Conflict of interest statement. None declared.

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Optimal TARGETs for cardiovascular safety and benefit in ESRD

Sir,

The TARGET investigators recently reported their study of combined calcimimetic (cinacalcet) and low-dose vitamin D sterol therapy in patients with end-stage renal disease (ESRD) and moderate-to-severe secondary hyperparathyroidism [1]. KDOQI chronic kidney disease bone and mineral disorder (CKD-MBD) biochemical targets for parathyroid hormone (PTH) and calcium–phosphate product (Ca × P) were achieved in 54% of patients with cinacalcet and vitamin D sterol dosing equivalent to paricalcitol 10 mcg per week. While we appreciate the efforts to improve metabolic control in this patient population, we are concerned about the significant rates of hypocalcaemia, which occurred because cinacalcet was titrated, while vitamin D sterol use was limited. We are also concerned about the lack of cardiovascular safety monitoring and have reservations about the general cardiovascular implications of this strategy. The incidence of hypocalcaemia ranged from 9% (using the stringent criterion of two serum calcium values <7.5 mg/dl) to 78% using the cut point of a single calcium value of <8.4 mg/dl. Hypocalcaemia prolongs the QT interval, which increases the propensity for ventricular arrhythmias and sudden cardiac death, especially in the presence of structural heart disease. Since haemodialysis itself increases the QT interval and QT dispersion [2] and because sudden cardiac death is common in ESRD patients, hypocalcaemia is not necessarily a benign laboratory abnormality. The TARGET trial excluded patients with prior myocardial infarction (MI) or recent unstable medical conditions. In clinical practice, at least 40% of patients with ESRD have prevalent cardiovascular disease, and patients on dialysis have a 30-fold higher cardiovascular disease-associated mortality than the general population [3]. Dialysis patients with MI have a twofold higher rate of cardiac arrest compared to non-dialysis patients with MI [4]. We are concerned that no data on EKG findings (especially the QT interval) or telemetry monitoring were reported by the TARGET investigators. It would be helpful to know the serum calcium levels of the nine patients who died, and whether they succumbed to an arrhythmic event. Hypocalcaemia also reduces myocardial contractility, an effect that could exacerbate the high rates of heart failure in ESRD patients. Finally, vitamin D sterol therapy has a variety of ‘non-classical’ effects, including inhibition of the renin–angiotensin–aldosterone system and anti-inflammatory and anticoagulant effects that are not shared by cinacalcet [5]. Accordingly, PTH and Ca × P product may not be optimal biomarkers for assessing the potential cardiovascular benefits or risks of strategies designed to meet the CKD-MBD targets. We suggest that the QT interval, brain natriuretic peptide, plasminogen activator inhibitor-1, C-reactive protein, angiotensin II and aldosterone levels would be more appropriate surrogate markers for evaluating cardiovascular risk and benefit in future trials of vitamin D sterols, cinacalcet or combination therapy.

Conflict of interest statement. The author has received honoraria for speaking at symposia sponsored by Abbott, manufacturer to paricalcitol.

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Reply

Sir,

We read with interest the letter by Dr Sane in response to our paper examining the use of combinations of cinacalcet with low-dose vitamin D sterols in the treatment of moderate-to-severe secondary hyperparathyroidism in subjects receiving dialysis [1]. Dr Sane points out that low serum calcium concentrations were observed in this trial, and he raises concern about the cardiovascular safety monitoring and the cardiovascular implications of the use of the treatment strategy examined in this study. We understand and appreciate Dr Sane’s concerns.

Because of the potential for decreased serum calcium concentrations to induce alterations in cardiac conduction and left ventricular function, early studies with the calcimimetic R-568 included monitoring of cardiac electrical activity with accompanying ionized calcium levels on a q 4 h basis in a 15-day study of 20 subjects. Despite notable decreases in blood ionized calcium [2], there was only one report of first degree AV block and incomplete bundle branch block with ST changes, which was deemed unrelated to study drug.

The absence of adverse cardiovascular effects of cinacalcet in patients receiving dialysis, even in the presence of hypocalcaemia, was reinforced by the data gathered from the phase 3 trials. Post hoc analyses of the phase 3 data showed a 39% decrease in the risk of hospitalization with cardiovascular disease (relative risk = 0.61) [3] and no clinically significant effect on the QT interval, regardless of the baseline serum calcium concentration. Mean (SE) uncorrected QT intervals from baseline to end of study were 0.61 (0.01) for cinacalcet and placebo, despite a higher rate of hypocalcaemia observed in cinacalcet-treated subjects during this period. Torsades de point was not reported in zero cinacalcet-treated and one placebo-treated subject during the trials.

With respect to the TARGET study, Dr Sane requested that information on patient serum calcium concentrations be provided; however, serum calcium concentrations were rarely collected within 24 h of death. Moreover, among the 16 subjects who died (the manuscript reported nine patients in error, and an error has been sent to the editor), the most common causes reported for death were infectious (8/16) and included sepsis (5), presumed pneumonia (2) and viral encephalitis (1). Cardiovascular causes of death were implicated in five cases and included myocardial infarction (MI), heart failure secondary to MI, cardiopulmonary arrest and unwitnessed death (2). Of the cardiovascular deaths, there were no reports of arrhythmias. The serum calcium was 9.9 mg/dl in the one case of acute MI, and serum calcium values were not provided at the time of the event in the other reports. Other causes of death (3) included pulmonary embolus, ischaemic bowel and haemorrhagic cerebrovascular accident.

Dr Sane suggests that the vitamin D sterols exert activity outside of the reduction of PTH that is not shared by cinacalcet. It is noteworthy that vitamin D sterols have not been prospectively tested in clinical trials to determine whether they exert favourable or deleterious effects on cardiovascular or other disease processes in CKD. It is troubling that despite the widespread use of intravenous vitamin D sterols in established dialysis patients, we have not observed a decrease in annual mortality rates published by the USRDS [4] over this time or in parathyroidectomy [5], cardiovascular disease or fractures in the dialysis population. The ongoing (and fully enrolled, N = 3883) Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVAPOLEVE) trial will test whether cinacalcet-t-standard therapy, including vitamin D sterols, versus standard therapy without cinacalcet reduces mortality and cardiovascular events in haemodialysis patients with secondary hyperparathyroidism.

Finally, we agree with Dr Sane that cardiovascular risk assessment is particularly complex in patients with CKD-MBD. Future studies aimed at evaluating cardiovascular risk should include other biomarkers in addition to parameters of mineral metabolism.

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