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NDT Perspectives

Should patients with CKD stage 5D and biochemical evidence of secondary hyperparathyroidism be prescribed calcimimetic therapy? An ERA-EDTA position statement

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ABSTRACT

This paper reflects the position of the CKD-MBD workgroup, an official working group of ERA-EDTA and of the ERBP advisory board, the official guideline-producing body of ERA-EDTA, on the topic of the use of calcimimetics in patients with CKD stage 5D, as based on two recent meta-analysis.

Keywords: calcimimetics

INTRODUCTION

Why this question?

Calcimimetic agents lower serum parathyroid hormone and calcium concentrations in patients with chronic kidney disease stage 5 on dialysis (CKD5d), but treatment effects on patient-relevant outcomes are still a matter of debate.

In light of the increasingly widespread use of these agents since their first availability in clinical practice in 2006, and the publication of a large randomized trial of cinacalcet in dialysis patients [1], the Methods Support Team of the ERBP has summarized the available evidence about calcimimetic therapy focussing especially on patient-relevant outcomes in adults with biochemical hyperparathyroidism and CKD stage 5D.

What did we find?

A systematic review and meta-analysis [2], which included all published RCTs and a Cochrane review [3], were used as the substrate with the evidence treated using Cochrane methodology. In total, 18 trials involving 7446 adults with CKD (the vast majority on haemodialysis) were included in this meta-analysis. All included trials evaluated cinacalcet (at a dose of 30 mg to 180 mg/day) compared with conventional therapy or with conventional therapy plus placebo for the treatment of secondary hyperparathyroidism. Compared with placebo or no treatment, cinacalcet had no effect on all-cause or cardiovascular mortality [relative risk (RR), 0.97; 95% confidence interval (95% CI), 0.89–1.05 and RR, 0.67; 95% CI: 0.16 to 2.87] for patients with CKD stage 5D (high-quality evidence). Furthermore, cinacalcet reduced the risk of hypercalcaemia (RR, 0.23; 95% CI, 0.05–0.97), but was also associated with side effects, such as increased risk of hypocalcaemia (RR, 6.98; 95% CI, 5.10–9.53), nausea (RR, 2.02; 95% CI, 1.45–2.81), vomiting (RR, 1.95; 95% CI, 1.74–2.18), and diarrhoea (RR, 1.15; 95% CI, 1.02–1.29). Overall, on average, routinely treating 1000 people with cinacalcet for 1 year has no effect on mortality, prevents about three patients from undergoing surgical parathyroidectomy, and leads to ~60 and 150 individuals experiencing hypocalcaemia, and nausea, respectively.

The bulk of the data included in this meta-analysis was derived from the Evaluation of cinacalcet Therapy to Lower

Cardiovascular Events (EVOLVE) [1] trial. This trial in 3883 participants with CKD stage 5D was the first trial specifically designed to evaluate cinacalcet treatment on patient-relevant outcomes, using a composite of time to all-cause mortality or first non-fatal cardiovascular event as a primary outcome. In the EVOLVE study, 3883 patients with moderate-to-severe secondary hyperparathyroidism were randomly assigned to receive either cinacalcet or placebo plus conventional therapy, including phosphate binders, vitamin D sterols, or both. After a median duration of study-drug exposure of 21.2 months in the cinacalcet group, versus 17.5 months in the placebo group the primary composite endpoint was reached in 938 of 1948 patients (48.2%) in the cinacalcet group and 952 of 1935 patients (49.2%) in the placebo group (hazard ratio 0.93; 95% CI, 0.85 to 1.02; $P = 0.11$). In an intention-to-treat analysis, cinacalcet did not significantly reduce the risk of death or major cardiovascular events in patients on haemodialysis with moderate-to-severe secondary hyperparathyroidism.

How did we translate the evidence into the statement? (Which considerations were taken into account in GRADE quality of evidence?)

Based on the available data, the ERBP group judges that there is evidence to support that prescribing calcimimetics does not result in a survival benefit, or in a reduction of cardiovascular events, in patients with CKD stage 5D. The meta-analysis [2, 3] derives the majority of patients, and patient-relevant events, from EVOLVE [1]. Many of the other included studies assessed only surrogate endpoints, and were not powered for relevant hard outcome endpoints in patients.

Although the EVOLVE trial [1] is to be considered as a large trial in the field of nephrology, its interpretation was debated because of some potential flaws. However, the ERBP group judges that these potential sources of bias do not interfere with the final recommendation of the current position statement.

There is some evidence to support that the sustained use of cinacalcet can result in a reduced future need for surgical parathyroidectomy. However, the ERBP group considered that as the 'need for parathyroidectomy' has never been systematically defined, was not carefully pre-specified in EVOLVE [1] and also that it is uncertain what clinical benefits might accrue from the putative delay in surgical parathyroidectomy, this observation needs to be interpreted with care. Several observational studies [4, 5], with associated risk of confounding by indication and selection bias, have demonstrated that survival of patients with secondary hyperparathyroidism who did undergo a surgical parathyroidectomy was improved compared with those who did not. The ERBP group felt that there was a clear need for another trial randomising patients with secondary hyperparathyroidism to cinacalcet, or to parathyroidectomy, or to no intervention, with assessment of hard endpoints (mortality, quality of life) in order to validate the argument that the reduced need for parathyroidectomy following the use of cinacalcet is a clinical finding of relevance to patients.

In conclusion, there are data to support lack of a beneficial impact on patient-relevant outcomes, and there is evidence for increased risk of side effects by the administration of calcimimetics in patients on dialysis.

What do the other guidelines say?

No guidelines on this subject (KDOQI, CARI, RA, NICE) have been produced on this topics since the release of the EVOLVE results.

SUGGESTIONS FOR FUTURE RESEARCH

(1) We advocate an RCT randomizing patients with advanced hyperparathyroidism to surgical parathyroidectomy versus medical therapy using calcimimetics versus placebo on top of standard care (operative management versus calcimimetic versus conservative management). This would allow head-to-head comparison of risks and benefits of the different strategies.

(2) We advocate a randomized trial on the effect of calcimimetics on patient-relevant outcomes in patients >65 years to validate the suggestion of an effect modification by age in the EVOLVE trial.

Recommendations

1. We do not recommend routine use of calcimimetic therapy to improve survival in patients with CKD stage 5D and biochemical evidence of secondary hyperparathyroidism (1A).

2. There is insufficient evidence whether parathyroidectomy or medical intervention with cinacalcet or standard care or a combination thereof should be preferred to control secondary hyperparathyroidism in patients with CKD stage 5D.

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CONFLICT OF INTEREST STATEMENT

Declaration of interests for the authors and the members of the CKD-MBD working group and the advisory board of ERBP can be found at www.ERA-EDTA.org/doi.php

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Lag-censoring analysis: lights and shades

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ABSTRACT

'Intention-to-treat' (ITT) analysis is the recommended approach for the data analysis of randomized clinical trials (RCT). ITT analysis considers patients in the active or in the control arm as originally allocated by randomization, independently of their actual adherence to the assigned treatment. Lag-censoring analysis is a statistical method which takes into account the compliance of patients to the study protocol because the investigator censors a patient when or shortly after he/she stops the treatment being tested. Herein we describe the methodology underlying lag-censoring analysis in general terms and by considering the application of this technique in the analysis of a large RCT in haemodialysis patients, the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial. Use and misuse of this technique are discussed.

Keywords: intention-to-treat analysis, lag-censoring analysis

INTRODUCTION

The randomized controlled trial (RCT) is the gold standard study design for testing scientific hypotheses in a clinical scenario. RCTs are conducted to test the efficacy of medical interventions and to collect information about adverse effects of the same interventions [1]. The key feature of standard RCTs is that participants are randomly assigned to undergo the treatment being tested or other alternative therapies. After randomization, the two (or more) study groups are followed up by an identical protocol, the only difference between the care patients receive (clinical tests, outpatient visits, etc.) is intrinsic to the interventions being compared. The fundamental advantage of randomization is that it prevents bias by prognosis and that any differences in known and unknown prognostic factors in the groups being compared are due to chance [1]. Unfortunately, randomized controlled trials often suffer from major problems for measuring efficacy, such as noncompliance, protocol deviations, and patient withdrawals, whether these