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No difference between alfacalcidol and paricalcitol in the treatment of secondary hyperparathyroidism in hemodialysis patients: a randomized crossover trial

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Alfacalcidol and paricalcitol are vitamin D analogs used for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease, but have known dose-dependent side effects that cause hypercalcemia and hyperphosphatemia. In this investigator-initiated multicenter randomized clinical trial, we originally intended two crossover study periods with a washout interval in 86 chronic hemodialysis patients. These patients received increasing intravenous doses of either alfacalcidol or paricalcitol for 16 weeks, until parathyroid hormone was adequately suppressed or calcium or phosphate levels reached an upper threshold. Unfortunately, due to a period effect, only the initial 16-week intervention period for 80 patients was statistically analyzed. The proportion of patients achieving a 30% decrease in parathyroid hormone levels over the last four weeks of study was statistically indistinguishable between the two groups. Paricalcitol was more efficient at correcting low than high baseline parathyroid hormone levels, whereas alfacalcidol was equally effective at all levels. There were no differences in the incidence of hypercalcemia and hyperphosphatemia. Thus, alfacalcidol and paricalcitol were equally effective in the suppression of secondary hyperparathyroidism in hemodialysis patients while calcium and phosphorus were kept in the desired range.

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Patients with chronic kidney disease have increased risk of cardiovascular disease and mortality compared with patients with normal renal function.[1–3] Epidemiological studies have found this increased risk to be associated with the disturbances in the mineral metabolism, including poorer cardiovascular and mortality outcomes in patients with elevated calcium and phosphate levels.[4–10]

Secondary hyperparathyroidism is a common complication in patients with renal failure and is associated with renal osteodystrophy,[11,12] risk of bone fracture,[13] and higher risk of cardiovascular morbidity and mortality.[7,14]

Vitamin D analogs are used to treat secondary hyperparathyroidism. However, vitamin D analogs increase the calcium and phosphate levels by increasing the intestinal calcium and phosphate absorption, as well as increasing the calcium and phosphate mobilization from the bone.[15] To suppress the secondary hyperparathyroidism without increasing calcium and phosphate, treatment modalities such as non-calcium-containing phosphate binders, selective vitamin D analogs, and calcimimetics have been developed.

Alfacalcidol (1α-hydroxyvitamin D_3) and paricalcitol (19-nor-1α,25 dihydroxyvitamin D_2) are frequently used vitamin D analogs, especially in Europe. Alfacalcidol has been used for treatment of secondary hyperparathyroidism and renal osteodystrophy since 1978. Paricalcitol was registered in Denmark in 2004 and was introduced as a less calcemic and phosphatemic vitamin D analog. In uremic rats,[16] paricalcitol suppressed parathyroid hormone (PTH) levels with less hypercalcemic and hyperphosphatemic effects than calcitriol (1α,25 dihydroxyvitamin D_3). Until now, no randomized controlled study addressed possible differences between alfacalcidol and paricalcitol.[17]

This investigator-initiated clinical trial compared alfacalcidol and paricalcitol. In a crossover study with forced

titration, we tested whether there is any difference in the ability of paricalcitol and alfacalcidol to reduce secondary hyperparathyroidism in hemodialysis patients without increasing *p*-calcium and *p*-phosphate outside the desired range.

RESULTS

Patient characteristics

Patients were recruited from June 2007 through December 2009. Patients were followed up until the last study visit (the last patient visit was in October 2010).

Because of the lack of eligible patients, the trial was stopped early. This decision was taken by the steering committee. No interim analysis took place. A final inclusion date was set 3 months ahead, and all investigators made a final recruitment effort. A total of 86 patients were randomized, of whom 80 patients completed the first treatment period and 71 patients completed both treatment periods (Figures 1 and 2). Demographic characteristics for randomized and analyzed participants are presented in Table 1.

Mineral metabolism

Changes in PTH levels, ionized calcium (Ca), and phosphate (P) for the patients who completed the crossover study are shown in Figure 3. There was a significant difference between the baseline mean PTH levels in period 1 and period 2 (552 ± 202 and 453 ± 249 pg/ml, respectively; $P = 0.01$). The PTH level was significantly higher before beginning of washout period 1 (317 ± 155 pg/ml) compared with washout period 2 (219 ± 187 pg/ml; $P < 0.01$). The PTH levels before and after washout 2 were significantly correlated (0.398; $P = 0.001$). Only four patients were formerly untreated and included directly at week 6 (paricalcitol–alfacalcidol: $n = 3$; and alfacalcidol–paricalcitol: $n = 1$).

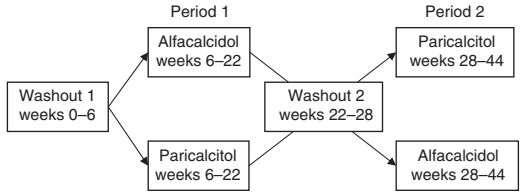

Figure 2 | Treatment periods and treatment arms.

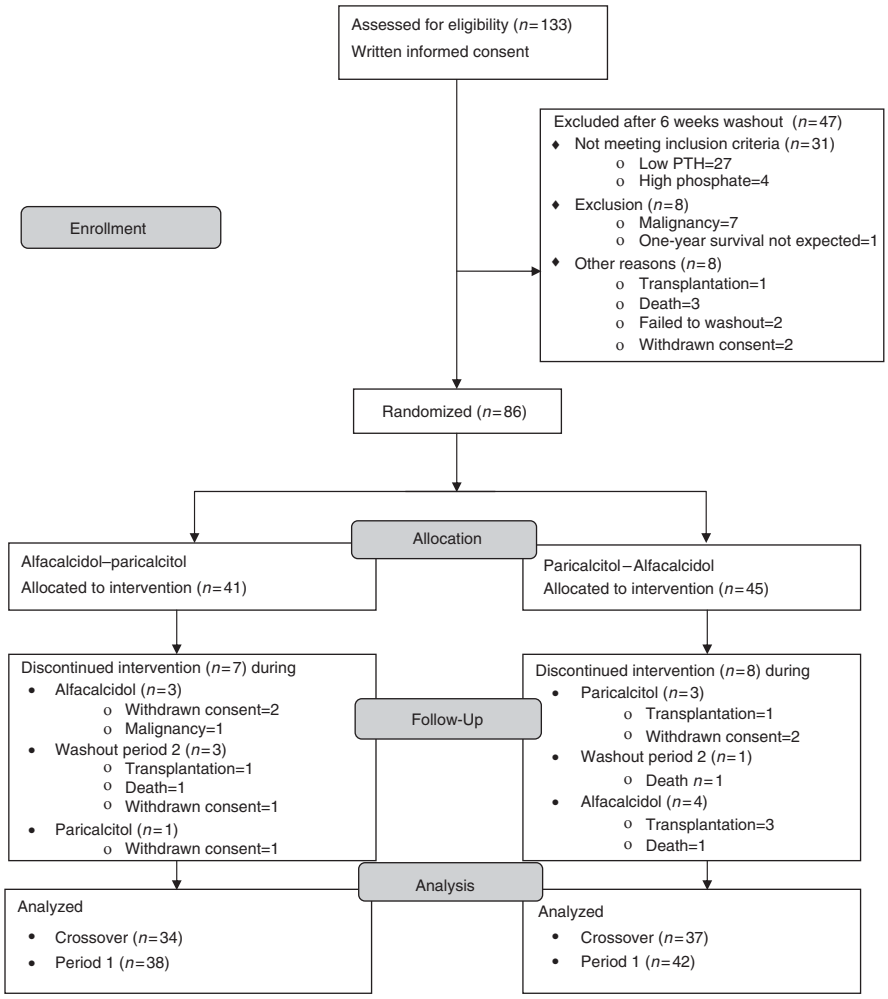

Figure 1 | Participants' flow through the study. PTH, parathyroid hormone.