]. Thus, paricalcitol-centred therapy may reduce the need for calcium-containing phosphate binders in patients with CKD-associated SHPT given that these are often administered to combat the hypocalcemic effect of cinacalcet treatment on hyperphosphataemia. Indeed, a lower use of calcium-containing phosphate binders was observed with paricalcitol-centred therapy compared with cinacalcet-centred treatment in the IMPACT-SHPT study [14].

The IMPACT-SHPT study was the first large, multinational, head-to-head study of cinacalcet- and paricalcitol-centred therapy. However, only patients with iPTH levels of 300–800 pg/mL at the time of randomization were included, which may limit the generalizability of these findings to a broader patient population (e.g. patients with iPTH levels >800 pg/mL). Also, although bone turnover markers and FGF-23 were assessed herein, the lack of clinically related endpoints (e.g. bone mineral density, fracture rate, vascular calcification) prevent definitive conclusions regarding the effects of paricalcitol- or cinacalcet-centred therapy on bone mineral or cardiovascular disease in patients with SHPT undergoing haemodialysis.

**CONFLICT OF INTEREST STATEMENT**

M.C. has received honoraria for speaking and advisory tasks from AbbVie Inc, Amgen Inc, Genzyme Corp, Shire, Roche, Vifor Pharma and funding from AbbVie Inc, Takeda and Shire. M. K. has received honoraria for speaking and advisory tasks from AbbVie Inc, Amgen Inc, Fresenius Medical Care, Genzyme Corp, Medice, Shire, Vifor Pharma and Mitsubishi Pharma and has received research funding from AbbVie Inc and Amgen Inc. K.J.M. has been a consultant for AbbVie Inc, Cytochroma Inc, KAI Pharmaceuticals and Shire and a speaker for AbbVie Inc and Genzyme Corp. D.G. has received speaker fees from and has been a consultant for AbbVie Inc, Amgen Inc, Fresenius Medical Care, Genzyme Corp, Novartis and Shire. S.K. is an employee of AbbVie Inc, owns AbbVie Inc stock and is a consultant for Amgen Inc, Genzyme Corp, Keryx Biopharmaceuticals, Inc and AbbVie Inc.

**REFERENCES**


**FUNDING**

AbbVie Inc provided funding for the IMPACT-SHPT study and was involved in the study design, research analysis, interpretation of data and reviewing and approval of the publication. The principal investigators of the IMPACT-SHPT study and authors on the publication prepared the manuscript and designed the figures without compensation. Medical writing and editorial support, funded by AbbVie Inc, were provided under the direction of the authors by Jillian Gee, Sophie Bolick and Jennifer Rossi, MedThink SciCom.
Effects of paricalcitol or cinacalcet on disease markers


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