What can we learn from a statistically inconclusive trial? Consensus conference on the EVOLVE study results

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Abstract

The link between serum parathyroid hormone (iPTH) and cardiovascular (CVS) mortality has not been fully elucidated. The EVOLVE Study was designed to test whether a drug such as cinacalcet, aimed at lowering iPTH, could reduce the astonishingly high cardiovascular risk in patients on maintenance dialysis (CKD-5D). Accordingly, the primary outcome of the study was the combined endpoint of time to death or hospitalization due to CVS factors or from any cause. Time to bone fracture and parathyroidectomy were regarded as secondary endpoints.

At study completion, the ‘Intention-To-Treat’ analysis documented a non-significant 7% (Hazard Ratio: 0.93; 95% Confidence interval: 0.85-1.02; P = 0.11) reduction of the primary composite endpoint. However, the intention to treat analysis does not take into account adherence to drug regimens or control for factors that may potentially jeopardize the conduction of the study. In particular, in spite of a careful pre-planned study sample calculation, the final power of the EVOLVE study was 54% instead of the assumed 90%, greatly reducing the reliability of study results. Furthermore, the pre-planned multivariable adjustment of the primary endpoint suggests a ‘nominally’ significant reduction of the risk of the primary composite endpoint when age is entered into the statistical model. The sensitivity analysis further corroborates this result. The ‘Lag Time Censoring Analysis (LTCA)’ evidenced a ‘nominally’ significant 15% risk
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red.. of the composite endpoint among patients allocated to cinacalcet if the patients' follow-up was terminated 6 months after the study drug discontinuation, as pre-planned in the protocol. It is interesting that the LTCA suggests that the effect of cinacalcet weakened over time and became insignificant after about 1 year from drug discontinuation.

Although authors could not detect any effect of cinacalcet on bone fracture associated with cinacalcet use, the secondary analyses of the EVOLVE trial suggest a ‘nominally’ significant 60-70% risk reduction of parathyroidectomy and a reassuring safety profile of prolonged exposure to cinacalcet.

In summary, the EVOLVE study adds to the list of inconclusive randomized clinical trials in Nephrology. However, the preplanned exploratory and sensitivity analyses suggest that when imbalances of patients' characteristics at study entry (i.e., age) or study drug discontinuation are considered, a ‘nominally’ significant risk reduction in CVS and parathyroidectomy associated with cinacalcet treatment is noted.

Key words: bone fracture, cinacalcet, EVOLVE, parathyroidectomy, survival

Introduction

Secondary Hyperparathyroidism (sHPT) is a common metabolic complication of chronic kidney disease (CKD). Numerous epidemiological studies link sHPT to bone mineral abnormalities, increased risk of bone fractures, cardiovascular (CV) disease (i.e., vascular calcification and left ventricular hypertrophy), parathyroidectomy and CV morbidity and mortality [1].

The majority albeit not all available observational studies supports the notion that intact parathyroid hormone (iPTH) correlates with the risk of death especially for iPTH levels above 600 pg/ml [2] (full text), [3] (full text). Nonetheless, whether iPTH is causally associated with unfavorable outcome has not been established yet. Furthermore, available data has considered iPTH as a uremic toxin per se and usually the association between iPTH and survival is adjusted for serum levels of calcium of phosphate that have been linked to both iPTH as well as poor survival [4]. The biological complexity of these abnormalities and the concomitant adjustment for correlated factors may explain the conflicting results of different studies and it would be advisable to study the association between iPTH and mortality without adjusting for other parameters of the chronic kidney disease mineral bone disorder (CKD-MBD). Regardless of these considerations, the link between iPTH and mortality is still debated [5] (full text).

Therapeutic options for sHPT

Multiple strategies are commonly adopted to treat sHPT: phosphorous intake restriction, calcium containing and calcium free phosphate binders, various vitamin D metabolites and in patients receiving dialysis (CKD5D), cinacalcet [6] (full text). Of note an adequate dialysis dose allows for phosphate removal and hyperphosphatemia and sHPT control.

Over the past decade the regulatory associations requirements for drug approval has progressively increased the demand for clinical trials designed to test the effect of a new drug on “hard endpoints” rather than surrogate or intermediate endpoints. The effect of cinacalcet is not only on iPTH but it also lowers serum calcium and phosphorous. In addition, preliminary results from “post hoc” analyses of clinical trials designed to investigate the effect of cinacalcet on serological biomarkers, suggested a favorable impact on CV hospitalization, bone fracture and parathyroidectomy, prompting the EVOLVE trial design to shed light on the impact of cinacalcet on hard endpoints.
The EVOLVE study

Rationale

The EVOLVE study was designed to test whether sHPT treatment with cinacalcet versus standard therapy (placebo) could improve survival in CKD5D patients. The primary endpoint was a composite of all-cause as well as CV mortality and time to the first non-fatal CV event (hospitalization due to acute myocardial infarction, unstable angina, CHF, peripheral arterial disease). The EVOLVE study recruited 3,883 patients from 22 countries and is the largest study ever conducted in maintenance dialysis patients [9] (full text), [10] (full text).

Power

The EVOLVE study design is event-driven, meaning that it was anticipated that the study would have been terminated once a total of 1,882 primary endpoint events were accrued. Indeed, according to the study sample calculation, a total of 1,882 events would have been enough to demonstrate a significant (alpha 0.05) 20% risk reduction of the primary endpoint among cinacalcet treated patients with a power of 90%.

However, a few issues are worth a mention due to the impact of the final results of the EVOLVE study:

- The event rate of the primary endpoint in the overall study cohort was lower than anticipated. Indeed, when the trial was designed it was anticipated an event rate of the primary endpoint of 23.2%/year. However, at study completion the recorded event rate was 20.8%/year. Thus, to increase the number of events, the EVOLVE follow-up was prolonged from the predicted 2.5 years to the actual 5 years resulting (overall study duration 6.5 years: 1.5 year study patients recruitment plus 5 years of follow-up). Irrespective to the study follow-up prolongation and the recording of 1,882 primary endpoint events, the calculated power at study completion was 54% instead of the anticipated 90%.

- 440 patients allocated to the placebo study arm discontinued the study medication. Of these, 384 (19.8% of the overall cohort allocated to the placebo study arm) were switched to cinacalcet (drop-in) due to a poor iPTH control. Similarly, in the cinacalcet study arm 1207 (62.0% of the overall cohort allocated to the cinacalcet arm) discontinued the drug (drop-out) due to adverse effects, kidney transplantation or parathyroidectomy (PTX). A total of 18.1% and 13.0% of patients allocated to the cinacalcet or the placebo study arm complained of adverse events. However, as the “Intention-to-Treat (ITT)” analyses mandates, all patients were considered as if they adhere with the allocated treatment irrespective of drug discontinuation or switching during follow-up.

- A few imbalances of patient characteristics between groups at baseline were noted. Patients allocated to cinacalcet were on average older and more likely to have experienced a transient ischemic attack (5.1% vs 3.8% in the cinacalcet and placebo group, respectively; p<0.05).

All the above-mentioned factors could explain why the Kaplan-Meyer survival analysis failed to demonstrate a significant risk reduction associated with cinacalcet use and the peculiar aspect of the survival curves. Indeed, during the first 2 years of follow-up the 2 survival curves diverge while they tend to converge thereafter. This maybe due to a change in the proportionality of the hazards and is likely conditioned by the drop-in of patients with higher levels of iPTH or due to a survival bias.
In consideration of the actual study power (54% vs the anticipated 90%), the secondary and sensitivity analyses included in the study protocol may reveal clinically relevant messages. Indeed, a power of 54% implies about a 50% chances to have not recorded a sufficient number of primary endpoint events to show a statistically significant difference between cinacalcet and placebo. In other words, there is about a 50% chance that a real survival benefit associated with cinacalcet may have been missed.

**Statistical analyses and factors that may have influenced the EVOLVE trial results**

**Intention-to-Treat (ITT) analyses.**

The ITT [10] (full text) showed a non statistically significant 7% relative risk reduction of the primary composite endpoint (Hazard ratio: 0.93; 95% Confidence Interval (CI): 0.85-1.02; P=0.11). Thus, the EVOLVE study failed to demonstrate a significant risk reduction of the primary endpoint. Nonetheless, all the above-mentioned factors likely affected the final result by reducing the study power.

**“Per protocol” analyses: Lag Time Censoring analyses**

A few remarks are worth mentioning to better examine the EVOLVE study results. ITT is the fundamental analyses required by the regulatory agencies for drug registration or to expand the drug indication of a compound already on the market. Nonetheless, ITT may not be the most suitable analyses to address specific clinical issues. ITT disregards what really happens during study follow-up, in particular it does not take into account drug adherence and the reasons that lead to drug discontinuation. The “lag time censoring (LTC)” analyses included in the study protocol among the sensitivity analyses is a way to account for the drug adherence. LTC censors the study participant after a pre-specified period of time (lag time) from drug discontinuation and it can provide useful indications on the real impact of a drug on the endpoint of interest. [11]

**“Per protocol” analyses: “Cox analyses” adjusted for baseline risk factors**

In the EVOLVE study, the multivariable adjusted analyses, adjusted for more than 40 pre-specified patient characteristics (including age), showed a “nominally” (because it is not the primary analyses of the study protocol) significant 12% reduction of the composite endpoint. Though exploratory in nature, all variables entered into the Cox model were checked for potential interactions with other variables and with the outcome of interest. Age is one of the variables entered into the survival models. Adjustment for age, resulted in a 3.2% increase of the relative risk of the primary endpoint in the placebo study arm due to an overall older age (about 1 year) of the patients allocated to cinacalcet. Of note, the variable selection is based on the potential baseline imbalances between groups but rather with their association with the outcome of interest. With regards of age, this variable is associated with the primary study outcome. However, the association between age and mortality is both quantitative as well as qualitative. Age confounded the association between cinacalcet and modified (interaction) the effect of cinacalcet (older subjects experience a greater benefit of cinacalcet). Indeed, the Forrest plot reported in the appendix of the EVOLVE study report (figure S2) [1] suggests a significant effect of cinacalcet in subjects older than 65 years of age (HR: 0.99 and 0.74 for subjects younger and older than 65 years of age, respectively). The increase effect of cinacalcet among older subjects (about 25.6% of the study population were older than 65 years of age) may be due to a greater incidence of the primary endpoint with a substantial increase in the power and accuracy of the statistical analyses.
With regards of drug adherence, the pre-specified “Lag Time Censoring” sensitivity analyses shows a nominally significant 15% risk reduction of the primary endpoint when the follow-up is terminated 6 month after drug discontinuation. The New England Journal of Medicine editors asked to further expand these analyses to 9,12 and 18 months from drug discontinuation. The new set of analyses suggest that the benefit associated with cinacalcet treatment progressively disappears after drug discontinuation and disappears after 1 year (Figure 1). In light of the substantial number of individuals that discontinued the study drug, the LTCA overcame some limitations of the ITT analyses. Though, drug discontinuation in the EVOLVE study was common (drop in and out), only 2.1% of the entire study cohort were lost to follow-up for more than 5 years and excluded from the ITT analyses. Thus, the majority of study patients who discontinued the drug for prolonged period of time (up to 5 years) during follow-up were included in the ITT analyses that tested the impact of cinacalcet independent of drug adherence. The LTCA results suggest that cinacalcet lowered the risk of the composite endpoint among those individuals who complied with drug assignment. [11]

Survival data among cinacalcet treated individuals who achieved and maintained throughout the study follow-up the suggested iPTH target is not available for comparison with placebo treated individuals who did not achieve and maintain the suggested iPTH target. Though this would be a post-hoc analysis, it could shed light on the potential harm associated with iPTH and the desired iPTH to achieve and maintain in CKD5D patients.

**Risk of parathyroidectomy (PTX)**

The lack of consensus on the indications to PTX complicates the endpoint definition. Some authors indicate surgery after 6 months of inefficacious conservative therapy or iPTH values above 800 pg/ml or in case of uncontrolled hypercalcemia or hyperphosphatemia, calciphylaxis, bone fracture associated to shPT. Notably, the incidence of PTX declined in the recent past possibly due to the available shPT drugs among the others cinacalcet.

The EVOLVE study results documented a “nominally” significant 56% risk reduction of PTX associated with cinacalcet use (this is a pre-specified secondary endpoint of the study). At study completion, authors report on 140 (incidence: 7%) and 278 (incidence 14%) PTX in the cinacalcet and placebo group, respectively.

### Tabella 1. Effetto del tempo dalla sospensione del trattamento ("Lag") sull’endpoint primario composito ("Lag Censoring analysis").

<table>
<thead>
<tr>
<th>Log Duration (months)</th>
<th>Cinacalcet (N=1948)</th>
<th>Placebo (N=1935)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>423 (21,7)</td>
<td>463 (23,9)</td>
<td>0,79 (0,69, 0,91)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>3</td>
<td>594 (30,5)</td>
<td>616 (31,8)</td>
<td>0,83 (0,74, 0,93)</td>
<td>0,002</td>
</tr>
<tr>
<td>6</td>
<td>638 (32,8)</td>
<td>658 (34,0)</td>
<td>0,85 (0,76, 0,95)</td>
<td>0,003</td>
</tr>
<tr>
<td>9</td>
<td>672 (34,5)</td>
<td>692 (35,8)</td>
<td>0,86 (0,77, 0,96)</td>
<td>0,005</td>
</tr>
<tr>
<td>12</td>
<td>705 (36,2)</td>
<td>722 (37,3)</td>
<td>0,87 (0,78, 0,96)</td>
<td>0,008</td>
</tr>
<tr>
<td>18</td>
<td>772 (39,6)</td>
<td>768 (39,7)</td>
<td>0,91 (0,82, 1,00)</td>
<td>0,054</td>
</tr>
</tbody>
</table>

Come si può notare l’efficacia del trattamento con cinacalcet, del 21%. Statisticamente “nominalmente” significativo al termine del trattamento, tende a ridursi con la sospensione di cinacalcet, pur restando significativo sino a 12 mesi dalla sospensione di cinacalcet (riduzione del rischio relativo dell’end point primario del 13%, con una p “nominale” di 0,008).

N= numero pazienti randomizzati
Due to a lack of consensus in the PTX indication, the EVOLVE study steering committee repeated the analyses with a pre-specified set of indication to PTX. These analyses confirmed the “nominally” significant risk reduction of PTX associated with cinacalcet.

Bone fracture

CKD stage IV and V patients are at increased risk of bone fractures compared to the general population. The reported prevalence are 0.7% and 0.1-0.2% in the CKD5D and general population, respectively.

Bone fracture is a clinically relevant outcome due to the related morbidity and mortality. It is estimated that the one-year mortality risk associated with a femur fracture is about 20% in the general population. In the CKD5D population it is reported a 2.4-fold increased risk when compared to the general population.

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Bone pathology in dialysis patients is complex and multifaceted. Bone abnormalities in CKD patients encompass bone mineralization, volume and turnover defects with negative repercussion on bone quality and strength. A large body of evidence suggests that low bone mineral density (BMD) is linked with increased risk of fracture in osteoporosis and that BMD assessment is the gold standard for risk of bone fracture evaluation in the general population. Nevertheless, BMD does not predict the risk of fracture and it is not a suitable biomarker for CKD patients. Indeed, a low BMD value in CKD5D should not be regarded
as evidence of osteoporosis but rather this piece of information needs to be integrated in the broad spectrum of abnormalities that characterize CKD-MBD as well as the many drugs such as warfarin, heparin and comorbid conditions such as ketoacidosis, neuropathy or myopathy that may be responsible for BMD loss. Thus, markers of bone turnover are likely the most accurate tools for risk of bone fracture prediction in CKD5D.

Cinacalcet lowers iPTH and its catabolic effect at the bone level. In light of the association between iPTH and bone fracture, the EVOLVE study results on the impact of cinacalcet on this clinically meaningful outcome were greatly awaited. In the EVOLVE study, bone fracture was one of the secondary study endpoints. The ITT analyses demonstrated a non-significant (p=0.21) 11% risk reduction of the first clinically significant bone fracture. However, the lack of statistical power, of a standardized definition of bone fracture or implementation of a screening for vertebral fracture (i.e. lateral-lateral lumbar spine plain X-ray) should be considered when interpreting these results. Notably the vertebral fractures are among the most common bone fracture in CKD5D patients and about half of these events are asymptomatic. Indeed, one study limitation of the EVOLVE study is that only symptomatic fracture were recorded during follow-up. The relatively young age of the study cohort (mean age 55 years) limits the generalizability of the results in light of the older mean age of the dialysis population in the developed countries. A past medical history of previous bone fracture, a potent predictor of a subsequent fracture, was reported by only 20% of the entire study cohort at study entry. Similarly, increased alkaline phosphatase, a marker of bone turnover, was found in about 59% of the recruited subjects.

Future analyses should investigate the correlation between PTH, markers of bone turnover and risk of bone fracture.

Calciphylaxis

Among the adverse events, a total of 6 and 18 cases (p<0.01) of calciphylaxis were recorded in the cinacalcet and placebo study arm, respectively. This finding suggests that cinacalcet may prevent the occurrence of this worrisome complication and may add to the commonly adopted strategies that encompass hyperbaric oxygen therapy, sodium thiosulphate, biphosphonate and surgery (parathyroidectomy and surgical debridement). However, to better elucidate this preliminary finding of cinacalcet on calciphylaxis, it would be advisable to perform ad hoc sub-analyses in the 24 patients who developed this serious complication.

Conclusions

The EVOLVE trial adds to the list of “non-conclusive” randomized clinical trials (RCT) in Nephrology. This definition relies on the lack of statistical power to demonstrate a survival benefit associated with different compounds. This is an important aspect to think of for future RCTs.

In summary the EVOLVE study take home messages are the following:

- Although the follow-up period of time was prolonged to accrue a sufficient number of events, the lower than expected incidence of the primary composite endpoint substantially reduced the statistical power of the study in spite of the anticipated by the study sample calculation.

- The age difference between study groups (patients allocated to cinacalcet were on average 1 year older than patients allocated to placebo) is a significant confounder that may have af-
fected the study results. Indeed, age is one of the most potent predictor of CV among CKD5D patients.

- The high drop out (patients who discontinued cinacalcet) and drop in rate (patients allocated to placebo who started cinacalcet due to iPTH increase judged worrisome by the investigators) are other factors that may have contributed to the statistically null results.

- The “per protocol Lag Time Censoring Analyses” suggested that when the study follow-up is terminated after 6 months from drug discontinuation, cinacalcet treated subjects showed a survival benefit when compared to placebo treated patients. The survival benefit associated with cinacalcet progressively disappeared until 12 months from drug discontinuation when it became statistically non significant.

- Cinacalcet treatment was associated with a “nominally” significant 60-70% risk reduction of PTX, a secondary endpoint of the EVOLVE study. Notably, as per the primary endpoint, these are ITT analyses that do not account for the patients who were started on cinacalcet during follow-up due to high iPTH values considered harmful by investigators (drop in). Thus, the risk reduction of PTX associated with cinacalcet maybe even larger than reported.

- The EVOLVE study did not document any significant risk reduction of bone fractures. Nonetheless, the EVOLVE study limitations may account for at least some of these results.

- Cinacalcet treatment was associated with a “nominally” significant lower incidence of episodes of calciphylaxis. Though of interest this finding deserve further elucidation.

- Treatment with cinacalcet was safe in a large study cohort of CKD5D patients even after a pronged exposure.

In summary, the EVOLVE study confirmed that cinacalcet is effective and safe in SHPT control. The impact on survival remains to be confirmed since the lower than expected statistical power hampers any conclusions. However, secondary and sensitivity analyses support the notion that cinacalcet impacts on mortality, parathyroidectomy and possibly calciphylaxis, though these analyses are by nature exploratory and hypothesis generating and warrant further testing [11].

Take home messages of the EVOLVE study

EVOLVE study: this is an inconclusive trial. Adjustments for confounders as well as accounting for drug discontinuation strongly suggest a survival benefit associated with cinacalcet. Similar “nominally” significant results were noted for the risk of parathyroidectomy and calciphylaxis. However, these are exploratory analyses and warrant further confirmations.

Francesco Locatelli ha partecipato ad advisory Board e/o è stato moderatore-relatore a simposi spon- sorizzati da Abbott, Amgen-Dompè, Bi Braun, Fresenius, Gambro Hospall,Mitsubishi, Shire.

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