Cinacalcet but not Vitamin D Use Modulates the Survival Benefit Associated with Sevelamer in the Independent Study

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BACKGROUND

Whether the concurrent use of calcium sensing modulator or vitamin D with either a calcium free or calcium containing phosphate binder impacts patient-centered outcomes remains to be elucidated. Studies testing the impact on survival of single interventions aimed at reversing one aspect of the deranged mineral metabolism in CKD and ESRD have often failed to show a substantial survival benefit, in respect to potential side effects and relative cost. However, in light of the complex cross-talk of calcium, phosphate, vitamin D, and parathyroid hormone, it is possible that these findings may be partly explained by the effect modification on outcomes of various combinations of available drugs. We hypothesized that the observed effect on mortality of allocation to the sevelamer group in the independent trial might be modified by reductions in PTH with cinacalcet and any such favorable interaction could be attenuated in patients exposed to calcium-based phosphate binders.

For the present study we tested for an interaction on survival of cinacalcet, vitamin D, and phosphate binders in a cohort of incident dialysis patients treated with either calcium carbonate or sevelamer as part of a randomized controlled clinical trial, the INDEPENDENT Study.

METHODS

We utilized data from 466 patients incident to dialysis recruited to the INDEPENDENT study (ClinicalTrials.gov: NCT00710788). Briefly, adult (>18 years), CKD-5 patients new to hemodialysis (requiring dialysis for less than 120 days) were enrolled at 18 dialysis center in Italy and allocated randomly in a 1:1 fashion to receive either open label sevelamer or calcium carbonate as phosphate binders (Fig 1). Patients older than 75 years, or with congenital prolongation of QT segment syndrome, corrected QT (QTc) longer than 440 ms, increased QT dispersion (QTd), with history of cardiac arrhythmia, coronary artery bypass (CABG), liver dysfunction, hypothyroidism, or under drugs that may prolong QT interval were excluded.

The impact of cinacalcet and vitamin D use as well as the interaction effect on all-cause survival of either cinacalcet or vitamin D and phosphate binder use was tested in the overall study cohort. Due to a lack of association between Vitamin D and mortality as well as a significant interaction between vitamin D and phosphate binder use (***data not shown***), we focus on the interaction between cinacalcet and phosphate binders use. Study participants were divided in four groups according to the use of cinacalcet in each study arms (i.e. Sevelamer vs Calcium salts treatment arm). Demographic, clinical and laboratory characteristics were collected at study inception. Continuous variables are presented as mean ± standard deviation or median (interquartile range) when appropriate. Categorical variables are presented as proportion. Cumulative event rates were calculated across study groups via the Kaplan-Meier Method and compared by the use of the product-limit method. The association between cinacalcet as well as the interaction of cinacalcet and types of phosphate binder use was estimated via the Cox proportional-hazards models to calculate hazard ratios (HR) and 95% Confidence Intervals (CI). To test for statistically significant effect modification, a term for interaction of cinacalcet and phosphate binder use was included in the Cox Models. The robustness of the association was tested by progressive adjustment of the Cox models with variables known to be associated with survival based on existing literature or imbalanced among study groups. **Model 1** was adjusted for demographic characteristics (age, sex, body weight); **model 2**: adjusted for model 1 and comorbidities as well as markers of cardiovascular disease (diabetes mellitus, coronary artery calcification, systolic and diastolic blood pressure, ejection fraction and pulse wave velocity); **model 3**: adjusted for model 2 and laboratory characteristics (serum sodium, calcium, phosphate, parathyroid hormone, C-reactive protein, triglycerides); **model 4**: adjusted for model 3 and medications (angiotensin receptor blockers, ace inhibitors, vitamin D). The most parsimonious model was then selected via a stepwise approach. All analyses were conducted as *intention-to-treat*. Two-tailed probability values ≤ 0.05 were considered statistically significant. Analyses were completed using R version 2.15.0 (2012-03-30) (The R Foundation for Statistical Computing).

RESULTS

A total of 466 patients were randomized to either sevelamer (N=232) or calcium carbonate (N=234). Of these, 33 (14.2%) in the sevelamer and 35 (15.0%) in the calcium arm exit the study for various reasons prior to study completion. Study participants characteristics according to the use of phosphate binder type and cinacalcet use are summarized in **table 1**. Overall, a total of 248 (53%) of the study cohort almost equally distributed in the two study arms were treated with cinacalcet.

	Total (n=466)	Calcium (n=108)	Calcium and cinacalcet (n=126)	Sevelamer (n=116)	Sevelamer and cinacalcet (n=116)	
Variable	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**P-Value**
Age (year)	65.6(14.8)	65.3(14.9)	64.0(15.8)	66.2(13.8)	67.0(14.4)	0.45
Male sex (%)	49.1	45.3	51.5	50	49.1	0.81
Diabetes mellitus (%)	30.9	25.9	31.7	32.7	32.7	0.64
ASCVD (%)	34.9	27.7	38.8	39.6	32.7	0.19
CAC (Agatston Unit)	**256(715)**	**434(940)**	**446(959)**	**72(235)**	**70(231)**	**< 0.0001**
Systolic Blood pressure (mmHg)	137(17)	137(16)	136(18)	137(16)	136(19)	0.98
Diastolic Blood pressure (mmHG)	76(9)	76(9)	76(9)	76(10)	75(8)	0.69
Ejection Fraction (%)	**56(10)**	**55(11)**	**54(11)**	**58(8)**	**57(8)**	**0.006**
PWVstart	8.78 (2.7)[466]	8.48 (2.4)[108]	8.66 (3.33)[126]	8.96 (2.73)[116]	9 (2.11)[116]	0.3
Pulse Wave Velocity (m/sec)	8.7 (2.7)	8.4(2.4)	8.6(3.3)	8.9(2.7)	9(2.1)	0.3
QTc (msec)	407(33)	408(28)	406(27)	409(38)	404(36)	0.78
QTd (msec)	26(11)	26(11)	25(10)	27(12)	27(11)	0.63

At univariate analyses, cinacalcet was not associated with all-cause survival. Nevertheless a significant interaction was noted with the phosphate binder regimen (P=0.005, interaction test). Subject allocated to Sevelamer experienced a significant survival benefit when concurrently treated with cinacalcet (**figure 1**). Progressive adjustment for potential confounders did not affect the interaction between sevelamer and cinacalcet (p=0.003 for interaction test) (**table 2 and 3**).

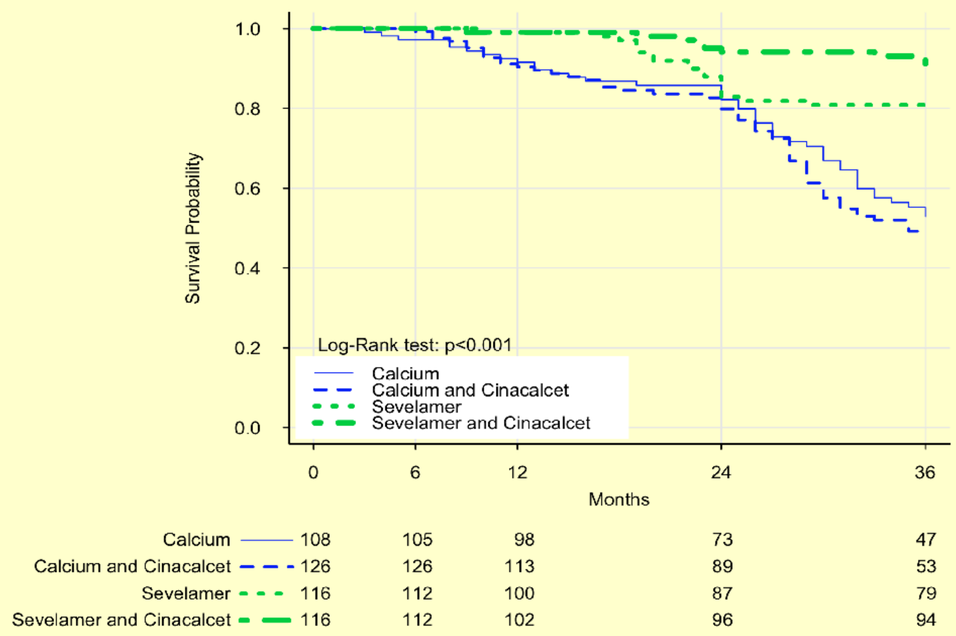

Table 2: predictors of all-cause mortality (stepwise selection procedure)

	exp(coef)	lower .95	upper .95	Pr(>|z|)
Use of Sevelamer (Y vs N)	0.37	0.2	0.68	0.001
Use of Cinacalcet (Y vs N)	1.36	0.89	2.09	0.14
Body weight (Kg)	0.96	0.95	0.98	<0.001
Diabetes (Y vs N)	8.89	5.92	13.35	<0.001
Coronary Artery Calcification (log(Agatston+1))	1.12	1.04	1.2	<0.001
Pusle wave velocity (m/sec)	1.14	1.08	1.2	<0.001
Systolic Blood pressure (mmHg)	1.01	1.0	1.02	0.018
Sodium (mEq/l)	1.11	1.04	1.17	<0.001
Phosphate (mg/dl)	0.88	0.76	1.01	0.08
Triglicerides (mg/dl)	0.99	0.99	0.99	0.003
Use of ACE inhibitor (Y vs N)	0.5	0.32	0.79	0.003
Use of Angiotensin Receptor Bloker (Y vs N)	0.29	0.17	0.48	<0.001
Phosphate binder*Cinacalcet interaction	0.29	0.11	0.72	0.007

Table 3: phosphate binder and cinacaclet interaction

Unadjusted	**HR**	**lower .95**	**upper .95**	**Pr(>|z|)**
Calcium salt use	Ref	-	-	-
Calcium salts+ cinacalcet use	1.12	0.75	1.67	0.54
Sevelamer use	0.36	0.21	0.61	<0.001
Sevelamer+cinacalcet use	0.15	0.07	0.31	<0.001
Model 1	**HR**	**lower .95**	**upper .95**	**Pr(>|z|)**
Calcium salt use	Ref	-	-	-
Calcium salts+ cinacalcet use	1.27	0.85	1.89	0.23
Sevelamer use	0.38	0.22	0.67	<0.001
Sevelamer+cinacalcet use	0.14	0.06	0.29	<0.001
Model 2	**HR**	**lower .95**	**upper .95**	**Pr(>|z|)**
Calcium salt use	Ref	-	-	-
Calcium salts+ cinacalcet use	1.19	0.77	1.83	0.43
Sevelamer use	0.34	0.18	0.62	<0.001
Sevelamer+cinacalcet use	0.11	0.05	0.23	<0.001
Model 3	**HR**	**lower .95**	**upper .95**	**Pr(>|z|)**
Calcium salt use	Ref	-	-	-
Calcium salts+ cinacalcet use	1.38	0.89	2.13	0.14
Sevelamer use	0.44	0.23	0.82	0.009
Sevelamer+cinacalcet use	0.16	0.07	0.36	<0.001
Model 4	**HR**	**lower .95**	**upper .95**	**Pr(>|z|)**
Calcium salt use	Ref	-	-	-
Calcium salts+ cinacalcet use	1.39	0.9	2.15	0.13
Sevelamer use	0.37	0.2	0.71	0.002
Sevelamer+cinacalcet use	0.14	0.06	0.32	<0.001

Limitations

- Post hoc analysis of a RCT designed for other purposes (unmeasured potential bias)
- Analysis conducted as per Inetntion to Treat (ITT)
- Dataset comprised of patients incident to dialysis only

Strengths

- A relatively large study sample allowed us to control for many potential confounders
- Carefully adjudicated outcome data

CONCLUSIONS

In conclusion, we showed a robust and independent effect modification of cinacalcet on the survival benefit associated with sevelamer use in a large cohort of incident to dialysis patients[4]. Although this effect was independent of numerous potential confounders, future endeavors should prospectively test the hypothesis generated by current results

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