Renin–angiotensin system (RAS) blockade is the gold standard for the treatment of diabetic nephropathy. However, patients with diabetes mellitus still have an increased risk of progressive deterioration of renal function associated with albuminuria.

de Zeeuw et al. published a paper, entitled Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial, in The Lancet in November 2010. This multinational, placebo-controlled, double-blind trial enrolled 281 patients with type 2 diabetes and albuminuria who were receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers to elucidate the efficacy of a vitamin D analogue (19-nor-1α,2-dihydroxyvitamin D3; paricalcitol) on albuminuria. Patients were assigned to receive 24 weeks treatment with placebo or 1 or 2 μg paricalcitol daily. The primary measure of efficacy was the percentage change in geometric mean urinary albumin:creatinine ratio (UACR) from baseline to the last measurement during the treatment period in the combined paricalcitol groups vs the placebo group.

The change in UACR from baseline to the last measurement in the 1 and 2 μg paricalcitol-treated groups was −20% (95% confidence interval [CI] −30 to −8) and −14% (95% CI −24 to −1), respectively (Table 1). The reduction in UACR in the 2 μg paricalcitol-treated group was sustained throughout the 24-week treatment period and reversed to baseline values after completion of treatment. However, the primary endpoint was negative: the UACR in the combined paricalcitol groups reduced by 15% compared with placebo (P = 0.071; Figure 1). The UACR fell by 18% in the 2 μg paricalcitol-treated group and by 11% in the 1 μg paricalcitol-treated group, but these differences failed to reach statistical significance (P = 0.053 and 0.23, respectively). In the secondary efficacy analysis, 24-h urine albumin was reduced by −28% (P = 0.009) in the 2 μg paricalcitol-treated group.

Several smaller randomized trials have indicated that paricalcitol reduces proteinuria in patients with chronic kidney disease. For example, Alborzi et al. showed that administration of 1 and 2 μg paricalcitol for 1 month reduced 24-h urinary albumin excretion by 48% (P < 0.001) and 46% (P = 0.01), respectively. Another randomized trial reported reduced protein excretion (−17.6%; P = 0.04) following 6 months treatment with paricalcitol.

Paricalcitol exhibits a renoprotective effect in animal models. In a model of type 2 diabetes using Lprdb/db mice, treatment with losartan or paricalcitol each alone moderately ameliorated albuminuria and glomerular damage. However, their combined use demonstrated a marked therapeutic synergism, manifested by the prevention of progressive albuminuria, restoration of the glomerular filtration barrier, and a reduction of glomerulosclerosis. These effects were accompanied by blockade of compensatory renal upregulation. In contrast, mice lacking the vitamin D receptor (VDR) were more susceptible to hyperglycemia-induced renal injury. Diabetic VDR-knockout mice developed more severe albuminuria and glomerulosclerosis compared with diabetic wild-type mice. In receptor-knockout mice, there was an increase in renin, angiotensinogen, transforming growth factor (TGF)-β, and connective tissue growth factor in association with renal injury. In vitro studies have shown that 1,25-dihydroxyvitamin D3 inhibits high glucose-induced fibronectin production in cultured mesangial cells and increased nephrin expression in cultured podocytes. 1,25-Dihydroxyvitamin D3 also suppressed high glucose-induced activation of the RAS and TGF-β in mesangial and justaglomerular cells.

In the VITAL study, hemodynamic changes were observed accompanied by reductions in reduced systolic blood pressure and estimated glomerular filtration rate. These hemodynamic changes were reversible after completion of paricalcitol treatment, suggesting that these changes were caused by the drug. However, the effect of lowering blood pressure is minimal and the relationship with renoprotection remains to be determined.

Vitamin D has anti-inflammatory actions. In previous clinical studies, paricalcitol reduced high-sensitivity C-reactive protein in patients with chronic kidney disease. However, in the VITAL study, no changes in C-reactive protein or tumor necrosis factor-α were observed.

Notably, most patients enrolled in the VITAL study were vitamin D deficient and had hyperparathyroidism. Ortiz et al., from Spain, pointed out that the therapeutic effect of paricalcitol may not be extrapolated to vitamin D-sufficient patients. Further examinations of bone and calcium–phosphate metabolism are needed following the long-term administration of the drug.

With regard to drug safety, de Zeeuw et al. concluded that both doses of paricalcitol (1 and 2 μg) were well tolerated.
However, they reported two acute myocardial infarctions, two cerebrovascular accidents, and three deaths, all of which were observed in the 2 µg paricalcitol-treated group. These adverse events require further investigation to determine whether they were associated with this dose of the drug. If they were, then this dose of paricalcitol may be too high for long-term administration. The use of other types of vitamin D must also be considered from the points of view of safety and cost-effectiveness. Again, the primary endpoint of that study was negative1, possibly because of its small study size, as mentioned by the authors. Although supplementation with vitamin D (or its analogue) may become a promising new therapeutic strategy, further larger and longer-term clinical studies with stringent renal outcomes, such as doubling of serum creatinine or end-stage kidney disease, are needed to prove its renoprotective efficacy and safety.

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Shinichi Okada1, Kenichi Shikata1,2*
1Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, and 2Center for Innovative Clinical Medicine, Okayama University Hospital, Okayama, Japan

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Table 1 | Efficacy analysis of 24 weeks treatment with 1 or 2 µg paricalcitol or placebo (Reprinted from de Zeeuw et al1, Copyright 2010, with permission from Elsevier.)

|                     | Placebo | Combined paricalcitol | 1 µg paricalcitol | 2 µg paricalcitol |
|---------------------|---------|-----------------------|-------------------|-------------------|
| **Geometric mean urinary albumin-to-creatinine ratio** |         |                       |                   |                   |
| Baseline to last measurement during treatment |         |                       |                   |                   |
| Patients (n)        | 88      | 184                   | 92                | 92                |
| Baseline (mg/mmol)  | 61      | 62                    | 63                | 61                |
| Last measurement during treatment (mg/mmol) | 60      | 51                    | 54                | 49                |
| % Change (95% CI)   | −3 (−16 to 13) | −16 (−24 to −9) | −14 (−24 to −1) | −20 (−30 to −8) |
| Last measurement during treatment to 60 days after treatment completion |         |                       |                   |                   |
| Patients (n)        | 72      | 139                   | 71                | 68                |
| Baseline (mg/mmol)  | 60      | 51                    | 57                | 45                |
| 60 days after treatment completion (mg/mmol) | 55      | 63                    | 75                | 52                |
| % Change (95% CI)   | −7 (−20 to 8) | 23 (11 to 36) | 34 (15 to 55) | 13 (−3 to 32) |
| **Mean 24-h urinary albumin** |         |                       |                   |                   |
| Baseline to last measurement during treatment |         |                       |                   |                   |
| Patients (n)        | 78      | 146                   | 74                | 72                |
| Baseline (mg)       | 609     | 662                   | 613               | 717               |
| Last measurement during treatment (mg) | 564     | 507                   | 554               | 463               |
| % Change (95% CI)   | −9 (−23 to 8) | −23 (−32 to −13) | −10 (−25 to 6) | −34 (−45 to −21) |
| Last measurement during treatment to 60 days after treatment completion |         |                       |                   |                   |
| Patients (n)        | 71      | 143                   | 73                | 70                |
| Baseline (mg)       | 623     | 486                   | 531               | 444               |
| 60 days after treatment completion (mg) | 599     | 614                   | 694               | 540               |
| % Change (95% CI)   | −1 (−16 to 16) | 25 (12 to 39) | 31 (12 to 54) | 19 (1 to 39) |

Figure 1 | Change in the urinary albumin : creatinine ratio (UACR) from baseline to the last measurement during the 24-week treatment period. Data show the geometric mean of UACR, with error bars representing 95% confidence intervals. The P values are for comparisons of paricalcitol with placebo. Reprinted from de Zeeuw et al1, Copyright 2010, with permission from Elsevier.
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