PARICALCITOL VERSUS PLACEBO FOR REDUCTION OF PROTEINURIA IN KIDNEY TRANSPLANT RECIPIENTS: *A DOUBLE-BLIND, RANDOMISED CONTROLLED TRIAL*

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OBJECTIVES

Proteinuria is a common problem encountered in the treatment of kidney transplant recipients and is associated with worse clinical outcomes, including an increased risk for death, cardio-vascular events, and allograft failure [1].

Previous research has demonstrated that addition of paricalcitol to renin-angiotensin-aldosteron system (RAAS) inhibition safely lowers albuminuria in patients with diabetic nephropathy [2].

In this study, we aimed to assess whether paricalcitol could be used to reduce proteinuria in kidney transplant recipients with increased urinary protein excretion despite treatment with RAAS inhibitors.

METHODS

In this single-center, placebo-controlled, double-blind trial, we enrolled a national cohort of kidney transplant recipients at least 3 months' post-transplant with urinary protein-to-creatinine ratio (UPCR) 20 mg/mmol or greater despite optimization of the RAAS blockade during the run-in phase.

Patients were assigned by computer-generated randomisation sequence to receive 24 weeks' treatment with 2 µg/day paricalcitol or placebo.

The primary endpoint was the percent change in geometric mean UPCR, and main secondary endpoints were the percent change in geometric mean urinary albumin-to-creatinine ratio (UACR) and median 24-hour proteinuria from baseline to last measurement during treatment. Analysis was by intention to treat.

This trial is registered with ClinicalTrials.gov, number NCT01436747, and European Clinical Trials Database (EudraCT), number 2011-006120-20.

RESULTS

Table 1. Efficacy analyses

	2 µg paricalcitol (n = 83)	placebo (n = 85)
geometric mean urinary protein-to-creatinine ratio		
baseline (mg/mmol)	74	52
last measurement during treatment (mg/mmol)	46	63
percentage change (95% CI)[a]	**-38% (-45 to -31)**	**21% (9 to 36)**
geometric mean urinary albumin-to-creatinine ratio		
baseline (mg/mmol)	30	19
last measurement during treatment (mg/mmol)	16	20
percentage change (95% CI)[b]	**-47% (-54 to -38)**	**11% (-5 to 29)**
median 24-hour proteinuria		
baseline (mg/day)	530	430
last measurement during treatment (mg/day)	350	450
percentage change (95% CI)[b]	**-35% (-42 to -28)**	**19% (8 to 30)**
median plasma IL-6 concentration		
baseline (ng/L)	2.5	2.1
last measurement during treatment (ng/L)	2.3	2.4
percentage change (95% CI)[b]	**-25% (-36 to -11)**	**44% (19 to 74)**
median plasma TGF-beta concentration		
baseline (ng/L)	8211	6074
last measurement during treatment (ng/L)	6935	8343
percentage change (95% CI)[b]	**-17% (-25 to -9)**	**28% (14 to 43)**

[a]*P*<0.001, two-factor analysis of variance; [b]*P*<0.001, analysis of covariance

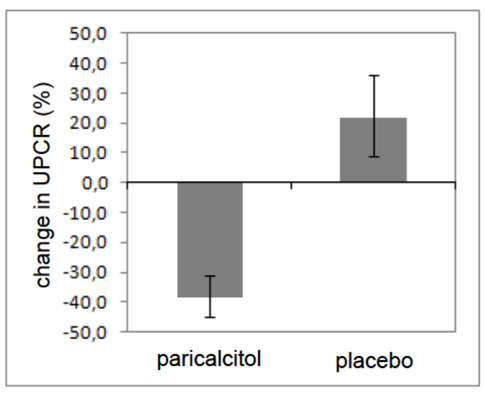

Figure 1. Change in UPCR from baseline to the last measurement during treatment

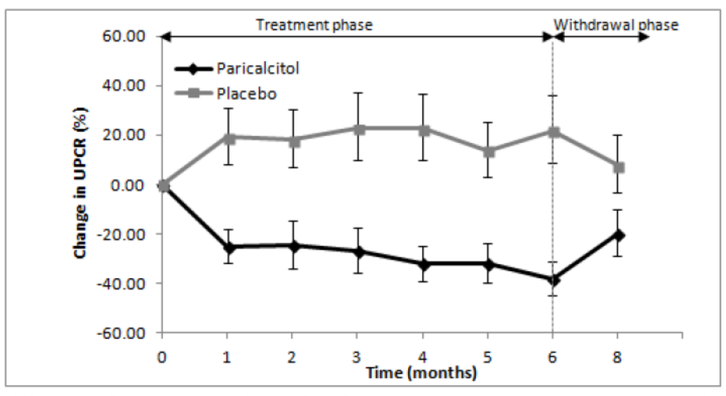

Figure 2. Change in UPCR during treatment phase and withdrawal phase

In 2012, 572 patients were screened for eligibility, of whom 190 (33%) had UPCR ≥20 mg/mmol. Of the remaining 168 patients who consented to undergo randomisation, 83 were allocated to paricalcitol, and 85 were allocated to placebo; all patients on paricalcitol and placebo received at least one dose of study drug and had UPCR data at baseline and at least one time point during treatment.

In the primary efficacy analysis, reduction in geometric mean UPCR from baseline to the last measurement during treatment was greater in the paricalcitol group than in the placebo group, with a between-group difference of -28% (95% CI -45% to -4%; *P*<0.001) (**Table 1; Figure 1**). Patients on 2 µg paricalcitol showed a sustained reduction in UPCR, ranging from -25% to -39% (*P*<0.001 *vs.* placebo) (**Figure 2**).

In the secondary efficacy analysis, reduction in geometric mean UACR and median 24-hour proteinuria was greater in the paricalcitol group than in the placebo group. Significant reduction in IL-6 and TGF-beta plasma concentrations were recorded in the paricalcitol group (**Table 1**).

Incidences of hypercalcemia, adverse events, and serious adverse events were similar between both patient groups.

CONCLUSIONS

In kidney transplant recipients, addition of 2 µg/day paricalcitol to RAAS inhibition safely lowers proteinuria, and could be used as an effective approach to lower allograft failure risk.
Biomarker analysis suggests that renoprotection may be caused by antiproliferative and antifibrotic effects.

References

[1] Knoll G. Proteinuria in kidney transplant recipients: prevalence, prognosis and evidence-based management. Am J Kidney Dis 2009; 54: 1131-1144.

[2] de Zeeuw D, Agarwal R, Amdahl M, *et al*. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. Lancet 2010; 376: 1543-1551.

The study has been supported by Slovenian Research Agency (grant P3-0323) and University Medical Centre Ljubljana (research grant 20110090). AbbVie donated the study drug and placebo.