Serum Calcium Reductions Among Patients on Hemodialysis Initiating Cinacalcet

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Introduction

- Current treatment guidelines for the management of secondary hyperparathyroidism (SHPT) patients on dialysis recommend the use of phosphate binders, vitamin D analogs, and calcimimetics to achieve target ranges for parathyroid hormone (PTH), calcium, and phosphorus.[1,2]
- Sensipar® (cinacalcet) is a calcimimetic approved for the treatment of SHPT in patients with chronic kidney disease receiving dialysis.[3] By virtue of its mechanism of action, cinacalcet lowers PTH and calcium.
- Physician response to and patient recovery from reduced serum calcium following cinacalcet initiation have not been described in real-world populations.

Objective

- To determine the incidence of low calcium following cinacalcet initiation in SHPT patients on hemodialysis.
- To evaluate patterns of clinician intervention after the development of cinacalcet-induced calcium reductions and their effect on recovery of calcium levels.

Methods

Population

- The cohort included all new cinacalcet users with calcium ≥ 8.4 mg/dL at cinacalcet initiation who received in-center hemodialysis at a large dialysis organization (LDO) between 01January2011 and 31December2013 and were enrolled in the LDO's prescription benefits service. New cinacalcet users were patients enrolled in the prescription benefit service for ≥90 days with no cinacalcet supply followed by a cinacalcet prescription fill.

Outcomes

- Patients were categorized as those who did not experience a reduction in calcium to < 8.4 mg/dL and those in whom calcium fell to levels < 7.5, 7.5-7.9, and 8.0-8.3 mg/dL. Index date was the date of first calcium level < 8.4 mg/dL.
  - Data were unavailable to determine if patients who experienced calcium reductions < 8.4 mg/dL had symptomatic manifestations
- Baseline patient characteristics were compared between these groups.
- We examined the frequency of physician response and the likelihood of calcium recovery according to different levels of calcium reduction. Physician responses were:
  - Cinacalcet discontinuation or dose reduction
  - Calcium-based binder addition or dose up-titration
  - Activated vitamin D addition or dose up-titration
  - Change to a more calcemic activated vitamin D
  - Increase in dialysate calcium concentration
  - Combination of any of the above responses
  - No response
- Serum calcium recovery was defined as the number and proportion of patients who manifested serum calcium at or above a priori stipulated thresholds (7.5, 8.0, or 8.4 mg/dL) by day 90 after the index date.

Results

Incidence of Calcium Reduction

- Of 13,723 patients who initiated cinacalcet, 6,437 (46.9%) patients experienced a reduction in calcium to < 8.4 mg/dL (Table 1).
- The majority of these (68.9%) had a calcium level of 8-8.3 mg/dL, while only 6.6% had a calcium < 7.5 mg/dL.
- Higher baseline PTH and alkaline phosphatase were associated with lower resulting calcium levels.

Table 1. Characteristics of Hemodialysis Patients at Cinacalcet Initiation and Development/Nondevelopment and Severity of Subsequent Calcium < 8.4 mg/dL (N = 13,723)

	Calcium	Calcium < 8.4 mg/dL, 6,437 (46.9)		
n (%)	≥ 8.4 mg/dL 7,286 (53.1)	< 7.5 mg/dL 423 (6.6)[a]	7.5-7.9 mg/dL 1,577 (24.5)[a]	8.0-8.3 mg/dL 4,437 (68.9)[a]
Age, years,[b] mean ± SD	54.9 ± 14.6	55.3 ± 15.3	56.8 ± 14.7	56.2 ± 14.2
Sex, n (%)				
Male	3,855 (52.9)	195 (46.1)	778 (49.3)	2,137 (48.2)
Female	3,431 (47.1)	228 (53.9)	799 (50.7)	2,300 (51.8)
Race/Ethnicity, n (%)				
White	1,417 (19.5)	115 (27.2)	348 (22.1)	990 (22.3)
Black	4,010 (55.0)	198 (46.8)	828 (52.5)	2,334 (52.6)
Asian	181 (2.5)	13 (3.1)	49 (3.1)	127 (2.9)
Hispanic	1,451 (19.9)	83 (19.6)	301 (19.1)	833 (18.8)
Other	227 (3.1)	14 (3.3)	51 (3.2)	153 (3.5)
Access/modality, n (%)				
CVC	750 (10.3)	84 (19.9)	219 (13.9)	541 (12.2)
AVF	4,828 (66.3)	246 (58.2)	976 (61.9)	2,863 (64.5)
AVG	1,708 (23.4)	93 (22.0)	382 (24.2)	1,032 (23.3)
ESRD etiology, n (%)				
Diabetes	2,617 (35.9)	179 (42.3)	702 (44.5)	1,890 (42.6)
Hypertension	2,854 (39.2)	135 (31.9)	514 (32.6)	1,542 (34.8)
Other	1,665 (22.9)	100 (23.6)	331 (21.0)	919 (20.7)
Missing	150 (2.1)	9 (2.1)	30 (1.9)	86 (1.9)
Post-dialysis Wt, kg,[c] mean ± SD	83.0 ± 23.8	84.9 ± 26.4	82.7 ± 23.3	83.9 ± 23.9
Time on dialysis, months,[b] median [p 25, p 75]	47 [23, 80]	42 [18, 76]	43 [21, 76]	44 [21, 77]
Ca, mg/dL,[c] mean ± SD	9.4 ± 0.6	9.1 ± 0.6	9.1 ± 0.5	9.1 ± 0.5
P, mg/dL,[c] mean ± SD	5.6 ± 1.6	5.8 ± 1.9	5.6 ± 1.7	5.5 ± 1.7
PTH, pg/ml,[c] median [p 25, p 75]	596 [392, 860]	767 [491, 1,154]	675 [456, 952]	638 [421, 896]
Kt/V,[c] mean ± SD	1.6 ± 0.3	1.6 ± 0.4	1.6 ± 0.3	1.6 ± 0.3
Albumin, g/dL,[c] mean ± SD	4.1 ± 0.3	3.9 ± 0.4	4.0 ± 0.3	4.0 ± 0.3
Alk phos, U/L,[c]	106.0 ± 65.7	140.7 ± 111.5	127.7 ± 84.5	118.9 ± 73.0
Dialysate Ca, mEq/L,[c] n (%)				
≤ 2	2,691 (37.0)	176 (41.6)	598 (37.9)	1,694 (38.2)
> 2 to < 2.5	596 (8.2)	33 (7.8)	124 (7.9)	386 (8.7)
2.5	3,915 (53.8)	203 (48.0)	822 (52.2)	2,271 (51.2)
≥ 3	81 (1.1)	11 (2.6)	32 (2.0)	84 (1.9)

Abbreviations: Alk phos, alkaline phosphatase; AVF, arteriovenous fistula; AVG, arteriovenous graft; Ca, calcium; CVC, central venous catheter; ESRD, end-stage renal disease; Kt/V, dialysis adequacy; P, phosphorus; PTH, parathyroid hormone; SD, standard deviation; Wt, weight.
Categories of low calcium based on the first calcium value ≤ 8.4 mg/dL after cinacalcet initiation.
[a] Numbers and percentages are calculated from the total number of patients (n = 6,437) who experienced calcium < 8.4 mg/dL.
[b] Described as of cinacalcet initiation date.
[c] Described as of value on or most recently preceding cinacalcet initiation.

Table 2. Therapeutic Response Within 90 Days of Index Low Calcium Among Patients who Developed Low Calcium

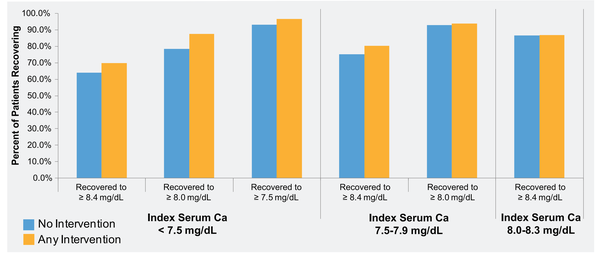
Response Measure	Index Calcium							
	Overall (<8.4 mg/dL)		<7.5 mg/dL		7.5-7.9 mg/dL		8.0-8.3 mg/dL	
	No. at risk	n (%)	No. at risk	n (%)	No. at risk	n (%)	No. at risk	n (%)
Cinacalcet								
Discontinued	5,433	933 (17.2)	356	101 (28.4)	1,317	246 (18.7)	3,760	586 (15.6)
Reduced Dose	4,500	251 (5.6)	255	14 (5.5)	1,071	58 (5.4)	3,174	179 (5.6)
Discontinued or Reduced Dose	5,433	1,184 (21.8)	356	115 (32.3)	1,317	304 (23.1)	3,760	765 (20.4)
Calcium-Based Binder								
Added	4,648	111 (2.4)	309	6 (1.9)	1,135	34 (3.0)	3,204	71 (2.2)
Up Titrated	785	60 (7.6)	47	2 (4.3)	182	10 (5.5)	556	48 (8.6)
Added or Up Titrated	5,433	171 (3.2)	356	8 (2.3)	1,317	44 (3.3)	3,760	119 (3.2)
Activated Vitamin D								
Added	639	413 (64.6)	62	39 (62.9)	162	105 (64.8)	415	269 (64.8)
Up Titrated	4,794	1,260 (26.3)	294	86 (29.3)	1,155	298 (25.8)	3,345	876 (26.2)
Added or Up Titrated	5,433	1,673 (30.8)	356	125 (35.1)	1,317	403 (30.6)	3,760	1,145 (30.5)
Changed to More Calcemic Activated Vit D[a]	4,493	7 (0.2)	271	1 (0.4)	1,058	2 (0.2)	3,164	3 (0.1)
Dialysate Calcium								
Increase Concentration	5,428	382 (7.0)	356	52 (14.6)	1,316	106 (8.1)	3,756	224 (6.0)
Vit D + Cinacalcet Comb.	5,433		356		1,317		3,760	
Vit D only		1,260 (23.2)		85 (23.9)		304 (23.1)		871 (23.2)
Cinacalcet Only		771 (14.2)		75 (21.1)		205 (15.6)		491 (13.1)
Vit D + Cinacalcet		413 (7.6)		40 (11.2)		99 (7.5)		274 (7.3)
Neither		2,989 (55.0)		156 (43.8)		709 (53.8)		2,124 (56.5)
Any Intervention[b]	5,433	2,741 (50.5)	356	226 (63.5)	1,317	688 (52.2)	3,760	1,827 (48.6)

Abbreviations: Ca, calcium; Vit, vitamin.
Index date is date of first calcium < 8.4 mg/dL following cinacalcet initiation. Categories of low calcium are based on calcium on index date. Analysis excludes patients with calcium < 8.4 mg/dL at the time of cinacalcet initiation.
[a] Represents change from doxercalciferol or paricalcitol to calcitriol.
[b] Any combination of added/increased vitamin D, stopped/decreased cinacalcet, added/increased calcium binder, or increased dialysate calcium.

Therapeutic Response Measures

- Among patients with calcium reductions who remained in the study for at least 90 days following index low calcium, 48.6% to 63.5% received 1 or more of the therapeutic responses, with the highest rate of response among those with the lowest serum calcium levels (Table 2). Of those who received therapeutic response:
  - 17.2% discontinued cinacalcet
  - 7.6% added or up titrated calcium-based binders
  - 30.81% added or up titrated activated vitamin D
  - Change to a more calcemic activated vitamin D or an increase in dialysate calcium was uncommon (0.2% and 7.0%, respectively).
- The majority of patients recovered to calcium ≥ 8.4 mg/dL within 90 days; only modest recovery differences were noted between patients who did versus did not receive intervention (Figure 1).

Figure 1. Calcium Recovery by Day 90, Stratified by Severity of Low Calcium and Presence or Absence of Intervention



Abbreviations: Ca, calcium.

Conclusions

- After cinacalcet initiation, calcium reductions to < 8.4 mg/dL were common, but calcium levels below 7.5 mg/dL were infrequent.
- Patients with more severe SHPT and higher bone turnover (as measured by higher PTH and alkaline phosphatase) at baseline were more likely to manifest calcium reductions < 8.4 mg/dL following cinacalcet initiation.
- Therapeutic response measures occurred in slightly more than half of all patients who developed low calcium; recovery was common and tended to occur within 90 days of index low calcium with or without directed therapeutic response.

References

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