Evaluation of the Impact of Cinacalcet Treatment on Missed Dialysis Sessions

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Introduction

- Patients receiving maintenance hemodialysis (HD) are typically treated with 3 outpatient dialysis sessions weekly. Approximately 8% of patients receiving HD miss ≥ 1 dialysis sessions each month,[1] and 35% of patients miss ≥ 1 session over 3 months.[2] These missed HD sessions contribute to poor outcomes and are associated with increased morbidity and mortality, and may confer additional risk to patients with secondary hyperparathyroidism (SHPT) and elevated serum parathyroid hormone (PTH).[1,2]
- Missed dialysis sessions are also used as a surrogate marker for patient hospitalization by dialysis providers, and are a key economic factor for dialysis organizations.
- Sensipar® (cinacalcet) is an oral calcimimetic indicated for SHPT in HD patients. Trials have shown that the use of cinacalcet lowers PTH, calcium, and phosphorus in patients. We hypothesized that it may also impact the rate of missed dialysis sessions.

Objectives

- To estimate the effect of cinacalcet use on rate of missed in-center HD sessions among patients with SHPT.

Methods

- *Study data.* Data were abstracted from the electronic health records of DaVita HealthCare Partners.
- *Patients.* We considered patients who were aged ≥ 18 years receiving HD at DaVita HealthCare Partners between 01 January 2010 and 30 June 2013 who were enrolled in DaVita Rx prescription services. Because interest was in incident cinacalcet use, we restricted observation to patients who had no cinacalcet supply for at least the first 90 days of study.
- *Exposure groups.* Eligible patients were ascribed as cinacalcet initiators if (after the 90-day run in period) they subsequently received a prescription fill for cinacalcet. The date of this fill was considered index day 0. For each cinacalcet initiator, we identified eligible controls as patients who had not received a cinacalcet fill through the corresponding date, ascribing that date as index.
- *Matching.* In order to minimize confounding by indication, cinacalcet initiators and eligible controls were propensity score matched (1:1 with replacement) using a maximum caliper width of ± 0.005; propensity scores were estimated using a pooled logistic model that predicted cinacalcet initiation on the basis of age, sex, race, ethnicity, etiology of ESRD, time on dialysis, vascular access, body mass index, diabetes, congestive heart failure, coronary artery disease, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, alcoholism, amputation, malignancy, liver disease, Charlson Comorbidity Index, baseline values (at index date) of PTH, phosphorus, calcium, alkaline phosphatase, the number of metabolic bone disease (MBD) parameters out of range, albumin, and dialysate calcium concentration, and utilization of sevelamer, lanthanum carbonate, calcium acetate and intravenous vitamin D. Patient characteristics in the matched cohorts were described as means, SDs, medians, interquartile ranges, counts and proportions and compared as standardized differences.
- *Censoring and crossover.* Patients were analytically censored at the time of death, modality conversion, transfer of care, withdrawal from dialysis, disenrollment from DaVita Rx, or end of study (30 June 2013). For cinacalcet initiators, crossover was ascribed at the time of cinacalcet discontinuation: the first of any 90+ day period during which there was no cinacalcet supply based on prescription fill data; for controls, crossover was ascribed at the time of cinacalcet initiation (both where applicable).
- *Study outcome.* The outcome of interest was the rate of missed dialysis treatments.
- *Estimating the association between cinacalcet use and missed dialysis sessions.* This association was estimated using a series of mixed effects negative binomial regression models in which missed treatment rate was the dependent variable and cinacalcet exposure status was the independent variable. In parallel analyses, associations were considered on an Intention-to-Treat (ITT) and As-Treated (AT) basis.

Methods

- ITT analyses considered patients beginning on index date and continued until censoring. The primary ITT analysis was weighted by the stabilized inverse probability (IP) of censoring to account for differential loss to follow-up between groups. Unweighted ITT analysis was also conducted to gauge the degree to which differential censoring may have biased estimates.
- AT analyses considered patients beginning on index date and continuing until censoring or crossover. The primary AT analysis was weighted by the stabilized IP of censoring or crossover. Unweighted AT analysis was conducted to gauge the degree to which differential censoring or crossover may have biased estimates. Sensitivity AT analyses were conducted in which only IP censoring, and only IP crossover weights were applied.
- *Estimation of IP of weights*. Stabilized IP weights were estimated using the method of Robins, Hernan, and Brumback.[3] In the primary AT analysis, separate IP crossover models (and IP censoring plus crossover models) were fit for cinacalcet initiators and controls because characteristics that lead to cinacalcet discontinuation (crossover event for users) likely differ from those that lead to cinacalcet initiation (crossover event for controls). In sensitivity analyses, cinacalcet users and controls were pooled into single IP crossover and IP censoring plus crossover models.

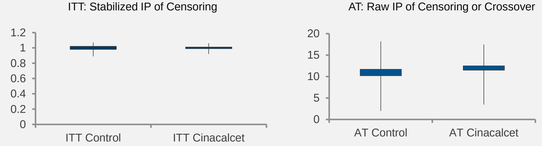
Results

Table 1. Baseline Patient Characteristics

Demographic [a]	Cinacalcet Initiators (N = 13,153)	Matched Controls (N = 13,153)	Std Diff [b]
Age, years, mean ± SD	55.1 ± 14.2	55.1 ± 14.1	0.0 %
Sex, n (%)			
Female	6607 (50.2)	6615 (50.3)	-0.12%
Race/ethnicity, n (%)			
White	2603 (19.8)	2506 (19.1)	+1.87%
Black	7010 (53.3)	7149 (54.4)	-2.11%
Hispanic	2765 (21.0)	2739 (20.8)	+0.49%
ESRD etiology, n (%)			
Diabetes	5433 (41.3)	5430 (41.3)	+0.06%
Hypertension	4690 (35.7)	4707 (35.8)	-0.27%
Time on dialysis, m, n (%)			
48+	6041 (45.9)	6063 (46.1)	-0.34%
Vascular access, n (%)			
Arteriovenous fistula	8460 (64.3)	8487 (64.5)	-0.44%
Diabetes, n (%)	8569 (65.2)	8514 (64.7)	+0.88%
Congestive heart failure, n (%)	1692 (12.9)	1738 (13.2)	-1.04%

[a] Index time is defined as the start of the quarter in which patients initiated cinacalcet and the corresponding date for matched controls. [b] Standardized differences <10% or ≥ -10% are indicative of sufficient balance. Abbreviations: ESRD, end-stage renal disease; SD, standard deviation; Std Diff, standard difference

Figure 1. Distribution of Weights for As-Treated and Intention-to-Treat Analyses



Depicted are p75, median, mean, and p25 values for distribution of weights.

Results

Table 2. Baseline Patient Laboratory Measures and Medication Use

Variable [a]	Cinacalcet Initiators (N = 13,153)	Matched Controls (N = 13,153)	Std Diff [b]
PTH range, pg/mL, n (%)			
300-499	3604 (27.4)	3836 (29.2)	-3.91%
500-699	2959 (22.5)	3247 (24.7)	-5.16%
700-899	1583 (12.0)	1557 (11.8)	+0.62%
≥ 900	2221 (16.9)	1947 (14.8)	+5.73%
Phos range, mg/dL, n (%)			
4.0-4.4	1625 (12.4)	1640 (12.5)	-0.36%
4.5-4.9	2131 (16.2)	2155 (16.4)	-0.49%
5.0-5.4	2339 (17.8)	2377 (18.1)	-0.76%
5.5-5.9	1122 (8.5)	1101 (8.4)	+0.58%
6.0-6.4	877 (6.7)	837 (6.4)	+1.26%
Calcium range, mg/dL, n (%)			
8.5-8.9	2896 (22.0)	2938 (22.3)	-0.77%
9.0-9.4	3965 (30.2)	4084 (31.1)	-1.95%
9.5-9.9	2819 (21.4)	2831 (21.5)	-0.22%
MBD parameters out of range, [c] n (%)			
0	2976 (22.6)	3020 (23.0)	-0.79%
1	5536 (42.1)	5668 (43.1)	-2.02%
2	3799 (28.9)	3588 (27.3)	+3.56%
3	842 (6.4)	877 (6.7)	-1.09%
CBB dose, mg/day, n (%)			
Not taking CBB	11,434 (86.9)	11,406 (86.7)	+0.62%
≤ 2001	339 (2.6)	349 (2.7)	-0.44%
> 2001-4002	493 (3.8)	485 (3.7)	+0.32%
> 4002-6003	394 (3.0)	392 (3.0)	+0.12%
> 6003	493 (3.8)	521 (4.0)	-1.09%
Sevelamer dose, mg/day, n (%)			
Not taking sevelamer	7233 (55.0)	7105 (54.0)	+1.95%
≤ 2400	642 (4.9)	633 (4.8)	+0.33%
> 2400-4800	1091 (8.3)	1157 (8.8)	-1.82%
> 4800-7200	1509 (11.5)	1543 (11.7)	-0.81%
> 7200-9600	1131 (8.6)	1150 (8.7)	-0.50%
> 9600	1547 (11.8)	1565 (11.9)	-0.43%
Lanthanum use, n (%)	923 (7.0)	910 (6.9)	+0.39%
IV vitamin D dose, µg/tx, n (%)			
Not taking IV vitamin D	1290 (9.8)	1102 (8.4)	+4.97%
≤ 0.5	594 (4.5)	591 (4.5)	+0.14%
> 0.5–1.0	1119 (8.5)	1076 (8.2)	+1.19%
> 1.0–1.5	1215 (9.2)	1243 (9.5)	-0.72%
> 1.5–2.0	1760 (13.4)	1806 (13.7)	-1.02%
> 2.0-2.5	1087 (8.3)	1125 (8.6)	-1.05%
> 2.5-3.0	1040 (7.9)	1036 (7.9)	+0.11%
> 3.0-3.5	785 (6.0)	821 (6.2)	-1.13%
> 3.5-4.0	991 (7.5)	1029 (7.8)	-1.09%
> 4.0	3272 (24.9)	3324 (25.3)	-0.90%

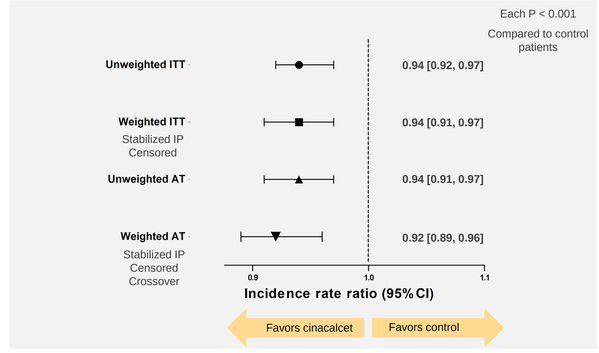
[a] Index time is defined as the start of the quarter in which patients initiated cinacalcet and the corresponding date for matched controls. [b] Standardized differences <10% or ≥ -10% are indicative of sufficient balance. [c] In-range defined as 3.5-5.5 mg/dL for phosphorus, 8.4-10.2 mg/dL for calcium and 150-500 pg/ml for PTH; variable reports the number of parameters out of range. Abbreviations: CBB, calcium-based phosphate binder; IV, intravenous; m, months; MBD, metabolic bone disease; PTH, parathyroid hormone; SD, standard deviation; Std Diff, standard difference

Table 3. Associations Between Cinacalcet Use and Rate of Missed Dialysis Sessions

Analysis	Incidence Rate Ratio (95% CI)	P-Value
Intention-to-treat		
Unweighted	0.94 (0.92-0.97)	< 0.001
Stabilized IP censoring weighted	0.94 (0.91-0.97)	< 0.001
As-treated		
Unweighted	0.94 (0.91-0.97)	< 0.001
Stabilized IP censoring weighted	0.94 (0.90-0.96)	< 0.001
Stabilized IP crossover weighted	0.93 (0.90-0.96)	< 0.001
Stabilized IP crossover [a] weighted	0.93 (0.91-0.96)	< 0.001
Stabilized IP censoring or crossover weighted	0.93 (0.90-0.96)	< 0.001
Stabilized IP censoring or crossover [a] weighted	0.92 (0.89-0.96)	< 0.001

[a] Indicates that separate analogous models were fit to estimate the probability of crossover (or crossover and censoring) among controls and cinacalcet patients. Abbreviations: CI, confidence interval; IP, inverse probability; NA, not available. P-values are comparisons with analogous controls.

Figure 2. Incidence Rate Ratios for Cinacalcet Use and Missed Dialysis Sessions



Discussion and Conclusion

- Baseline characteristics of cinacalcet initiators and matched controls were well balanced.
- In unweighted analyses, use of the oral calcimimetic cinacalcet was associated with a clinically meaningful 6% relative reduction in the rate of missed dialysis treatments.
- In AT analyses that were weighted by the stabilized IP of crossover and censoring (to account for selection effects), cinacalcet use was associated with an 8% relative rate reduction in missed dialysis treatments, and thus this result does not appear to be due to selection bias imposed by differential dropout or crossover of patients in response to changes in clinical status.
- The possibility of residual bias due to unmeasured confounding cannot be ruled out despite efforts to address using advanced analytic methods for confounding and selection bias control.

References

1. Saran R et al. Nonadherence in hemodialysis: associations with mortality, hospitalization, and practice patterns in the DOPPS. Kidney Int; 64 (1): 254-262.
2. Leggat JE et al. Noncompliance in hemodialysis: predictors and survival analysis. Am J Kidney Dis. Jul 1998; 32 (1): 139-145.
3. Robins JM et al. Marginal structural models and causal inference in epidemiology. Epidemiology. Sep 2000; 11 (5): 550-560.

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