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

Antonio Bellasi1, Mario Cozzolino2, Domenico Russo3, Donald A. Molony4 and Biagio Raffaele Di iorio5

1Ospedale Sant’Anna-Como; 2University of Milan; 3University “FEDERICO II” Napoli; 4University of Texas-Houston and 5PO “A Landolfi” – Solofra.

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, phosphata, vitamin D, and parathyroid hormone, it is possible that these findings may be partially explained by the effect modification of outcomes on various combinations of available drugs. We hypothesized that the observed effect of mortality on allocation to the sevelamer group in the independent trial may be modified by reductions in PTH in 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 406 patients incident to dialysis recruited to the INDEPENDENT study (ClinicalTrials.gov: NCT01570785). Briefly, study (all 18 years), 12 patients new to hemodialysis (requiring dialysis for 1-120 days) were enrolled at 12 dialysis centers in Italy and assigned randomly in a 1:1 fashion to receive either standard care of dialysis and vitamin D (cholecalciferol) and phosphate binders (FG1). Patients older than 75 years, in whom a complete protocol of QT segment parameters, corrected QT (cQT) (range 400-450 ms, deemed QT dispersion (cQT) and normal heart rhythms, and patent coronary arteries were necessary for dialysis and for persistent hyperphosphatemia, was placed or who declined randomization were excluded. Patients older than 75 years, in whom a complete protocol of QT segment parameters, corrected QT (cQT) (range 400-450 ms, deemed QT dispersion (cQT) and normal heart rhythms, and patent coronary arteries were necessary for dialysis and for persistent hyperphosphatemia, was placed or who declined randomization were excluded. The study was approved by the institutional human research ethics committee. The study was approved by the institutional human research ethics committee.

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.

At univariate analyses, cinacalcet was not associated with all-cause survival in patients with or without the phosphate binder use (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).

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. Although this effect was independent of numerous potential confounders, future endeavors should prospectively test the hypothesis generated by current results.