Prescription Patterns and Mineral Metabolism Abnormalities in the Cinacalcet Era: Results from the MBD-5D Study

Masafumi Fukagawa,* Shingo Fukuma,† Yoshihiro Onishi,‡ Takahiro Yamaguchi,§ Takeshi Hasegawa,∥ Tadao Akizawa,* Kiyoshi Kurokawa,** and Shunichi Fukuhara†

Summary

Background and objectives Prescription patterns for hemodialysis patients with secondary hyperparathyroidism have varied widely since market introduction of cinacalcet. This study examined associations between prescription patterns and subsequent laboratory values.

Design, setting, participants, & measurements Using a Mineral and Bone Disorder Outcomes Study for Japanese CKD Stage 5D Patients subcohort, 1716 prevalent hemodialysis patients (4048 sets for repeated measures between January 2008 and July 2009) with an intact parathyroid hormone (iPTH) level >180 pg/ml who used intravenous vitamin D receptor activator (VDRA) without cinacalcet were selected. Prescription patterns were defined based on cinacalcet administration (starting or not) and VDRA dosage change (decreased [<−25%], stable [−25% to 25%], or increased [>25%]). Proportion differences (PDs) were determined for decreasing iPTH levels by at least one category (<180, 180–299, 300–499, and ≥500 pg/ml) and for achieving target phosphorus (3.5–6.0 mg/dl) and calcium (8.4–10.0 mg/dl) levels, adjusting for potential confounders.

Results The starting cinacalcet and increased VDRA patterns were associated with decreasing iPTH levels (PD, 0.25 and 0.13; 95% confidence intervals [95% CIs], 0.19–0.31 and 0.09–0.17, respectively); combination use had an additive association (PD, 0.34; 95% CI, 0.20–0.42). The starting cinacalcet and decreased VDRA combination was associated with simultaneously achieving target phosphorus (PD, 0.12; 95% CI: 0.04–0.20) and calcium (PD, 0.09; 95% CI, 0.01–0.17) levels.

Conclusions Certain combinations of cinacalcet and VDRA were associated with decreasing iPTH and achieving targets for phosphorus and calcium. Combinations may prove advantageous versus VDRA alone in managing secondary hyperparathyroidism.


Introduction

Prescription patterns for hemodialysis patients with secondary hyperparathyroidism have begun to vary widely since cinacalcet introduction (1–3), and the effects of these patterns on laboratory values (1–9) and clinical outcomes (10,11) have attracted attention. Before cinacalcet introduction, the only treatment option available for elevated parathyroid hormone (PTH) levels was vitamin D receptor activator (VDRA) (12). However, since cinacalcet introduction, the number of treatment options has increased, and physicians can now choose from several suitable prescription patterns, according to the status of patients’ laboratory values and the therapeutic purposes. For example, physicians may be better able to administer an adequate VDRA dosage with concomitant therapy with cinacalcet. Although several studies have examined the effect of cinacalcet on subsequent laboratory values in patients (1,6–8), little is known about the additive effect of cinacalcet administration and VDRA dosage change (4,13).

Secondary hyperparathyroidism is characterized by elevated levels of PTH, comprising a major component of CKD mineral and bone disorder (CKD-MBD) (14). CKD-MBD is a common complication in hemodialysis patients and is associated with not only bone disease (15–17) but also mortality and cardiovascular disease (17–20). Clinical guidelines therefore recommend maintaining target levels of intact PTH (iPTH), phosphorus, and calcium (21–23). Specifically, the Japanese Society for Dialysis Therapy guidelines (released in 2006) recommend target levels of iPTH, phosphorus, and calcium at 60–180 pg/ml, 3.5–6.0 mg/dl, and 8.4–10.0 mg/dl, respectively. The target level of iPTH in Japan is lower than that in other countries (21–23), accounting for the characteristics of Japanese hemodialysis patients that differ from those in other countries, such as comparatively longer time on hemodialysis therapy (24). Generally, physicians assign patients MBD-related prescriptions according to the drugs’ therapeutic purposes, such as

*Division of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, Isehara, Japan; †Department of Healthcare Epidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan; ‡Institute for Health Outcomes and Process Evaluation Research (iHope International), Kyoto, Japan; §Division of Biostatistics, Tohoku University Graduate School of Medicine, Sendai, Japan; ¶Division of Nephrology, Department of Internal Medicine, Showa University Fujigaoka Hospital, Yokohama, Japan; ∥Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; **National Graduate Institute for Policy Studies, Tokyo, Japan

Correspondence: Dr. Shunichi Fukuhara, Department of Healthcare Epidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan. Email: fukuhara.shunichi.6m@kyoto-u.ac.jp
decreasing PTH levels or achieving target levels of phosphorus and calcium.

Here, we attempted to clarify the associations between prescription patterns and subsequent levels of iPTH, phosphorus, and calcium in the cinacalcet era. We defined prescription patterns by two factors—cinacalcet administration and VDRA dosage change—and examined the separate and additive associations of these factors using data from the Mineral and Bone Disorder Outcomes Study for Japanese CKD Stage 5D Patients (MBD-5D) (25).

**Materials and Methods**

**Study Design**

The MBD-5D study, which started just when cinacalcet became available in Japan (January 2008), was a 3-year prospective observational study involving prevalent hemodialysis patients with secondary hyperparathyroidism and comprises a whole cohort of all patients enrolled (8229 patients) and a subcohort of patients randomly selected (3276 patients) from the whole cohort. The study involved relatively large dialysis facilities (>100 patients) in Japan, and patients were informed of an opt-out option before the study started. The study protocol was approved by the ethics committee. Precise design details of the MBD-5D study were previously reported (25).

In this study, we used subcohort data obtained during the first 1.5 years of the MBD-5D study. Data were collected at enrollment (visit 0) and every 3 months subsequently from January 2008 through June 2009 (visit 1–6). We defined five imbricated sets of measures from seven visits (visit 0–6), and each set comprised three consecutive visits: reference, treatment, and outcome (Figure 1). We conducted set-level analyses to take full advantage of repeated-measures data. To note, although 3276 patients were initially allocated to the subcohort, this number decreased over time due to death (n=208), stopping hemodialysis (n=1), parathyroidectomy (n=56), and loss to follow-up (n=57) during the 1.5 years of follow-up.

All patients enrolled in this study had iPTH levels of at least 180 pg/ml and received intravenous VDRA without cinacalcet at reference visits.

**Exposure, Outcomes, and Covariates**

Prescription patterns were defined based on cinacalcet and VDRA dosage. Cinacalcet patterns were defined as starting or not starting, based on the presence or absence of cinacalcet administration at treatment visits, respectively. Patterns of VDRA dosage were defined as decreased, stable, or increased, based on the proportion of dosage change between reference visits and treatment visits (decreased, <−25%; stable, −25% to 25%; and increased, >25%, respectively). Prescription patterns in patients were thus categorized into one of six groups, combining the patterns of cinacalcet administration (two groups) and VDRA dosage change (three groups). These six prescription patterns are as follows: decreased VDRA, stable VDRA, increased VDRA, starting cinacalcet and decreased VDRA, starting cinacalcet and stable VDRA, and starting cinacalcet and increased VDRA. VDRA dosages are shown as calcitriol dosage equivalents, with 10 μg of maxacalcitol equivalent to 1.5 μg of calcitriol (26).

The main outcome measure was proportion difference (PD) for decreasing iPTH levels (at least one category when categorized as <180, 180–299, 300–499, and ≥500 pg/ml). The secondary outcome measures were PD for achieving

<table>
<thead>
<tr>
<th>Date</th>
<th>Jan ’08</th>
<th>Apr ’08</th>
<th>Jul ’08</th>
<th>Oct ’08</th>
<th>Jan ’09</th>
<th>Apr ’09</th>
<th>Jul ’09</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit #</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

**Sets of measurements**

- **1**
  - First reference
  - First treatment
  - First outcome

- **2**
  - Second reference
  - Second treatment
  - Second outcome

- **3**
  - Third reference
  - Third treatment
  - Third outcome

- **4**
  - Fourth reference
  - Fourth treatment
  - Fourth outcome

- **5**
  - Fifth reference
  - Fifth treatment
  - Fifth outcome

*Figure 1. Set-level analyses of three consecutive visits: reference, treatment, and outcome. We defined five imbricated sets of measures from seven visits (visit 0–6) between January 2008 and July 2009 and conducted set-level analyses accounting for correlation between repeated measures within patients. In generalized estimating equation models, we included patient characteristics measured at study enrollment, laboratory data measured at reference visits, and treatment data measured at treatment visits. Outcome data were measured at outcome visits.*
target levels of phosphorus (3.5–6.0 mg/dl) and calcium (8.4–10.0 mg/dl), which were defined based on Japanese clinical guidelines (23). Whole PTH levels measured using a third-generation PTH assay were converted to iPTH levels using the following equation: iPTH (pg/ml) = whole PTH (pg/ml) × 1.7 (23,27). We used values of calcium that were corrected for albumin concentration (28).

We also collected covariate demographic data (age, sex, and dialysis duration) and baseline laboratory data (levels of iPTH, phosphorus, and calcium) at the reference visit, and covariate data on dialysis (single-pool Kt/V and dialysate calcium level) and other medications (calcium-based phosphate binder, non-calcium–based phosphate binder, and oral VDRAs) at the treatment visit.

Statistical Analyses
To take full advantage of repeated-measures data, we used set-level data for all analyses. Figure 1 shows the framework of set-level data.

Set-level characteristics were described at baseline (reference or treatment visit). Continuous variables were expressed as medians and interquartile ranges, whereas categorical variables were expressed as proportions. The P values were calculated from generalized estimating equations with robust variance estimation, often used to analyze correlated data (29–31), to determine the difference between two groups based on cinacalcet patterns at the treatment visit.

We used generalized estimating equations with robust variance estimation to estimate PDs and 95% confidence intervals (95% CIs) for the association between prescription patterns and decreased iPTH levels, with the stable VDRA group established as the reference group. We adjusted for potential confounders such as age, sex, dialysis duration, presence of calcium- or non-calcium–based phosphate binders, dialysate calcium, single-pool Kt/V, and levels of iPTH, phosphorus, and calcium.

In sensitivity analyses to examine the robustness of the association, we examined models including these factors along with VDRA dosage change and levels of iPTH, phosphorus, and calcium at the visit directly before the reference visit. We also examined associations among sets with iPTH levels ≥300 pg/ml (2209 sets) and ≥500 pg/ml (853 sets) according to the cut-off points established in the guidelines of Kidney Disease Outcomes Quality Initiative and Kidney Disease Improving Global Outcomes (21,22).

To examine the additive association of starting cinacalcet and increased VDRA, we divided sets into four groups on the basis of cinacalcet administration (starting or not) and VDRA dosage (increased [≥25%] or not [<25%]). We estimated adjusted PDs for decreasing iPTH levels and assessed the presence or absence of an additive association when patients received the starting cinacalcet and increased VDRA treatment simultaneously. If an additive association was noted, the sum of the PDs for separate associations of starting cinacalcet and increased VDRA do not depart from the PD for combination of starting cinacalcet and increased VDRA. This theory is based on the concept of biologic interaction (32,33).

In addition to the above investigation regarding decreasing iPTH levels, we also estimated PDs and 95% CIs for the association between prescription patterns and achieving target levels of phosphorus (3.5–6.0 mg/dl) or calcium (8.4–10.0 mg/dl) after adjusting for potential confounders. Sets with missing data on levels of phosphorus (n=20) or calcium (n=19) at outcome visits were excluded from analysis. As above, we used generalized estimating equations with robust variance estimation. In addition, to examine the association between prescription patterns and new achievement of target levels of phosphorus or calcium, we also analyzed those sets for which phosphorus or calcium levels exceeded the target range at baseline (>6.0 mg/dl for phosphorus levels or >10.0 mg/dl for calcium levels). All analyses were carried out with SAS 9.2 (SAS Institute, Cary, NC) and STATA 11.0 software (STATA, College Station, TX).

Results
A total of 4048 sets of 1716 patients (median 2 sets per patient; range, 1–5 sets per patient) were analyzed in this study. During 1.5 years of follow-up, 579 patients (33.7%) started receiving cinacalcet, with a mean dosage of 25.1 mg/d (SD 11.8) at start and 29.0 mg/d (SD 14.3) 3 months later. To note, these starting and titration dosages are lower than those in a previous study in the United States (1).

Table 1 shows set-level characteristics overall and by cinacalcet patterns. With regard to patient characteristics, the median age was 61 years, the median iPTH level was 319 pg/ml, the median phosphorus level was 5.7 mg/dl, the median calcium level was 9.7 mg/dl, and 4.1% of participants used oral VDRA in addition to intravenous VDRA. Patients who started receiving cinacalcet tended to be younger, tended to have longer dialysis duration, higher levels of iPTH, calcium, phosphorus, higher Kt/V, and were more likely to receive phosphate binders than those who did not start cinacalcet.

Association between Prescription Patterns and iPTH levels
Table 2 shows unadjusted and multivariable-adjusted associations between prescription patterns and decreasing iPTH levels. After adjusting for potential confounders, the starting cinacalcet and increased VDRA patterns were both associated with decreased iPTH levels (PD, 0.25; 95% CI, 0.19–0.31; and PD, 0.13; 95% CI, 0.09–0.17, respectively). In addition, starting cinacalcet was associated with decreasing iPTH levels in any VDRA category. An additive association with decreasing iPTH levels was noted with the starting cinacalcet and increased VDRA combination (PD, 0.34; 95% CI, 0.25–0.42).

Figure 2 shows separate and combined associations of increased VDRA and starting cinacalcet, according to adjusted PD for decreasing iPTH levels. The combined association (33%) was nearly equal to the sum of the associations of the two factors (12% and 23%). We noted a similar association between the combination pattern of starting cinacalcet and increased VDRA and decreasing iPTH levels even after adjusting for changes in VDRA dosage (PD, 0.33; 95% CI, 0.23–0.44), and levels of iPTH, phosphorus, and calcium (PD, 0.32; 95% CI, 0.22–0.42) at one visit before the reference visit. In addition, we found consistent results among sets with iPTH levels...
Association between Prescription Patterns and Levels of Phosphorus and Calcium

Table 3 shows adjusted associations between prescription patterns and achieving target levels of phosphorus and calcium. We included 4026 sets for phosphorus and 4027 for calcium, regardless of whether target ranges for levels had been achieved at reference visits. The combination pattern of starting cinacalcet and decreased VDRA was associated with achieving target levels of both phosphorus (PD, 0.12; 95% CI, 0.04–0.20) and calcium (PD, 0.09; 95% CI, 0.01–0.17). Furthermore, patterns involving starting cinacalcet in general were also associated with achieving target levels of calcium (PD, 0.08; 95% CI, 0.02–0.14).

Table 4 shows adjusted associations between prescription patterns and improvements in hyperphosphatemia and hypercalcemia toward respective target ranges. We analyzed sets with elevated levels of phosphorus (≥6.0 mg/dl; 1528 sets) or calcium (≥10.0 mg/dl; 1263 sets) at reference visits and found that the combination pattern of starting cinacalcet and decreased VDRA was associated with improvement in both hyperphosphatemia (PD, 0.23; 95% CI, 0.10–0.36) and hypercalcemia (PD, 0.17; 95% CI, 0.07–0.28). Furthermore, the starting cinacalcet pattern was also associated with improvement in hypercalcemia (PD, 0.22; 95% CI, 0.14–0.31).

Table 1. Set-level characteristics (overall and by cinacalcet patterns)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (4048 Sets)</th>
<th>Not Starting (3469 Sets)</th>
<th>Starting (579 Sets)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61 (53–70)</td>
<td>62 (53–70)</td>
<td>59 (52–66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>59.1</td>
<td>59.5</td>
<td>57.2</td>
<td>0.31</td>
</tr>
<tr>
<td>Dialysis duration (yr)</td>
<td>9.9 (5.6–16.0)</td>
<td>9.5 (5.1–15.6)</td>
<td>12.3 (8.3–17.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intact parathyroid hormone (pg/ml)</td>
<td>319 (239–466)</td>
<td>304 (232–441)</td>
<td>415 (303–603)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.7 (9.1–10.2)</td>
<td>9.6 (9.1–10.1)</td>
<td>10.1 (9.7–10.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>5.7 (4.9–6.5)</td>
<td>5.6 (4.9–6.5)</td>
<td>5.8 (5.1–6.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.4 (1.3–1.6)</td>
<td>1.4 (1.3–1.6)</td>
<td>1.4 (1.3–1.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Dialysate calcium (≥3.0 mEq/L)</td>
<td>46.2</td>
<td>45.1</td>
<td>52.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Phosphate binder use</td>
<td>89.6</td>
<td>89.0</td>
<td>93.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>calcium based</td>
<td>63.8</td>
<td>65.4</td>
<td>54.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>non-calcium based</td>
<td>54.4</td>
<td>51.7</td>
<td>70.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral VDRA useb</td>
<td>4.1</td>
<td>4.2</td>
<td>3.8</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Data are the median (interquartile range) or percentage. Characteristics measured at baseline (visits of reference or treatment). VDRA, vitamin D receptor activator.

aOverall sets were divided into two groups on the basis of cinacalcet patterns at treatment visits.

bSets with oral VDRA in addition to intravenous VDRA.

Table 2. Association between prescription patterns and decrease in iPTH

<table>
<thead>
<tr>
<th>Prescription Pattern</th>
<th>iPTH</th>
<th>Unadjusted Model</th>
<th>Adjusted Modelc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACa</td>
<td>Proportionb</td>
<td>PD</td>
</tr>
<tr>
<td>Not Decreased</td>
<td>–67.8</td>
<td>45.8</td>
<td>0.00</td>
</tr>
<tr>
<td>Not Stable</td>
<td>–56.7</td>
<td>45.3</td>
<td>0.14</td>
</tr>
<tr>
<td>Not Increased</td>
<td>–127.6</td>
<td>60.3</td>
<td>0.15</td>
</tr>
<tr>
<td>Starting Decreased</td>
<td>–141.8</td>
<td>61.8</td>
<td>0.22</td>
</tr>
<tr>
<td>Starting Stable</td>
<td>–205.1</td>
<td>67.4</td>
<td>0.34</td>
</tr>
<tr>
<td>Starting Increased</td>
<td>–266.8</td>
<td>80.9</td>
<td></td>
</tr>
</tbody>
</table>

iPTH, intact parathyroid hormone; VDRA, vitamin D receptor activator; AC, absolute change; PD, proportion difference; 95% CI, 95% confidence interval.

aMeans of AC in iPTH between reference and outcome visits.

bProportions of patients with decrease in iPTH.

cAdjusted for age, sex, dialysis duration, iPTH levels, phosphorus levels, calcium levels, use of calcium- or non-calcium-based phosphate binders, single-pool Kt/V, and dialysate calcium.

≥300 pg/ml (PD, 0.32; 95% CI, 0.25–0.40) and ≥500 pg/ml (PD, 0.35; 95% CI, 0.22–0.48) at baseline.
Discussion

This study showed that prescription patterns based on cinacalcet and VDRA were associated with subsequent levels of iPTH, phosphorus, and calcium, after adjusting for potential confounders. In particular, patterns involving either starting cinacalcet or increased VDRA were associated with decreasing iPTH levels, and their combination produced an additive association. We also found that the combination of starting cinacalcet and decreased VDRA was associated with achieving target levels of both phosphorus and calcium. These findings may indicate clinically effective prescription patterns appropriate for various therapeutic purposes.

With the introduction of cinacalcet, physicians can now choose effective combination patterns comprising cinacalcet and VDRA to help achieve target levels of iPTH, phosphorus, and calcium (1). One-third of patients in the study cohort started on cinacalcet during 1.5 years of combination therapy with VDRA. Because this study started just when cinacalcet was introduced in Japan, we were able to observe how cinacalcet prescription spread in daily practice and to examine the association between cinacalcet administration and subsequent laboratory values. Time trends of MBD-related medications in the MBD-5D study were previously reported (3). In this study, we noted that changes in prescription patterns of VDRA dosage varied widely, with some patients receiving decreased dosages and others increased dosages.

Several studies have reported the effect of cinacalcet on decreasing iPTH levels (1,4,5), with associations between cinacalcet administration and decreased iPTH levels in this study found to be consistent with those in randomized control studies (4,5) and a previous observational study (1). However, little is known about the effect of concomitant therapy with cinacalcet and VDRA (15), particularly with regard to the effect of VDRA dosage change in concomitant therapy. We therefore established six exposure categories for prescription patterns based on cinacalcet administration and VDRA dosage change. Results of observation revealed an additive association of starting cinacalcet and increased VDRA with decreased iPTH levels. Furthermore, their combined association nearly equaled the additive associations of the individual associations of the two factors (Figure 2). These observed additive associations can be explained by a biologically plausible mechanism given that cinacalcet and VDRA have separate target receptors (34): Cinacalcet is a positive allosteric modulator of calcium-sensing receptor, whereas VDRA, as its name suggests, activates vitamin D receptor (35). The combination of starting cinacalcet and increased VDRA may prove beneficial in effectively decreasing iPTH levels. However, no health benefits of decreasing iPTH with cinacalcet were examined in this study, and clarifying optimal regimens for reducing iPTH with cinacalcet will be the subject of future studies.

Although a number of previous studies have reported that cinacalcet administration reduced levels of phosphorus and calcium (1,4,5,7–9), few have examined the effects of concomitant therapy with VDRA. We found that a combination pattern involving starting cinacalcet and decreased VDRA was effective in achieving target levels of phosphorus and calcium. Furthermore, this combination was effective in achieving those targets even when administered to patients with either or both hyperphosphatemia and hypercalcemia. Thus, combination therapy with starting cinacalcet and decreased VDRA may be useful in controlling levels of phosphorus and calcium simultaneously.

The major strength of this study was that we defined prescription patterns based on two factors of cinacalcet administration and VDRA dosage change, allowing us to examine the separate and combined associations of these

![Figure 2](image-url)
oratory values in the cinacalcet era. Of the associations of actual prescription patterns with lab-
ited by the study protocol, thereby enabling examination
daily practice, in which prescription patterns are not lim-
MBD-5D study (3). Finally, this cohort included data from

to take full advantage of repeated-measures data from the

The third strength was that we conducted set-level analyses
association, the results of which supported robustness.
compounds. The second strength was that we conducted
study should prove useful for physicians prescribing these
compounds on target patients. Because such concomitant
therapy is common in daily practice, the results from this
study should prove useful for physicians prescribing these
compounds. The second strength was that we conducted sensitivity analyses to examine the robustness of the
association, the results of which supported robustness.

The third strength was that we conducted set-level analyses to take full advantage of repeated-measures data from the
MBD-5D study (3). Finally, this cohort included data from
daily practice, in which prescription patterns are not limited
by the study protocol, thereby enabling examination of the associations of actual prescription patterns with laboratory values in the cinacalcet era.

Several obvious limitations to this study warrant mention. First, we cannot rule out confounding by indication. Physicians decide prescription patterns according to patients’ demographics and laboratory values, among other parameters. We attempted to compensate for this by adjusting for available covariates data from the reference and treatment visits and adjusting for covariates from the visit before reference visits in sensitivity analyses and found consistent results. However, residual confounding from unmeasured factors may have persisted.

Second, patients in this study may not be representative of hemodialysis patients with high iPTH levels in other countries, particularly given that target levels of iPTH are lower in Japan than in other countries. However, we found similar associations in patients with iPTH levels \( \geq 300 \) and \( \geq 500 \) pg/ml according to the target range in other countries, and therefore our results may not be limited to only Japanese hemodialysis patients (21,22). Third, although we considered VDRA dosage in
determining prescription patterns, we did not consider cinacalcet dosage. However, \( >85\% \) of starting dosages were \(<25\) mg/d, and dosage differences between patients were small. Fourth, data on methods of serum albumin measurement (bromcresol purple or bromcresol green) (36), which may affect corrected calcium values, were unavailable in the dataset. Fifth, iPTH levels in a number of patients \((n=86)\) were calculated based on whole PTH levels (27). However, given that we found consistent results even after excluding these patients, we believe this was a negligible limitation. Sixth, data on patient adherence to medications may prove advantageous in managing secondary hyperparathyroidism compared with VDRA alone. A randomized trial is needed to examine the health benefits of these findings.

### Table 3. Association between prescription patterns and achievement in target levels of phosphorus and calcium

<table>
<thead>
<tr>
<th>Prescription Pattern</th>
<th>AC(^a) (pg/ml)</th>
<th>Proportion(^b) (%)</th>
<th>PD(^c)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4026 sets)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not</td>
<td>Decreased</td>
<td>-0.29</td>
<td>64.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Not</td>
<td>Stable</td>
<td>-0.12</td>
<td>60.9</td>
<td>Reference</td>
</tr>
<tr>
<td>Not</td>
<td>Increased</td>
<td>-0.01</td>
<td>61.6</td>
<td>0.00</td>
</tr>
<tr>
<td>Starting</td>
<td>Decreased</td>
<td>-0.82</td>
<td>72.5</td>
<td>0.12</td>
</tr>
<tr>
<td>Starting</td>
<td>Stable</td>
<td>-0.49</td>
<td>61.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Starting</td>
<td>Increased</td>
<td>-0.35</td>
<td>67.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4027 sets)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not</td>
<td>Decreased</td>
<td>-0.14</td>
<td>62.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Not</td>
<td>Stable</td>
<td>0.13</td>
<td>65.5</td>
<td>Reference</td>
</tr>
<tr>
<td>Not</td>
<td>Increased</td>
<td>0.32</td>
<td>65.4</td>
<td>-0.02</td>
</tr>
<tr>
<td>Starting</td>
<td>Decreased</td>
<td>-0.69</td>
<td>65.7</td>
<td>0.09</td>
</tr>
<tr>
<td>Starting</td>
<td>Stable</td>
<td>-0.35</td>
<td>69.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Starting</td>
<td>Increased</td>
<td>-0.16</td>
<td>60.3</td>
<td>0.03</td>
</tr>
</tbody>
</table>

VDRA, vitamin D receptor activator; AC, absolute change; PD, proportion difference; 95% CI, 95% confidence interval; iPTH, intact parathyroid hormone.

\(^a\)Means of AC between reference and outcome visits.

\(^b\)Proportions of patients with achievement of target levels.

\(^c\)Adjusted for age, sex, dialysis duration, intact PTH levels, phosphorus levels, calcium levels, use of calcium- or non–calcium-based phosphate binders, single-pool Kt/V, and dialysate calcium.
Table 4. Association between prescription patterns and improving hyperphosphatemia and hypercalcemia toward the target range

<table>
<thead>
<tr>
<th>Prescription Pattern</th>
<th>ACa (pg/ml)</th>
<th>Proportionb (%)</th>
<th>PD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperphosphatemia</strong> (1528 sets)b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Decreased</td>
<td>−0.16</td>
<td>51.9</td>
<td>0.05</td>
<td>−0.02 to 0.13</td>
</tr>
<tr>
<td>Not Stable</td>
<td>−0.83</td>
<td>44.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Increased</td>
<td>−0.80</td>
<td>42.0</td>
<td>−0.03</td>
<td>−0.10 to 0.04</td>
</tr>
<tr>
<td>Starting Decreased</td>
<td>−1.58</td>
<td>69.0</td>
<td>0.23</td>
<td>0.10–0.36</td>
</tr>
<tr>
<td>Starting Stable</td>
<td>−0.10</td>
<td>46.2</td>
<td>0.03</td>
<td>−0.06 to 0.11</td>
</tr>
<tr>
<td>Starting Increased</td>
<td>−0.82</td>
<td>46.2</td>
<td>0.02</td>
<td>−0.12 to 0.16</td>
</tr>
<tr>
<td><strong>Hypercalcemia</strong> (1263 sets)b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Decreased</td>
<td>−0.53</td>
<td>42.0</td>
<td>0.05</td>
<td>−0.03 to 0.12</td>
</tr>
<tr>
<td>Not Stable</td>
<td>−0.22</td>
<td>35.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Increased</td>
<td>−0.25</td>
<td>39.4</td>
<td>0.00</td>
<td>−0.08 to 0.09</td>
</tr>
<tr>
<td>Starting Decreased</td>
<td>−0.89</td>
<td>57.7</td>
<td>0.17</td>
<td>0.07–0.28</td>
</tr>
<tr>
<td>Starting Stable</td>
<td>−0.61</td>
<td>64.1</td>
<td>0.22</td>
<td>0.14–0.31</td>
</tr>
<tr>
<td>Starting Increased</td>
<td>−0.31</td>
<td>48.0</td>
<td>0.10</td>
<td>−0.02 to 0.22</td>
</tr>
</tbody>
</table>

**VDRA, vitamin D receptor activator; AC, absolute change; PD, proportion difference; 95% CI, 95% confidence interval; iPTH, intact parathyroid hormone.**

*bMeans of AC between reference and outcome visits.

*bProportions of patients with achievement of target levels.

*bAdjusted for age, sex, dialysis duration, intact PTH levels, calcium levels, use of calcium- or non–calcium-based phosphate binders, single-pool Kt/V, and dialysate calcium.

*bAdjusted for age, sex, dialysis duration, intact PTH levels, phosphorus levels, use of calcium- or non–calcium-based phosphate binders, single-pool Kt/V, and dialysate calcium.

Acknowledgments

We thank the following MBD-5D study advisory investigators: Masashi Suzuki (Shirakabe Hospital), Yoshindo Kawaguchi (Shionomida Hospital), Akira Saito (Yokohama Daichi Hospital), Yoshiaki Nishizawa (Osaka City University Graduate School of Medicine), Yusuke Tsukamoto (Shiwa General Hospital), Satoshi Kuritaka (Tsukinomori Clinic), Takashi Akiba (Tokyo Women’s Medical University), Eriko Kinugasa (Showa University Northern Yokohama Hospital), Yuzo Watanabe (Kasugai Municipal Hospital), Yoshitaka Tominaga (Nagoya Daini Red Cross Hospital), Takashi Shigematsu (Wakayama Medical University), Masaaki Inaba (Osaka City University Graduate School of Medicine), Jun Minakuchi (Kawashima Hospital), Hideki Hirakata (Fukuoka Red Cross Hospital), Keitaro Yokoyama (Jikei University School of Medicine), Naoki Kimata (Tokai University School of Medicine), Fumihiko Koiwa (Showa University Fujigaoka Hospital), Ryoichi Ando (Musashino Red Cross Hospital), Junicho J. Kazama (Niigata University), Takatoshi Katakura (Tokai University School of Medicine), Hirotaka Komatsu (Tokai University School of Medicine), Daijo Inaguma (Nagoya Daini Red Cross Hospital), Eiji Ishimura (Osaka City University Graduate School of Medicine), Hideki Tabara (Osaka City University Graduate School of Medicine), Kazuhiko Tsuruya (Kyushu University), and Akira Fujimori (Konan University).

Funding for the MBD-5D study was provided by Kyowa Hakko Kirin (manufacturer of intravenous calcitriol, cinacalcet hydrochloride, and sevelamer hydrochloride).

Disclosures

M.F. has acted as a consultant for Kyowa Hakko Kirin, has received honoraria from Kyowa Hakko Kirin, and has received grants (research support) from Kyowa Hakko Kirin. T.A. has acted as a consultant for Kyowa Hakko Kirin, has received grants (research support) from Kyowa Hakko Kirin, and is a member of the speakers’ bureau of Kyowa Hakko Kirin. S. Fukuhara has acted as a scientific advisor for Kyowa Hakko Kirin and has received grants (research support) from Kyowa Hakko Kirin.

References


Received: December 21, 2011 Accepted: May 18, 2012

M.F. and S. Fukuma contributed equally to this study.

Published online ahead of print. Publication date available at www.cjasn.org.