

Cinacalcet Use Patterns and Effect on Laboratory Values and Other Medications in a Large Dialysis Organization, 2004 through 2006

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Background and objectives: Cinacalcet was introduced in mid-2004 to treat secondary hyperparathyroidism in dialysis patients. We aimed to characterize adult patients who received cinacalcet prescriptions and to determine (1) dosage titration and effects on laboratory values, active intravenous vitamin D use, and phosphate binder prescriptions and (2) percentage who achieved National Kidney Foundation Kidney Disease Outcomes Quality Initiative targets for serum parathyroid hormone, calcium, and phosphorus and experienced biochemical adverse effects.

Design, setting, participants, & measurements: This observational study evaluated 45,487 prevalent patients from a dialysis organization database linked with the Centers for Medicare and Medicaid Services End-Stage Renal Disease database. Patient characteristics, laboratory values (albumin, parathyroid hormone, calcium, phosphorus), intravenous vitamin D, and oral medication (cinacalcet, phosphate binders) prescriptions were evaluated for cinacalcet patients.

Results: By June 2006, almost 32% of patients had received cinacalcet prescriptions. Mean baseline corrected calcium was 9.8 mg/dl and phosphorus was 6.3 mg/dl, and median parathyroid hormone was 577 pg/ml, *versus* 9.5 mg/dl, 5.3 mg/dl, and 215 pg/ml, respectively, for noncinacalcet patients. Patients with cinacalcet prescriptions for ≥ 6 mo had corrected calcium reduced by 4.2%, phosphorus by 7.0%, and parathyroid hormone by 29.9% by 12 mo. More cinacalcet patients attained Kidney Disease Outcomes Quality Initiative targets with less hyperparathyroidism, hypercalcemia, and hyperphosphatemia but more hypoparathyroidism and hypocalcemia. Over 12 mo, vitamin D use and use consistency increased, phosphate binder dosages increased, and mean cinacalcet daily dosage reached 55 mg.

Conclusions: Patients with cinacalcet prescriptions exhibited more severe hyperparathyroidism and hyperphosphatemia than noncinacalcet patients. Positive effects were less dramatic than in Phase III clinical trials, possibly as a result of modest, slow dosage titration.

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Secondary hyperparathyroidism (SHPT) is present in a large proportion of hemodialysis patients. Before cinacalcet hydrochloride (Sensipar; Amgen, Thousand Oaks, CA) introduction, the primary SHPT treatments were phosphate binders to control serum phosphorus and active intravenous vitamin D to suppress parathyroid hormone (PTH). Current Kidney Disease Outcomes Quality Initiative (KDOQI) bone and mineral disease guidelines recommend serum calcium targets of 8.4 to 9.5 mg/dl, phosphorus of 3.5 to 5.5 mg/dl, and parathyroid hormone (PTH) of 150 to 300 pg/ml (1).

Cinacalcet became commercially available in May 2004. Previous randomized, controlled trials among patients with persistent SHPT despite intravenous vitamin D and phosphate binder use (2–4) demonstrated that addition of cinacalcet considerably reduced serum calcium, phosphorus, and PTH values. Extension studies and *post hoc* analyses suggested long-term favorable effects on these biochemical factors and that patients who received cinacalcet were more likely to reach target values than patients who received standard therapy (5,6). In these trials, cinacalcet was consistently titrated upward every 2 to 3 wk to a maximum dosage of 180 mg/d or until a biochemical end point or adverse event occurred.

To examine cinacalcet prescription results in actual practice, our objectives were to determine (1) characteristics of patients who received cinacalcet prescriptions after market introduction; (2) dosage titration and effect on laboratory values, intravenous vitamin D use, and phosphate binder prescriptions in patients with cinacalcet prescriptions for ≥ 6 mo; and (3) percentage of patients who achieved KDOQI targets and experiencing hyperparathyroidism, hypercalcemia, hyperphosphatemia, hypoparathyroidism, and hypocalcemia.

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Materials and Methods

Patients and Data Sources

Patient data from DaVita, Inc., were obtained through a data licensing agreement. All prevalent patients in the database August 1, 2004, were selected; data were collected through June 30, 2006. Using patient identifiers, data were linked to the Centers for Medicare and Medicaid Services (CMS) End-Stage Renal Disease (ESRD) database by the US Renal Data System through a data use agreement with the National Institute of Diabetes and Digestive and Kidney Diseases. Study approval was obtained from the Hennepin County Medical Center Human Subjects Research Committee (Minneapolis, MN) and the Exempla Healthcare institutional review board (Denver, CO).

The DaVita database provided information on demographics, weight and height, laboratory values, dialysis treatment, intravenous vitamin D use, home medications, censoring (mortality, outside transfer, modality change), dialysis duration, and insurance coverage. The CMS Medical Evidence Report (form CMS-2728) provided information on diabetes as a comorbid condition and ESRD cause.

Home Medications and Total Daily Dosage Determinations

The DaVita home medication files contain detailed medication information. Drug-specific files were created for cinacalcet, sevelamer hydrochloride, lanthanum carbonate, calcium carbonate, and calcium acetate by searching for their generic and trade names. Each file was reviewed by study personnel to verify drug names, administration frequency, and total daily dosage. Dosage information appeared in a free text field; total daily dosage was calculated by manual inspection. Because dosage information was sometimes unclear, the following assumptions were made to estimate total daily dosages:

- Unspecified calcium carbonate dosage was assumed to be 500 mg, calcium acetate 667 mg, sevelamer 800 mg, lanthanum carbonate 500 mg, and cinacalcet 30 mg.
- If unspecified, “with meals” was assumed to be three times per day, “with snacks” one snack per day, and “with meals and snacks” four times per day.
- Elemental calcium was calculated as 0.40 of calcium carbonate and 0.25 of calcium acetate.
- Difficult-to-interpret or unconventional dosages (e.g., cinacalcet 800 mg) were adjudicated by study investigators on the basis of specific criteria.

Final drug-specific sequence files contained unique dates and corresponding dosage information for each prescription start, stop, and dosage change. Start and stop dates were used to establish length of treatment and patient drug prescriptions in particular time frames.

Intravenous Vitamin D Dosages and PTH

Three vitamin D analogs (calcitriol, paricalcitol, and doxercalciferol) were used during the study; 94% of doses were for paricalcitol. Thus, all doses were converted to paricalcitol-equivalent doses (0.26 to 1.00 for calcitriol to paricalcitol; 0.76 to 1.00 for doxercalciferol to paricalcitol) (7). Vitamin D use consistency was defined by percentage (0, >0 to ≤80, and >80) of available hemodialysis sessions with vitamin D administration in 1 mo. Both intact-PTH (iPTH) and bioactive PTH assays were used during the study period. Using information supplied by DaVita, bioactive PTH values were divided by 0.52 to convert to iPTH values.

Analyses

Prevalent hemodialysis patients who were aged ≥18 yr and receiving treatment in a DaVita dialysis center before September 1, 2004, were

included. Patients who transferred to a non-DaVita unit, changed modalities (peritoneal dialysis, kidney transplant), died, or reached study end (June 30, 2006) were censored at that point. Cinacalcet patients were defined as having a cinacalcet prescription record before July 1, 2006, and noncinacalcet patients as having no record before that date.

For some analyses, cinacalcet patients were defined by at least one cinacalcet prescription record during each time period assessed. For assessment of SHPT treatment groups over time, patients were required to survive through February 2005. Patients with SHPT in January 2005 were defined by any record of intravenous vitamin D use, cinacalcet prescription, or PTH >300 pg/ml from August 2004 through January 2005; patients with SHPT in subsequent months were similarly defined. In each month starting in January 2005, patients were classified into treatment categories: Cinacalcet hydrochloride only, cinacalcet hydrochloride plus vitamin D, or vitamin D only (defined as >50% available treatment sessions with vitamin D use and/or >50% available days with cinacalcet in that month) and no treatment with evidence of SHPT. Patients were required to survive the whole month to be included in the analysis for that month.

Additional analyses included patients who received cinacalcet prescriptions before July 1, 2006, and subsequently for ≥180 d. A gap in therapy of >30 d was considered discontinuation. During a gap in therapy of ≤30 d, 0 mg was assigned as the cinacalcet dosage. At least one prescription for a specific phosphate binder was required in a month for a patient to be counted in the denominator for that month. A 0-mg dose was assigned for any days without prescribed use. Monthly averages were used to determine mean daily cinacalcet and phosphate binder dosages and weekly vitamin D dosages and to determine whether patients achieved KDOQI target ranges or experienced biochemical adverse events.

Descriptive statistics (mean ± SD, median and interquartile range, and percentage) were used to describe patient characteristics, including demographics, drug dosages, and laboratory values. Statistical analyses included *t* test and χ^2 tests for demographic variables. Paired *t* test was used to compare baseline to month 1 laboratory values. *P* < 0.05 was considered significant. Data files were created and analyses done using SAS 9.1.3 for Windows (SAS Institute, Cary, NC).

Results

Of DaVita patients, 99.5% could be linked to the CMS ESRD database; 45,487 patients aged ≥18 yr were available for analysis. During observation quarter 1 (August through October 2004), approximately 10% of patients (*n* = 4515) received cinacalcet prescriptions, increasing to almost 32% by June 2006 (Figure 1). Cinacalcet patients were younger than noncinacalcet

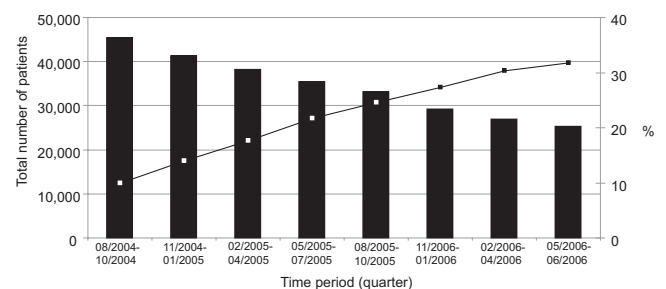


Figure 1. Number of patients remaining in study each quarter (bars) and percentage of cinacalcet patients during each quarter of the study period (line). Cinacalcet patients were defined by at least one prescription for cinacalcet during the quarter.

patients, less likely to be white, more likely to be black, and less likely to have diabetes; they were on dialysis longer and had higher body mass index (Table 1). At baseline, patients who later received cinacalcet prescriptions had significantly higher serum calcium, phosphorus, and PTH levels than noncinacalcet patients, with PTH >2.5 times higher. Other laboratory values were similar between groups.

Of cinacalcet patients, 98% received vitamin D sometime during the observation period. Vitamin D monotherapy was the most common SHPT treatment (Table 2); however, the proportion of patients who had SHPT and used only vitamin D decreased from 62% in January 2005 to 49% in June 2006, and

vitamin D plus cinacalcet increased from 10 to 24%. Cinacalcet alone was prescribed for <8% of patients. The untreated SHPT population decreased from 24 to 19%.

Cinacalcet daily dosage was 34 ± 16 mg in month 1, increasing to 55 ± 32 mg by month 12 for patients with cinacalcet prescriptions for ≥ 6 mo (Figure 2). The percentage of patients who received non-calcium-based phosphate binders (sevelamer, lanthanum carbonate) increased from 78% in month 1 to almost 82% in month 12 (Table 3), whereas the percentage who received calcium-containing binder prescriptions remained stable between 38 and 39%. Prescribed elemental calcium binder dosages remained stable during 6 mo of cinacalcet prescrip-

Table 1. Patient characteristics, August 1, 2004^a

| Baseline Measure | Patients | | | P |
|---|---------------|---------------|---------------|---------|
| | All | Cinacalcet | No Cinacalcet | |
| <i>n</i> | 45,487 | 10,337 | 32,788 | |
| Age (yr; mean [SD]) | 60.8 (15.2) | 56.8 (14.8) | 62.8 (14.9) | <0.0001 |
| Age (yr; %) | | | | <0.0001 |
| 18 to 44 | 15.4 | 21.0 | 12.6 | |
| 45 to 64 | 40.6 | 46.6 | 37.8 | |
| 65 to 74 | 23.2 | 19.9 | 24.9 | |
| ≥ 75 | 20.8 | 12.5 | 24.6 | |
| ESRD duration (yr; mean [SD]) | 3.3 (3.4) | 4.7 (3.6) | 3.0 (3.2) | <0.0001 |
| ESRD duration (yr; %) | | | | <0.0001 |
| 0 to 2 | 44.5 | 21.8 | 49.2 | |
| >2 | 55.5 | 78.2 | 50.8 | |
| BMI (kg/m ² ; mean [SD]) | 26.8 (6.7) | 27.7 (7.0) | 26.5 (6.5) | <0.0001 |
| Men (%) | 54.2 | 52.2 | 55.1 | <0.0001 |
| Race (%) | | | | <0.0001 |
| black | 35.5 | 47.0 | 30.8 | |
| white | 37.5 | 29.0 | 40.7 | |
| Medicare (%) | 75.6 | 78.0 | 74.5 | <0.0001 |
| History of diabetes (%) | 51.2 | 44.7 | 54.3 | <0.0001 |
| Laboratory values (mean [SD]) ^b | | | | |
| albumin (g/dl) | 3.8 (0.5) | 3.9 (0.4) | 3.8 (0.5) | <0.0001 |
| Kt/V (delivered) | 1.6 (0.3) | 1.6 (0.3) | 1.6 (0.3) | 0.0644 |
| phosphorus (mg/dl) | 5.5 (1.7) | 6.3 (1.7) | 5.3 (1.6) | <0.0001 |
| corrected calcium (mg/dl) | 9.6 (0.7) | 9.8 (0.8) | 9.5 (0.7) | <0.0001 |
| corrected Ca \times P (mg ² /dl ²) | 52.8 (16.1) | 60.9 (16.6) | 50.5 (15.3) | <0.0001 |
| PTH (pg/ml; median [IQR]) | 251.9 (271.2) | 576.9 (505.8) | 215.4 (209.6) | <0.0001 |
| PTH (pg/ml; %) | | | | <0.0001 |
| <150 | 24.7 | 3.8 | 30.5 | |
| 150 to 300 | 34.8 | 10.7 | 38.8 | |
| 300 to 600 | 26.2 | 38.0 | 23.1 | |
| >600 | 14.4 | 47.5 | 7.6 | |
| Primary cause of ESRD (%) | | | | <0.0001 |
| diabetes | 44.0 | 38.7 | 46.6 | |
| hypertension | 28.6 | 30.7 | 27.7 | |
| glomerulonephritis | 10.9 | 13.7 | 9.7 | |
| polycystic kidney disease | 2.5 | 3.2 | 2.2 | |
| unknown | 4.0 | 4.5 | 3.9 | |

^aBMI, body mass index; Ca \times P, calcium-phosphorus product; IQR, interquartile range; PTH, parathyroid hormone

^bValues for cinacalcet patients are for the month before cinacalcet initiation.

Table 2. Treatment groups for SHPT by month, starting January 1, 2005^a

| Month | Treatment Groups (<i>n</i> [%]) | | | |
|-------|----------------------------------|----------------|---------------------------|--------------------|
| | Cinacalcet Only | Vitamin D Only | Cinacalcet plus Vitamin D | No Treatment, SHPT |
| 1 | 1484 (4.6) | 19,765 (61.6) | 3231 (10.1) | 7587 (23.7) |
| 4 | 1891 (6.0) | 17,665 (56.0) | 3845 (12.2) | 8131 (25.8) |
| 7 | 2094 (6.9) | 16,259 (53.7) | 4590 (15.2) | 7334 (24.2) |
| 10 | 2038 (7.5) | 13,959 (51.6) | 4798 (17.7) | 6265 (23.2) |
| 13 | 1784 (7.0) | 13,369 (52.6) | 5156 (20.3) | 5087 (20.0) |
| 16 | 1811 (7.6) | 11,994 (50.1) | 5290 (22.1) | 4834 (20.2) |
| 18 | 1771 (7.7) | 11,241 (49.0) | 5544 (24.2) | 4389 (19.1) |

^aSHPT, secondary hyperparathyroidism.

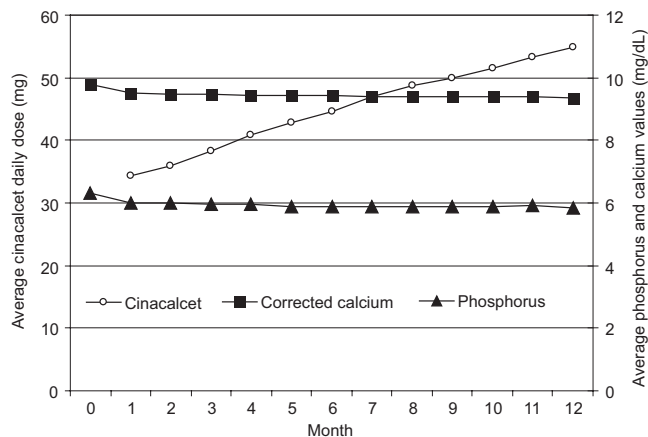


Figure 2. Mean cinacalcet daily dosage and mean monthly serum phosphorus and corrected calcium values in each month during 12-mo time frame for patients with cinacalcet prescriptions for ≥ 6 mo.

tions, then increased; non-calcium-based binder dosages steadily increased over time. The percentage of patients who received vitamin D increased slightly from 82 to 85%. The weekly intravenous paricalcitol-equivalent dosage for patients who received vitamin D in each month increased from 13.1 to 14.3 μg during 12 mo. It is interesting that the proportion of patients with consistent vitamin D use increased from 57 to 66%. Mean corrected calcium and phosphorus and median PTH decreased during 12 mo, with the largest decrements from baseline to month 1 after first cinacalcet prescription (Figures 2 and 3). During that time, corrected calcium decreased 2.7%, phosphorus 4.4%, and PTH 21.6%. These changes were statistically significant.

Patients were more likely to achieve KDOQI target values after long-term cinacalcet prescription than during the baseline month (Figure 4). Fewer than 10% of patients achieved target iPTH (150 to 300 pg/ml) in the baseline month and $>24\%$ in month 12. During that time, the percentage of patients who met corrected calcium targets increased from 32.9 to 47.7% and phosphorus targets from 32.2 to 40.6%; however, only 6.2% of patients met all targets at month 12.

The percentage of patients with hyperparathyroidism (PTH >600 pg/ml) decreased from 48.8 to 34.2%, with hypercalcemia

(corrected calcium >10.2 mg/dl) from 26.6 to 12.8%, and with hyperphosphatemia (phosphorus >6 mg/dl) from 52.3 to 41.4% (Figure 5). The percentage with hypoparathyroidism (PTH <150 pg/ml) increased from 3.7 to 11.0% and with hypocalcemia (corrected calcium <8.4 mg/dl) from 2.3 to 10.1%.

Discussion

We characterized a large dialysis population who received first-time prescriptions for cinacalcet. Characteristics differed between patients who did and did not receive cinacalcet prescriptions. Baseline values for cinacalcet patients showed that, on average, they were well-nourished (mean albumin 3.9 g/dl) and adequately dialyzed (mean Kt/V 1.6). Cinacalcet patients had more severe SHPT (mean PTH values almost three times higher) and higher phosphorus and calcium values than non-cinacalcet patients.

Although most cinacalcet patients were receiving intravenous vitamin D at baseline, their mean baseline PTH value was almost 600 pg/ml. Vitamin D use became more consistent, and weekly dosage rose slightly over time for cinacalcet patients. Possibly, clinicians used cinacalcet to provide a therapeutic “safety window” related to serum calcium and phosphorus, or vitamin D management practice patterns changed with release of the KDOQI Clinical Practice Guidelines for Bone Disease (1).

This observational study is among the first to describe phosphate binder dosages in patients with cinacalcet prescriptions for ≥ 6 mo. Non-calcium-containing phosphate binders predominate as monotherapy or combined with calcium-containing binders. Including combination therapy, $>75\%$ of patients with SHPT received prescriptions for non-calcium-containing phosphate binders. Regardless of binder type, mean dosages increased, possibly indicating progressing disease and rising phosphorus levels or more aggressive hyperphosphatemia treatment after KDOQI guideline release (1). Thus, cinacalcet with higher phosphate binder dosages may have contributed to reduced serum phosphate concentrations over time, although phosphorus concentrations did not decrease for noncinacalcet patients (data not shown). Mean prescribed elemental calcium dosages from calcium acetate and calcium carbonate were just below and above, respectively, the KDOQI suggested limit of 1500 mg/d from phosphate binders, despite our use of conservative dosages when dosage information was missing.

Table 3. Cinacalcet effect on other bone disease medications^a

| Parameter | Study Month | | | | | | | | | | | |
|--|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| <i>n</i> | 5662 | 5662 | 5662 | 5662 | 5662 | 5662 | 5233 | 4785 | 4410 | 4014 | 3562 | 3160 |
| Lanthanum prescription | 8.8 | 11.5 | 12.0 | 14.5 | 16.4 | 17.6 | 18.3 | 19.2 | 19.4 | 19.4 | 20.1 | 20.5 |
| Lanthanum dosage (mg/d) | 2293 (1228) | 2336 (1236) | 2424 (1197) | 2409 (1225) | 2368 (1228) | 2511 (1213) | 2631 (1241) | 2675 (1292) | 2719 (1273) | 2698 (1263) | 2693 (1237) | 2748 (1264) |
| Sevelamer prescription | 73.2 | 74.9 | 73.6 | 73.4 | 72.6 | 71.7 | 70.7 | 70.4 | 69.8 | 70.5 | 70.6 | 70.3 |
| Sevelamer dosage (mg/d) | 8751 (4412) | 8746 (4420) | 8835 (4332) | 8857 (4311) | 8881 (4334) | 8862 (4323) | 8894 (4331) | 8966 (4290) | 9014 (4336) | 9079 (4327) | 9123 (4332) | 9146 (4308) |
| Lanthanum or sevelamer | 77.9 | 80.5 | 80.0 | 80.5 | 80.4 | 80.6 | 80.5 | 80.7 | 80.4 | 81.1 | 81.5 | 81.6 |
| Calcium binder prescription | 38 | 39 | 38.3 | 39 | 38.7 | 38.9 | 38.4 | 38.6 | 38.5 | 38.5 | 38.6 | 38.7 |
| Calcium binder dosage (mg) ^b | 1625 (1276) | 1602 (1277) | 1647 (1237) | 1675 (1265) | 1701 (1304) | 1691 (1315) | 1715 (1345) | 1749 (1377) | 1766 (1351) | 1796 (1384) | 1823 (1430) | 1825 (1460) |
| Ca acetate binder dosage (mg/d) ^b | 1370 (749) | 1345 (809) | 1393 (740) | 1395 (751) | 1401 (745) | 1400 (750) | 1411 (761) | 1420 (774) | 1436 (770) | 1442 (787) | 1459 (782) | 1444 (780) |
| Ca carbonate binder dosage (mg/d) ^b | 1770 (1515) | 1687 (1499) | 1724 (1475) | 1737 (1479) | 1778 (1547) | 1738 (1548) | 1759 (1593) | 1779 (1602) | 1760 (1526) | 1798 (1548) | 1801 (1588) | 1822 (1609) |
| Combination binder prescription ^c | 21.5 | 23.4 | 22.3 | 23.1 | 22.9 | 23.1 | 22.6 | 22.9 | 22.7 | 23 | 23.3 | 23.4 |
| Intravenous vitamin D use ^d | | | | | | | | | | | | |
| 0 | 18.2 | 17.8 | 16.6 | 16.0 | 16.5 | 16.6 | 16.5 | 15.5 | 15.0 | 15.7 | 14.9 | 15.4 |
| 0 to ≤80 | 25.0 | 24.9 | 21.8 | 21.0 | 21.0 | 21.2 | 19.7 | 21.2 | 20.1 | 19.0 | 19.6 | 18.9 |
| >80 | 56.7 | 57.3 | 61.6 | 63.0 | 62.5 | 62.2 | 63.8 | 63.3 | 64.9 | 65.3 | 65.5 | 65.7 |
| Intravenous vitamin D dosage (μg/wk) | 13.1 (12.7) | 13.3 (12.8) | 13.6 (12.7) | 13.4 (12.9) | 13.4 (12.8) | 13.3 (12.7) | 13.5 (12.9) | 13.6 (13.0) | 13.8 (13.0) | 14.0 (13.2) | 14.3 (13.5) | 14.3 (13.8) |

^aData are mean (SD) or percentage of patients.^bElemental calcium dosage; *n* = number of cinacalcet patients at the end of the month.^cCalcium based and non-calcium based.^dPercentage of available hemodialysis treatment sessions.

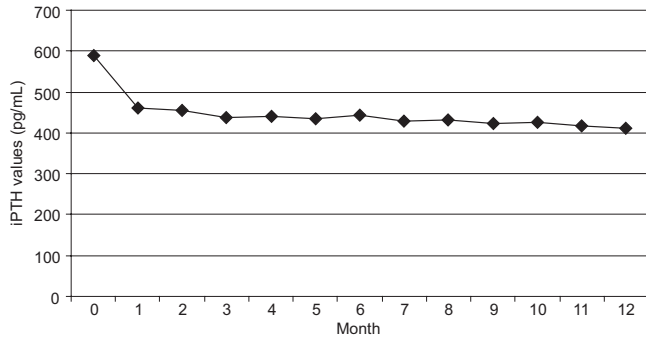


Figure 3. Median intact parathyroid hormone (iPTH) values (pg/ml) in each month during 12 mo time frame for patients with cinacalcet prescriptions for ≥ 6 mo.

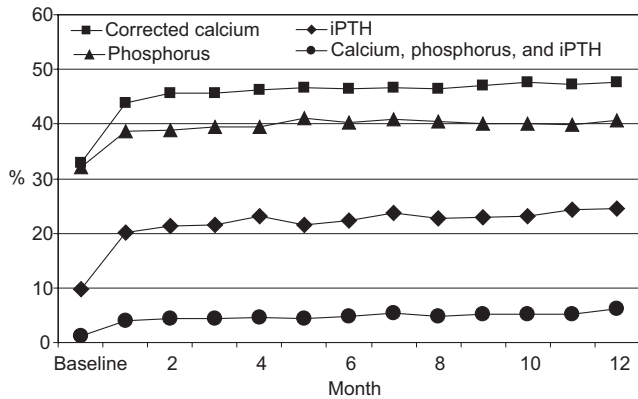


Figure 4. Percentage of patients who reached KDOQI target ranges for corrected calcium (8.4 to 9.5 mg/dl), phosphorus (3.5 to 5.5 mg/dl), iPTH (150 to 300 pg/ml), and all three targets in each month during 12-mo time frame for patients with cinacalcet prescriptions for ≥ 6 mo.

By January 1, 2005, 9% of new cinacalcet patients had prescriptions for lanthanum carbonate, increasing to $>20\%$ by study month 12. Lanthanum carbonate was approved by the Food and Drug Administration (FDA) in October 2004, with uptake in the severe SHPT population more rapid than in the overall population (data not shown). Lanthanum carbonate was sometimes prescribed instead of sevelamer and sometimes combined with sevelamer or calcium-containing binders. Despite this new therapy, we noted little decline in the proportion of patients who received sevelamer prescriptions.

After April 2004 FDA approval, cinacalcet was prescribed for almost 10% of the prevalent hemodialysis population by October 2004 and for almost 32% of surviving patients by June 2006. During Phase III clinical trials, cinacalcet dosages were titrated from 30 up to 180 mg every 2 to 3 wk during 3 to 4 mo in patients with SHPT to reduce rapidly iPTH serum concentrations to ≤ 250 pg/ml (2,3). In one trial, median cinacalcet dosage was 60 mg in patients with iPTH ≤ 300 pg/ml. In these trials, by 6 mo, calcium was reduced by 6.8 to 7%, phosphorus by 7 to 8.4%, and iPTH by 40 to 43%. Cinacalcet dosage titration under typical practice conditions was much slower. Mean ci-

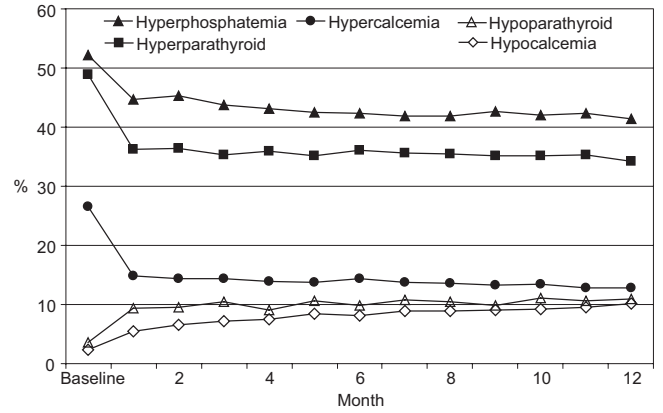


Figure 5. Percentage of patients who experienced a biochemical adverse event: Hyperparathyroidism (iPTH >600 pg/ml), hypercalcemia (corrected calcium >10.2 mg/dl), hyperphosphatemia (phosphorus >6 mg/dl), hypoparathyroidism (iPTH <150 pg/ml), or hypocalcemia (calcium <8.4 mg/dl) in each month during the 12-mo time frame for patients with cinacalcet prescriptions for ≥ 6 mo.

nacalcet daily dosage reached 55 mg after 12 mo, and corrected calcium declined by 4.2%, phosphorus by 7.0%, and PTH by 29.9% at 12 mo.

Cinacalcet patients were more likely to reach KDOQI target calcium, phosphorus, and iPTH values after 12 mo of treatment than in the month before treatment began, but these changes were also smaller than observed during a shorter time in Phase III clinical trials. Proportions of cinacalcet patients with average serum corrected calcium >10.2 mg/dl, phosphorus >6 mg/dl, and iPTH >600 pg/ml were reduced by more than 50, 21, and 30%, respectively. Decreases in laboratory values could reflect both cinacalcet influence and practice pattern changes with KDOQI guideline release; however, for noncinacalcet patients, calcium and phosphorus concentrations remained stable and iPTH values increased during the study period (data not shown), suggesting that cinacalcet was more influential than KDOQI guidelines. Despite these favorable effects, hyperparathyroidism and hyperphosphatemia persisted for a substantial proportion of long-term cinacalcet patients. Why these patients were not titrated more aggressively is unclear, although barriers may include adverse biochemical events and cost.

Before cinacalcet introduction, $>20\%$ of patients with iPTH >300 pg/ml were not receiving therapy in any given month. Cinacalcet prescriptions reduced this untreated population by approximately 20%, a conservative estimate because cinacalcet was already prescribed for approximately 13% of patients by our study start date. In addition, the SHPT management trend seemed to shift away from vitamin D monotherapy toward combining cinacalcet and vitamin D. Cinacalcet monotherapy was less common, but substantial proportions of patients with SHPT remained untreated.

Our data set is uniquely suited to studying prescribing patterns for oral (prescription and over-the-counter) and dialysis-related intravenous medications and their effects on laboratory and other outcomes. Laboratory variable and intravenous vita-

min D data collection was excellent; however, the quality of home medication data reporting may be a study limitation. New or changed home medication orders, with generic and trade drug names chosen from a drop-down list, were input into the electronic medical record by nurses. Dosages and patient instructions, however, were entered as free text. The percentage of monthly medication records with missing dosage information varied by drug (3.1% for cinacalcet, 5.3% for calcium acetate, 22% for lanthanum carbonate, 57% for sevelamer, and 67.8% for calcium carbonate). We manually added dosages when they were missing: 169 mg of elemental calcium for calcium acetate (the only marketed strength), 200 mg of elemental calcium for calcium carbonate (the most conservative adult dosage), 800 mg for sevelamer (the most predominant prescribed adult dosage), and 500 mg for lanthanum carbonate (the most predominant prescribed adult dosage during most of the study timeframe). Importantly, calculated dosages were prescribed dosages, because we have no information regarding whether patients were taking the medications.

Another potential limitation was accuracy of medication start dates. Medication orders from dialysis prescribers were entered daily in the electronic medical record, so start dates of medications typically prescribed by nephrologists (e.g., cinacalcet, phosphate binders) should be accurate. The rapid laboratory response to cinacalcet within the first month after prescription supports accurate start dates for the main drug of interest. A significant number of home medication stop dates were missing. Thus, a medication sequence file was created for each drug for each patient, effectively creating a stop date when a new dosage regimen was prescribed.

We described cinacalcet prescription after FDA approval in a large hemodialysis population and evaluated patient characteristics and biochemical outcomes and effect on other medications used to treat bone and mineral disorders. Cinacalcet use in improving clinical outcomes is currently under investigation in a multinational, randomized, double-blind, placebo-controlled study of hemodialysis patients with SHPT (8).

Conclusions

Our data suggest rapid cinacalcet uptake among hemodialysis patients in the first 2 yr after market introduction. Despite severe biochemical abnormalities in calcium, phosphorus, and PTH, slow dosage titration occurred. Patients with cinacalcet prescriptions for ≥ 6 mo experienced reduced serum calcium, phosphorus, and PTH and were more likely to achieve KDOQI targets and less likely to experience adverse biochemical events, except hypoparathyroidism and hypocalcemia. Overall, cinacalcet effect on serum biochemical factors in practice has been smaller than in clinical trials.

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