Effect of protocol adherence on efficacy of cinacalcet in hemodialysis patients with secondary hyperparathyroidism and coronary calcification; the ADVANCE study

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INTRODUCTION

- Cardiovascular calcification is a common finding in patients with renal impairment who receive hemodialysis [1, 2]. Coronary artery calcification (CAC) is associated with raised serum levels of calcium (Ca) and phosphorus (P) [1, 2] and with raised levels of intact parathyroid hormone (iPTH) [3]. These elevations increase mortality risk [4].
- The use of vitamin D sterols to reduce PTH levels in hemodialysis patients is associated with increases in Ca and P [5]. Preclinical models suggest that vascular calcification is associated with vitamin D administration [6] and that this is reversible by calcimimetics [7].
- Cinacalcet and vitamin D sterols are effective in reducing plasma PTH levels in patients with secondary hyperparathyroidism (sHPT) who receive hemodialysis [8, 9].
- The objective of the ADVANCE study was to evaluate the effect of treatment with cinacalcet and vitamin D sterols on cardiovascular calcification. For the primary endpoint (progression of CAC based on Agatston scores), differences between the cinacalcet group and vitamin-D-only group were not significant; however, CAC progression by volume scores for coronary artery and aortic valve progression (both scores) were significantly less in the cinacalcet group. Reductions in iPTH, Ca, P and Ca x P levels were significantly greater in the cinacalcet group [10].
- The vitamin D sterol doses in the cinacalcet group of the ADVANCE study exceeded the protocol target. The objective of this post hoc analysis of the study was to evaluate treatment response in patients who met the protocol-specified target dose for vitamin D sterols.

METHODS

Study design and patients

- Prospective, randomized and controlled trial comparing progression of vascular and cardiac valve calcification over 52 weeks. Study participants were patients with sHPT and baseline coronary artery calcification (CAC) Agatston scores of ≥30 determined by multi-detector computed tomography (MDCT) scan who had been undergoing hemodialysis for ≥3 months.

Treatment Assignment

- Patients were randomly assigned to two treatment groups. In the group on cinacalcet plus vitamin D sterols, the cinacalcet dose (30–180 mg/day) was titrated over the first 20 weeks of the study and vitamin D sterols (starting dose equivalent to ≤6 µg paricalcitol i.v. per week) were to be given at each hemodialysis visit (as suggested by the protocol). The control group received vitamin D sterols alone at a variable dosage.
- All study participants were permitted use of calcium-based phosphate binders at a stable dosage.
- Cinacalcet dose was titrated to achieve a target level of iPTH of 150–300 pg/mL. Doses of vitamin D sterols and/or phosphate binders could be changed in response to changes in Ca and P levels, in accordance with treatment guidelines.

Assessments and study endpoints

- MDCT chest imaging at baseline, 28 weeks, and 52 weeks.
- The primary endpoint was the percentage change in CAC (Agatston score) from baseline to week 52. Secondary endpoints included: percentage change from baseline to week 52 in calcification (Agatston scores) for thoracic aorta, aortic valve, and mitral valve; the percentage of subjects with >15% CAC progression at week 52; and change in plasma PTH, and serum levels of Ca, P, and Ca x P from baseline to the average of week 44 and 52. An additional endpoint was the change in calcification at all sites measured by volume scores.
- Adverse events (AEs) and serious AEs (SAEs) occurring at any time up to 7 days after the final study visit (or up to the later of 30 days after last formal contact or last cinacalcet dose for SAEs) were recorded.

Post-hoc analysis

- In the current analysis, patients who took cinacalcet were sub-grouped according to actual vitamin D sterol dose taken:
  - Vitamin D "adherent" group (n=70): patients who achieved the target vitamin D sterol dose at week 2 (equivalent to ≤6 µg paricalcitol i.v. per week), whether or not this dose was maintained for the rest of the study.
  - Vitamin D "non-adherent" group (n=45): patients who exceeded the target vitamin D sterol dose at week 2.
  - The Week 2 dose was chosen because this allowed time for patients' vitamin D regimens to be adapted.
- Primary and secondary endpoint data for the vitamin D "adherent" group were compared with the control arm (n=120). Differences between groups were compared using a generalized Cochran-Mantel-Haenszel (CMH) test on ranks, stratified by CAC score at baseline. The stratum-adjusted median differences and corresponding 95% confidence intervals were determined by inverting the CMH test and conducting a numerical search.
- Two sensitivity analyses were performed to assess possible biases introduced by sub-grouping the cinacalcet group by vitamin D sterol dose. A matched analysis compared the adherent group with a sample of 70 control patients matched by baseline vitamin D dose, and an adjusted analysis compared all patients in each of the adherent and control groups after adjusting for baseline vitamin D dose.

RESULTS

Patients

- Patient demographics and clinical characteristics at baseline in the two cinacalcet subgroups were similar to the control group and baseline values for iPTH and Ca were also similar (Table 1).
  - Mean serum phosphorus concentrations were higher in the adherent group (6.20 [SD, 1.94] mg/dL) than in the control group (5.44 [1.70] mg/dL).
  - Incidence of congestive heart failure and peripheral vascular disease was highest in the control group, and myocardial infarction and coronary artery disease incidence was highest in the non-adherent group.
  - The percentage of patients in the adherent group who were using vitamin D sterols at baseline was lower than in the control group, and the median dose was lower. Use of calcium-containing phosphate binders was similar across the three groups (Table 2).

Table 1. Demographics and clinical characteristics at baseline

	Cinacalcet + vitamin D sterols		
	Adherent to vitamin D (n=70)	Non-adherent to vitamin D (n=45)	Control (n=120)
Women (n, %)	27 (39%)	18 (40%)	54 (45%)
Age, years (mean, SD)	62.1 (12.1)	61.2 (13.2)	62.4 (12.5)
Time on hemodialysis, months (median and Q1–Q3 interval)	35.9 (19.2–65.8)	40.8 (21.5–62.9)	36.8 (21.7–70.0)
Body mass index, kg/m^2 (mean, SD)	26.6 (5.0)	26.5 (4.4)	28.2 (6.7)
Co-morbidities:			
Diabetes mellitus	27 (39%)	20 (44%)	57 (48%)
Hypertension	68 (97%)	40 (89%)	116 (97%)
Peripheral vascular disease	16 (23%)	8 (18%)	36 (30%)
Cerebrovascular accident	10 (14%)	8 (18%)	13 (11%)
Myocardial infarction	5 (7%)	6 (13%)	10 (8%)
Coronary artery disease	19 (27%)	17 (38%)	36 (30%)
Congestive heart failure	7 (10%)	6 (13%)	32 (27%)
Hormone and mineral values:			
iPTH, pg/mL (mean, SD)	517 (348)	516 (309)	570 (448)
Serum calcium, mg/dL (mean, SD)	9.34 (0.67)	9.47 (0.65)	9.27 (0.52)
Serum phosphorus, mg/dL (mean, SD)	6.20 (1.94)	5.84 (1.79)	5.44 (1.70)

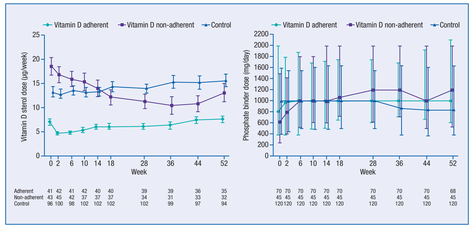
Table 2. Use of vitamin D sterols and calcium-containing phosphate binders at baseline. Mean doses for vitamin D sterols exclude data from patients taking zero doses, but median phosphate binder doses are from all patients (including those taking zero doses)

	Cinacalcet + vitamin D sterols		
	Adherent to vitamin D (n=70)	Non-adherent to vitamin D (n=45)	Control (n=120)
Use of vitamin D sterols (n, %)	41 (59%)	43 (96%)	96 (80%)
Vitamin D dose [i.v. paricalcitol equivalent, µg/week] (mean and SEM)	6.97 (0.65)	18.51 (1.75)	13.20 (1.04)
Phosphate binder dose [mg/day] (median, Q1, Q3)	800 (375, 2000)	616 (240, 1500)	1000.5 (400, 1590.4)

Abbreviation: SEM, standard error of the mean

- Use of vitamin D sterols and phosphate binders during the study in the two cinacalcet subgroups and the control group is shown in Figure 1.
- The median cinacalcet doses were identical in the two cinacalcet subgroups, being 30 mg/day at all time points except for Week 52 (median dose in both groups, 29 mg/day; interquartile ranges, 18–54 mg/day in adherent group and 16–60 mg/day in non-adherent group).

Figure 1. Mean dose (with standard error) of vitamin D sterols (µg/week) and median dose (with interquartile range) of calcium-containing phosphate binder (mg/day elemental calcium). Patients not taking any vitamin D sterols were not included in this calculation but for phosphate binders, patients with zero doses are included. Numbers of patients at each time point are shown below the graph.



Efficacy outcomes

- Progression of calcification in the adherent group was consistently less than in the control group according to Agatston and volume scores for all sites measured; differences between the adherent and non-adherent groups, however, were neither consistent in direction, nor statistically significant (Table 3). Median differences between adherent and control groups in calcification progression are shown in Figure 2.
- The percentage of patients in the adherent group who had >15% progression of coronary artery calcification was markedly lower than in the control group for those with high Agatston scores at baseline (≥1000), but for those with lower baseline scores, the percentages were similar for adherent and control groups. The difference in percentages for all patients was not statistically significant (Figure 3). Percentages in the non-adherent group were generally similar to those in the control group.
- Reductions in iPTH, Ca, P and Ca × P values in the adherent group were significantly greater than in the control group ($p<0.05$) (Figure 4), but not significantly different to those in the non-adherent group.
- The results of the sensitivity analyses indicated that differences between groups in baseline vitamin D sterol use did not largely affect the results.

Table 3. Progression of calcification (Agatston and volume scores); values are median and interquartile (Q1 and Q3) values for percentage change in score

	Cinacalcet + vitamin D sterols			
	Adherent to vitamin D	Non-adherent to vitamin D	Control	p value[1]
Coronary artery				
Number of patients	70	45	119	
Agatston	17.8 (–1.8, 54.7)	39.5 (4.5, 65.5)	31.3 (7.6, 81.1)	0.017
Volume	21.3 (0.9, 47.1)	22.3 (3.4, 65.3)	30.1 (10.3, 78.0)	0.004
Aorta				
Number of patients	54	35	102	
Agatston	23.8 (2.2, 39.8)	12.1 (0.0, 57.5)	33.1 (3.8, 69.4)	0.166
Volume	16.5 (1.5, 43.2)	16.1 (3.1, 59.4)	29.3 (6.4, 71.6)	0.091
Aortic valve				
Number of patients	37	19	51	
Agatston	6.0 (–16.8, 34.4)	6.7 (–15.8, 73.5)	51.5 (–9.9, 123.4)	0.017
Volume	2.8 (–20.1, 28.2)	14.8 (–10.7, 63.4)	35.3 (–13.3, 78.0)	0.022
Mitral valve				
Number of patients	33	19	64	
Agatston	6.7 (–22.0, 117.5)	21.5 (–8.3, 54.9)	54.4 (–3.9, 177.7)	0.087
Volume	8.5 (–17.5, 100.3)	25.6 (–8.4, 37.7)	42.0 (–10.6, 125.1)	0.138

1 P value for difference between adherent and control groups (all differences between adherent and non-adherent groups were non-significant)

Figure 2. Median differences (and 95% CI) between adherent group and control group in the percentage change in calcification scores.

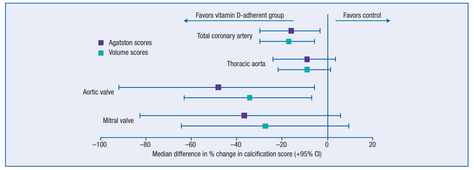
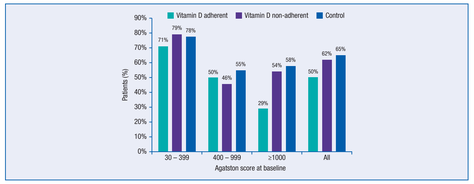


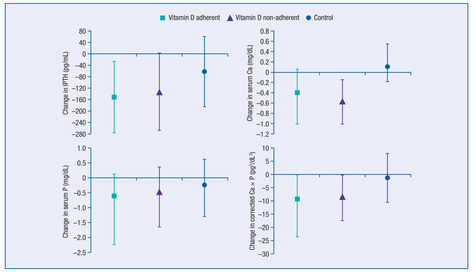
Figure 3. Percentages of patients with >15% progression of coronary artery calcification (CAC) categorized by Agatston score at baseline.



Tolerability

- The incidence of AEs (89, 78 and 86% of patients, respectively) and SAEs (44, 40, and 39%) was similar in the adherent, non-adherent and control groups. Events attributable to cinacalcet occurred in 24% and 20% of adherent and non-adherent groups respectively; 5 patients (4 in the control group) had AEs attributable to vitamin D sterols.
- Hypocalcemia adverse events occurred in 11, 4 and 0% of patients in adherent, non-adherent and control groups, respectively. The corresponding rates for hypercalcemia adverse events were 0, 2 and 5%.
- Two patients died, one each in the adherent and control groups.

Figure 4. Changes from baseline to the mean of values at weeks 44 and 52 in concentrations of iPTH, Ca, P and Ca × P (median and interquartile range).



STUDY LIMITATIONS

- The dose of vitamin D sterols was not titrated to a target PTH level, and the study design was open-label.
- Sub-grouping the cinacalcet group by vitamin D sterol dose has the potential for confounding by indication, i.e. patients who are more ill take higher doses of vitamin D. However, sensitivity analyses suggest that baseline differences in vitamin D dose did not bias the main efficacy results in this *post hoc* analysis.

CONCLUSIONS

- This *post hoc* subgroup analysis of the ADVANCE study showed that treatment with cinacalcet combined with a low dose of vitamin D sterols at week 2, i.e. equivalent to ≤6 µg paricalcitol i.v. per week, may be associated with less progression of cardiovascular calcification than vitamin D sterols alone in patients receiving hemodialysis, and significantly improved hormone and mineral profile.
- The median doses of cinacalcet in the adherent and non-adherent groups were identical. The mean dose of vitamin D sterols remained low in the adherent group throughout the study, whereas in the non-adherent group, it started higher but fell continuously during the study.

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