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COMMENTARY

Cinacalcet does not provide cardiovascular protection in hemodialyzed patients

Pierre-Yves Martin

Nephrology Division, Department of Medical Specialties, Geneva University Hospital, Geneva, Switzerland.

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Commentary on: EVOLVE Trial Investigators, Chertow GM, Block GA, Correa-Rotter R, Drüeke TB, Floege J, Goodman WG, Herzog CA, Kubo Y, London GM, Mahaffey KW, Mix TC, Moe SM, Trotman ML, Wheeler DC, Parfrey PS. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med 2012;**367**:2482–2494

Secondary hyperparathyroidism is one of the key abnormalities of bone metabolism in chronic kidney disease (CKD). These abnormalities have been intensively studied these last two decades. In addition to the consequences observed on bone, it has been demonstrated that these abnormalities were associated with vascular calcification and an increased risk of cardiovascular (CV) mortality.[1] For these reasons, such abnormalities are considered as a systemic disorder called CKD–MBD for mineral and Bone Disorder. Cinacalcet is the first calcimimetic agent. It suppresses directly parathyroid hormone (PTH) secretion and contrary to vitamin D receptor agonists, it decreases calcium and in a lower magnitude phosphorus.[2] This profile of action makes it the best PTH-modifying drug and did raise the hope that we may have a drug that reduces the CV risks of CKD patients. The EVOLVE trial was designed to answer this question with a primary composite end point, including time until death, myocardial infarction, hospitalization for unstable angina, heart failure or a peripheral vascular event.[3] A total of 3883 patients undergoing hemodialysis with secondary hyperparathyroidism were assigned to receive either cinacalcet or placebo. After a follow-up to 64 months, the unadjusted intention-to-treat analysis did not show a significant reduction of the primary composite end point (7% reduction in the cinacalcet group). This is a disappointing result because there were many reasons to expect a favorable effect of cinacalcet on CV risks. How can we explain this result?

The study was one of the major prospective investigator-driven studies conducted in hemodialysis patients, including patients in many countries around the world, and the efforts of the EVOLVE trial investigators, as well as AMGEN who did support the study have to be acknowledged. The design was carefully prepared, but the investigators did calculate a rate of events based on previous studies and it came out that it was lower than expected and they had to extent the study significantly to have enough power. Unfortunately, the median age was also 1 year younger in the control group, which may play a role in this population at high risk of CV events. However, the most striking characteristic of the results is the high percentage of discontinuation in both groups (67 and 70%) at the end of the study. The high rate of discontinuation for protocol-specified reason was not surprising and did not differ between groups, but the rate of discontinuation for non-protocol–specified reasons was very high especially in the placebo group. The main reasons were patient's request and switch to commercial cinacalcet. Subsequently, 19.8% of patients in the placebo group began receiving cinacalcet before the occurrence of a primary event corresponding to an annual rate of 7.4% (drop-in). In the cinacalcet group, the treatment-related adverse effects such as nausea, vomiting and hypocalcemia were more frequent (18.1% versus 13.0% in the placebo group). As a consequence, the surrogate markers of cinacalcet action such as PTH, calcium and phosphates decrease are not as different between both groups as it has been observed in previous studies when cinacalcet was not commercially available. Indeed, the investigators did anticipate this situation when designing the study, as they conducted prespecified companion analyses with lag censoring, in which data were censored 6 months after patients stopped using a study drug. The lag-censoring analyses show nominally 15% reduction in primary composite end point in the cinacalcet group with a 17% reduction in death hazard ratio and a 28% reduction in heart failure hazard ratio. Another set of analyses adjusted for baseline characteristics or other parameters also suggest that cinacalcet may nominally significantly reduce CV events. With that in mind, it is difficult to be convinced that the negative result in intention-to-treat analysis can be definitive…. But we cannot expect another study to resolve this dilemma in hemodialyzed patients.

This study shows the limitation of using surrogate biomarkers, which substitute for clinical end points.[4] Since 2004, this drug was commercially available and its efficacy was largely emphasized and its use encouraged based on surrogate end points that predicted improved cardiovascular outcomes. Therefore, the nephrologists participating to the study were uncomfortable with high PTH values in the control group despite clinical uncertainty about the benefit of normalizing these

values, and it explains the high drop-in of this study. The lesson of the study is that regulators and clinicians trialists have to assess the effects of new drugs on hard outcome data rather than surrogate end points before drug registration.[5]

As cinacalcet is not yet registered for CKD patients stage 3 and 4, efforts have to be done to demonstrate that cinacalcet might have a role in decreasing CV events in CKD patients. Meanwhile, the results of EVOLVE should impact on the use of cinacalcet in hemodialyzed patients by minimizing the importance of strict PTH control on their overall pronostic. Therefore, the nephrologist has to conduct a risk–benefits analysis in each hemodialyzed patient with high PTH before prescribing cinacalcet. This analysis should take into account the other alternatives to lower PTH, such as optimal dosage of vitamins D sterols, and better use of phosphate binders. The increase rate of treatment-related adverse effects and the decrease rate of parathyroidectomy observed in the cinacalcet group, as well as the high cost of cinacalcet have to be included in this analysis. Such an analysis would probably have a negative impact on the use of cinacalcet and the enthusiasm for prescribing this drug has already declined.

Conflict of Interest

The author declares no conflict of interest.

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