Paricalcitol for reduction of albuminuria in diabetes

Albeit based on robust methods, the study by Dick de Zeeuw and colleagues (Nov 6, p 101) raises several concerns. First, little attention is given to the fact that the primary endpoint—ie, the effect of the vitamin D receptor activator (VDRA) on urinary albumin-to-creatinine ratio (UACR)—is actually negative. The positive results on secondary endpoints should thus be used only to generate new hypotheses, not to support the efficacy of the intervention. Besides, any reduction in UACR must also be interpreted in the context of its biological variation in the context of its biological variation in patients with diabetes, which is estimated at 61%.2

Second, the mean concentration of vitamin D in the patients included (40 nmol/L) is far below the current recommendations34 and reflects a severe deficiency. Subgroup analysis according to the 25-hydroxyvitamin D concentration would be of interest.

Third, the cost-effectiveness of a strategy based on paricalcitol in this indication has to be balanced with the use of the much cheaper native vitamin D for which there are physiological reasons to expect some efficacy.5

Finally, the long-term safety of this strategy is questionable. Paricalcitol logically decreased concentrations of parathyroid hormone (from 90-7 to 40 μg/L in the 2 μg group). These supraphysiological doses of selective VDRA could increase the risk of low bone turnover (with the inherent increased risk of vascular calcifications). Data on calcitriol would be valuable in this regard. Risk of renal stones or nephrocalcinosis in the long term should also be discussed.

We declare that we have no conflicts of interest.

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In the VITAL study,1 Dick de Zeeuw and colleagues conclude that paricalcitol could be a novel approach to lower residual albuminuria and renal risk in patients with diabetes. However, several facts undermine this suggestion.

First, the reduction in urinary albumin-to-creatinine ratio (UACR) from baseline to last measurement did not reach significance (p=0.053). Second, the proportion of patients who achieved at least a 15% UACR reduction in the same time would be non-significant if only one additional patient from the 2 μg paricalcitol group had not met this goal. Third, it seems that a relatively high paricalcitol dose (2 μg/day) is needed for any antiproteinuric effect to be shown since the 1 μg group did not have such an effect. Of note, the 2 μg group had a significantly higher dropout rate owing to adverse events than the 1 μg and placebo groups, and all three deaths in the study occurred in the 2 μg group. Finally, although significant, the small reduction (254 mg) in the mean 24-h urinary albumin between baseline and the last measurement in the 2 μg group cannot be regarded as clinically significant until the emergence of larger and longer-duration randomised controlled trials to assess hard endpoints such as renal or overall survival.

In my opinion the use of high-dose paricalcitol for the prevention of renal damage in patients with diabetes and chronic kidney disease is of uncertain efficiency and safety and thus should not be recommended on the basis of the current data.

I declare that I have no conflicts of interest.

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We have two issues with the design and presentation of the VITAL trial.1 First, most patients enrolled in VITAL were vitamin D insufficient (mean 25-hydroxyvitamin D concentration 40–42 nmol/L). The therapeutic or adverse effect pattern might not be extrapolated to patients who are vitamin D sufficient. Thus, we suggest the conclusions be changed to “paricalcitol...safely lowers residual albuminuria in vitamin D insufficient patients with diabetic nephropathy”.

25-hydroxyvitamin D insufficiency is associated with adverse outcomes, and vitamin D supplementation decreases inflammation even in dialysis patients, probably through local, auto, or paracrine activity of extrarenal calcitriol generation.1 Calcitriol protects podocytes and has shown antalbuminuric effects in preclinical studies.24 Thus, it is unclear to what extent the noted therapeutic effects of paricalcitol are the result of correction of deficient activation of vitamin D receptors caused by vitamin D insufficiency or of a therapeutic action beyond what might be achieved by restoring 25-hydroxyvitamin D. Guidelines available at the time of study design suggest that vitamin D supplementation should be started when serum 25-hydroxyvitamin D is less than 75 nmol/L.2
Second, the potential adverse effects of paricalcitol on mineral metabolism are not carefully documented. Apparently there were no pre-established criteria for dose reduction. Thus we wonder what triggered dose reduction in patients assigned to 2 μg/day, what were serum calcium and phosphate concentrations at the time of dose reduction, and whether additional biochemical abnormalities were present in patients with suppressed parathyroid hormone concentrations.

Finally, the effect of paricalcitol on serum phosphate concentrations or phosphate binder use is conspicuously missing.

We declare that we have no conflicts of interest.

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Dick de Zeeuw and colleagues’ report that oral administration of 2 μg/day paricalcitol for 24 weeks safely lowers residual albuminuria in patients treated with inhibitors of the renin-angiotensin-aldosterone system for diabetic nephropathy.

Although de Zeeuw and colleagues provide a wide range of data, they do not report serum phosphorus concentrations during the 24 weeks of paricalcitol administration. Since observational studies have shown that higher concentrations correlate with mortality in diabetic populations with and without renal disease, their value might be of extreme importance.

Another issue that also needs underlining is that diabetic patients with end-stage renal disease (ESRD) often have low-turnover bone disease. Long-term paricalcitol administration during the months or years before reaching ESRD might aggravate adynamic bone disease (a difficult-to-reverse form of renal bone disease) in diabetic patients who will eventually need dialysis.

Despite the encouraging results of de Zeeuw and colleagues’ study, long-term clinical trials with oral paricalcitol in patients with diabetes and renal disease are urgently warranted, and with more meaningful endpoints such as mortality or ESRD.

I declare that I have no conflicts of interest.

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Authors’ reply

The VITAL study reported that paricalcitol lowers albuminuria in patients with type 2 diabetes and residual high albuminuria after guideline therapy, including an inhibitor of the renin-angiotensin-aldosterone system. The reason why we interpreted the antialbuminuric data with somewhat more confidence than do Pierre Delanaye and colleagues and Theodoros Kassimatis has to do with the fact that paricalcitol’s effect (in particular the 2 μg dose) is highly significant when looking at 24-h urine albuminuria, and looking at urinary albumin-to-creatinine ratio (UACR) effects over all timepoints available. As mentioned by Delanaye and colleagues and Kassimatis, the effect size and the power of the study are not high, and we fully agree that VITAL is a hypothesis-generating study with a strong argument to do a final study on hard renal endpoints.

We thank Alberto Ortiz and colleagues for calling attention to the fact that most patients with chronic kidney disease (CKD) are vitamin D deficient. This point makes it impossible to assess the efficacy of paricalcitol in those who were vitamin D replete. As mentioned in our Article, a study with calcitriol did also show modest antiproteinuric effects in IgA nephropathy. Future comparative studies should establish whether the effect of raising 25-hydroxyvitamin D concentrations with cholecalciferol or ergocalciferol can reduce albuminuria to a similar extent to paricalcitol.

Regarding paricalcitol dose reductions in our trial, the protocol specified that patients would have dose reductions in the event of over-suppression of parathyroid hormone or of hypercalcaemia. The finding that dose reductions occurred in 42% of patients in the 2 μg group indicates that the majority were able to receive high-dose paricalcitol throughout. The 2 μg group did show the antialbuminuric effects despite this down-titration.

Although we agree with Costas Fourtounas that observational studies in CKD patients have shown associations between higher serum phosphate concentrations and increased mortality in patients who are mostly vitamin D deficient, future studies should clearly establish that paricalcitol is safe and effective.