A Study of the Association Between Cinacalcet Adherence and Biochemical Outcomes

Andrew Lee[1], Vasily Belozeroff[1], Shaowei Wan[1], Richard Mutell[2], Christopher Bond[2], William Goodman[1]

[1]Amgen Inc., Thousand Oaks, CA; [2]DaVita Clinical Research®, Minneapolis, MN

INTRODUCTION

- Cinacalcet (Sensipar®) is used to treat secondary hyperparathyroidism (sHPT) in dialysis patients[1]
- Adherence to a daily cinacalcet regimen in real life practice is less than that demonstrated in clinical trials[2]
- As with other oral medications, non-adherence to cinacalcet may prevent patients from experiencing the full benefits of therapy
- Retrospective studies have shown that adherence can have an impact on clinical and economic outcomes,[3-7] but the algorithm and the terminology of adherence varied among different studies[3]

OBJECTIVES

- The primary objective was to evaluate the association between adherence and clinical outcomes, specifically PTH level, among dialysis patients
- The secondary objective was to compare different methods of adherence measurements by using medication possession ratio (MPR) and discontinuation/continuation as indicators of adherence

METHODS

- **Data:** DaVita Rx® data contain patient-level data on pharmacy fills for patients enrolled in the DaVita Rx® pharmacy program. Data was merged with DaVita® Clinical Data Warehouse (CDW) data that contained patient level information on demographics, laboratory result, and physician orders for first time cinacalet patients between January 1, 2009 and December 31, 2010
- **Inclusion criteria:**
  - Primary cohort (Cohort 1)
    - Patients in both the DaVita Rx® and DaVita® CDW database from January 1, 2009 through December 31, 2010
    - Age ≥ 18 years as of January 1, 2009
    - Patients receiving hemodialysis ≥ 3 times per week
    - Patients who are first time cinacalcet users defined as no cinacalcet fill before January 1, 2009
    - Patienst with ≥ 12 months of follow up
  - Sensitivity analysis cohorts
    - Cohort 2: subjects from primary cohort who were first time cinacalcet users with a new order record in CDW ± 30 days from initial fill date
    - Cohort 3: exclusion of subjects from primary cohort who had clinically justifiable reasons for discontinuation of cinacalcet
    - Cohort 4: subjects from primary cohort who were first time cinacalcet users with a new order record in CDW ± 30 days from initial fill date and excluding subjects who had legitmate clinical reasons for discontinuation of cinacalcet

METHODS cont.

- **Exposure:**
  - Two methods of adherence measurements were used:
    - Medication Possession Ratio (MPR) defined as Total Day Supply / Observation period for 12 months following first cincalcet use
      - Discontinuers (≥ 180 day gap between refills)
      - Low adherence (< 0.8 MPR)
      - High adherence (≥ 0.8 MPR)
    - Discontinuation categorized based on prescription orders from the CDW (as ordered by physician)
      - Continuous orders
      - Multiple starts and stops
      - Single stops (discontinuers)
- **Outcomes:**
  - Percent of patient-months with controlled PTH by adherence category
- **Analysis:**
  - Generalized Linear Mixed Effect Model
    - Random effect
      - Individuals
    - Fixed effects
      - MPR groups
      - Age
      - Vintage
      - BMI
      - Sex
      - Race
      - Primary cause of ESRD
      - Primary insurance

Table 1. Reasons for Change or Discontinuation on Cinacalcet Orders

	N	%
Clinically justifiable reasons for discontinuation		**31.35%**
Patient transfer/discontinued dialysis/death	25 521	21.32
Healthcare provider discontinued	3722	3.6
Labs	4740	4.01
Hospitalization	439	0.38
Parathyroidectomy	377	0.33
Side effects	1069	0.93
Discontinues not specified	870	0.76
Transplant	15	0
Labeled contraindication	18	0.02
Other reasons for discontinuation		**2.71%**
Patient discontinued	1364	1.19
Temporary hold	360	0.31
Not on med list	336	0.29
Entry error/duplicate order	324	0.28
Patient cost	265	0.23
Trying to control with another drug	239	0.21
Patient refused/never taken	224	0.19
Per protocol	121	0.11
Insurance does not cover	93	0.08
Nursing home discontinued	79	0.07
Completed therapy	25	0.02
Patient could not obtain	21	0.02
In study	15	0.01
Prior authorization (PA)	10	0.01
Changed modality	9	0.01
Donut hole	5	0.00
Sample ran out	4	0.00
Awaiting refill	1	0.00
Dose/Frequency change		**65.94%**
Dose/Frequency change	75 829	65.94

RESULTS

Figure 1. Patient Selection Flow Chart

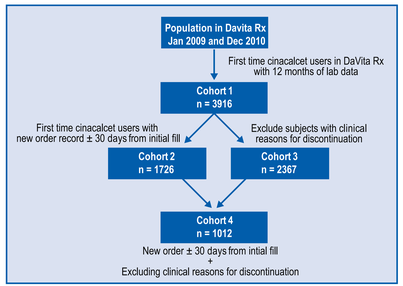


Table 2. Patient Characteristics by Cohort

	Cohort 1 n = 3916	Cohort 2 n = 1726	Cohort 3 n = 2367	Cohort 4 n = 1012
Age (years) mean (SD)	52.46 (14.12)	51.81 (14.18)	52.63 (13.95)	52.00 (14.13)
Vintage (years) mean (SD)	4.34 (3.86)	3.86 (3.63)	4.33 (3.84)	3.82 (3.57)
BMI (kg/m^2) mean (SD)	29.15 (7.42)	29.32 (7.78)	29.19 (7.12)	29.25 (7.68)
Sex (%)				
Female	49.06	48.44	48.63	48.72
Male	50.94	51.56	51.37	51.28
Race (%)				
Native American	0.46	0.29	0.34	0.30
Black	58.66	56.20	60.54	56.92
Hispanic	18.34	20.16	18.42	19.96
Asian/Pacific Islander	2.15	1.62	2.03	1.38
White	17.16	18.25	15.63	17.89
Other	2.27	2.14	1.94	2.08
Primary Cause ESRD (%)				
Diabetes	31.59	32.04	32.19	32.51
Hypertension	37.33	26.38	37.77	36.07
Polycystic Disease	2.30	2.43	2.45	2.57
Other	38.78	29.14	27.59	28.85
Primary Insurance (%)				
Medicaid	11.51	12.92	11.41	13.14
Medicare	78.01	76.59	78.45	77.57
No Insurance	0.59	0.70	0.55	0.59
VA	0.18	0.12	0.13	0.10
Other	9.53	9.44	9.17	8.20

- Characteristics similar to the United States Renal Data System dialysis population

Table 3. Fixed Effect Model on PTH Values

Cohort 1

Variables	F Value	P Value
MPR group	3.01	0.049
Age	93.30	<0.0001
Vintage	28.62	<0.0001
Body mass index	4.39	0.036
Race	8.53	<0.0001
Gender	5.88	0.015
Primary insurance	1.54	0.17
Primary cause of ESRD	1.21	0.31

Cohort 2

Variables	F Value	P Value
MPR group	1.34	0.26
Age	52.29	<0.0001
Vintage	8.17	0.0043
Body mass index	2.99	0.084
Race	6.74	<0.0001
Gender	5.45	0.020
Primary insurance	2.24	0.048
Primary cause of ESRD	1.72	0.16

Cohort 3

Variables	F Value	P Value
MPR group	0.84	0.43
Age	37.23	<0.0001
Vintage	33.55	<0.0001
Body mass index	1.58	0.21
Race	3.92	0.0003
Gender	10.74	0.0011
Primary insurance	0.78	0.56
Primary cause of ESRD	1.44	0.23

Cohort 4

Variables	F Value	P Value
MPR group	0.89	0.41
Age	12.35	0.00050
Vintage	12.11	0.00050
Body mass index	4.07	0.044
Race	4.11	0.00020
Gender	6.35	0.012
Primary insurance	1.75	0.12
Primary cause of ESRD	1.93	0.12

- MPR was a significant predictor of PTH control in the main analysis, but was inconsistent across sensitivity analysis cohorts

Table 4. Percentage of Patient-months with Biochemical Control by Adherence - Cohort 1

	Low-Adherers n = 555	High adherers n =1822	Discontinuers n = 1539	P Value
PTH < 600 pg/mL % months in range	0.91 ± 0.34	0.93 ± 0.35	0.88 ± 0.36	0.00030
300 to 600 pg/mL % months in range	0.52 ± 0.31	0.54 ± 0.33	0.50 ± 0.33	0.0021
150 to 300 pg/mL % months in range	0.37 ± 0.26	0.41 ± 0.28	0.35 ± 0.32	< 0.0001
< 30% of baseline % months in range	0.39 ± 0.31	0.37 ± 0.33	0.37 ± 0.32	0.37
6 month mean (SD)	453.13 (454.71)	456.89 (439.82)	508.21 (545.33)	0.0046
12 month mean (SD)	454.07 (404.85)	489.02 (503.80)	506.58 (506.67)	0.096
Calcium 8.4 to 9.5 mg/dL % months in range	0.79 ± 0.27	0.78 ± 0.29	0.76 ± 0.29	0.093
Phosphorous 3.5 to 5.5 mg/dL % months in range	0.59 ± 0.34	0.60 ± 0.36	0.56 ± 0.35	0.0014

Data represents mean ± standard deviation

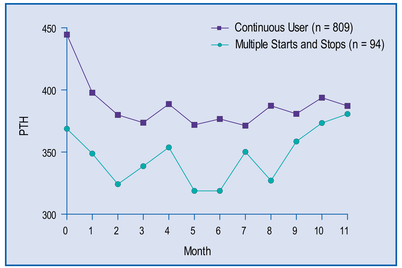
- Proportion of months in control was associated with adherence, mostly driven by discontinuers; however, the absolute diference among subgroups may not be clinically meaninginful

Table 5. Percentage of Patient-months with PTH Control by Pattern of Presecription as Ordered by Physician

First Time Cinacalcet Rx Patients Classified by Physician Order Pattern			
PTH Level	Continuers n = 903	Discontinuers n =740	P Value for Difference
PTH < 600 pg/mL	0.94 ± 0.33	0.84 ±0.38	< 0.0001
PTH 300 to 600 pg/mL	0.55 ± 0.33	0.47 ± 0.33	< 0.0001
PTH 150 to 300 pg/mL	0.41 ± 0.28	0.34 ± 0.27	< 0.0001

Values represent percent months in range; Data represents mean ± standard deviation
Continuers = continuous users grouped with patients with multiple starts and stops
Discontinuers = patienst with a single prescription which was stopped during the observation period

Figure 2. Patient PTH Control by Months Among Continuous Users and Patients with Multiple Starts and Stops Based on Prescription as Ordered by Physician



- Continuous users had higher PTH at cinacalcet initiation than patients with multiple stops and starts, but the magnitude of PTH reduction appears comparable
- Patients with multiple starts and stops had a higher variablitity of PTH than continuous users

LIMITATIONS

- MPR calculation based on the DaVita Rx® data may lead to patient miscalssification due to
  - potential continuation of cinacalcet therapy after discontinuation from DaVita Rx® program
  - Accumulation of unused pills
- Measurement of MPR is aggregated over 12 months, the relationship between MPR and monthly PTH reported here may not be reflective of short-term adherence cycles, including patients who discontinued cinacalcet for legitimate reasons in Cohorts 3 and 4
- Cross sectional design may not be able to capture the longitudinal causal relationship between the cinacalcet adherence and PTH control
- Follow-up work should consider merging the Pharmacy prescription data with the CDW order data and explore longitudinal models (eg, variable length of follow up) to address the limitations

CONCLUSIONS

- The MPR-based analysis showed an association between adherence and PTH control, but the results were not consistent across the sensitivity analyses
  - Compared to low adherence and discontinuers, high adherence patients with the greatest MPR (≥ 0.80) do have a higher proportion of controlled PTH months, but the differences between the groups do not appear to be clinically meaningful
- The prescription order-based analysis showed that continuous users had better PTH control compared to discontinuers. Furthermore, compared to continuous users, patienst with multiple stops and starts had higher PTH variability
- Our analyses suggest of a relationship between cinacalcet adherence and improved PTH control, although limitations of data and methodological choices clearly warrant further exploration and more in depth analyses.

REFERENCES

[1]K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. Oct 2003;42(4 Suppl 3):S1-201.
[2]Ginicherman Y, Moloney K, McKee C, Coyne DW. Assessment of adherence to cinacalcet by prescription refill rates in hemodialysis patients. Hemodial Int. Jan 2010;14(1):68-72.
[3]Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. Pharmacoepidemiol Drug Saf. Aug 2006;15(8):565-574; discussion 575-567.
[4]Pruijm M, Teta D, Halabi G, Wuerzner G, Santschi V, Burnier M. Improvement in secondary hyperparathyroidism due to drug adherence monitoring in dialysis patients. Clin Nephrol. Sep 2009;72(3):199-205.
[5]Philipneri MD, Rocca Rey LA, Schnitzler MA, et al. Delivery patterns of recommended chronic kidney disease care in clinical practice: administrative claims-based analysis and systematic literature review. Clin Exp Nephrol. Feb 2008;12(1):41-52.
[6]Pinsky BW, Takemoto SK, Lentine KL, Burroughs TE, Schnitzler MA, Salvalaggio PR. Transplant outcomes and economic costs associated with patient noncompliance to immunosuppression. Am J Transplant. Nov 2009;9(11):2597-2606.
[7]Williams TD, Dunette R, Kochevar JJ. Results of alternative definitions for Statin refill compliance, persistence and gaps in a retrospective database analysis. Poster presentation at ISPOR 11th International Meeting 2006. Philadelphia, PA.

CONFLICTS OF INTEREST

- This research was financially supported by Amgen, Inc., Thousand Oaks, CA and conducted in collaboration with Da Vita Clinical Research®

American Society of Nephrology, Philadelphia, PA; November 8-13, 2011