Paricalcitol exerts potent immunomodulatory effects on Tregs and Th17 cells in patients with severe kidney disease

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Background

Patients with chronic kidney disease (CKD) frequently have low serum 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] or calcitriol. With CKD progression, the tendency to vitamin D substrate insufficiency leads to progressive calcitriol deficiency. Importantly, calcitriol has significant immunomodulatory effects in addition to its role in calcium homoeostasis. A variety of immune cells, including activated T cells express the intracellular vitamin D receptor and are responsive to calcitriol. While the exact mechanisms still require clarification, there is now compelling evidence that the hormonally active calcitriol can activate regulatory T cells (Tregs) and reduce the activity of the proinflammatory Th17 cells. Paricalcitol (19-nor-1,25-dihydroxyvitamin D2) is a synthetic analogue of vitamin D approved for treatment of secondary hyperparathyroidism. Recent observations demonstrated important differences between paricalcitol and calcitriol. However, so far there have been a limited number of studies addressing the immunomodulatory effects of paricalcitol in severe CKD patient (ESKD).

Objectives

In this study we aimed to evaluate the effects of oral paricalcitol and calcitriol supplementation in various inflammation T cells and markers (Tregs, Th17, IL-17, IL-21, IL-6, TNF-α). Corollarly, T cell immune response to hepatitis B (HBV) vaccination (blood antibody titers) was also clinically determined in patients with chronic end-stage kidney disease (stage 5D CKD).

Patients and Methods

Stained cells were assessed by flow cytometer. The frequency of Tregs ($CD4^+/CD25^+/Foxp3^+$) and Th17($CD4^+/IL17^+$) cells is expressed as a percentage of $CD4^+$ T cells by sequential gating on lymphocytes and $CD4^+$ T cells. The levels of serum cytokines and other markers were examined by ELISA. Ten patients were included in each treatment arm (Paricalcitol [Pari] (2 μg/tid) and Calcitriol [Calci] (0.25 μg/tid)). All patients underwent hemodialysis (HD) with high-flux membranes and ultrapure water. The dialysate calcium concentration was 1.5 mmol/L. All patients included were HBV vaccination non-responders (Titers < 10 UI/L). After 6 months of active vitamin D treatment, a full course of four 40 μg anti-HBV i.m. vaccination (1, 2, 3, 6 mo) were scheduled. Immunological evaluation was realized 6 months later (T0+12 months).

Results

Mean HD vintage was 41.1 16.2 months. Twenty-five percent of the patients had diabetes. We observed a significant increase in Tregs and a decrease in Th17 cells numbers in both treated patients with a significantly higher increase in Tregs of 43% and decrease in Th17 cells of 32% in paricalcitol-treated patients compared with those treated with calcitriol. This was in association with decreased IL-17, IL-21, IL-6 and TNF-α levels. $CD4^+/CD25^-$ T cells from the paricalcitol group showed reduced proliferative activity in co-culture with Tregs compared with calcitriol-treated patients ($p = 0.002$), suggesting an improved suppressive activity of Tregs with paricalcitol. Six months after HBV vaccination, all paricalcitol-treated patients significantly improved their anti-HBs Ab titers (> 100 UI/L) compared with those on calcitriol treatment.

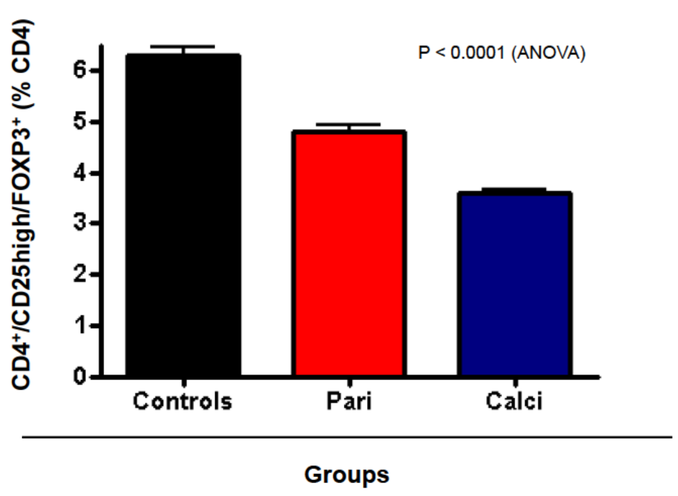
Baseline characteristics according to vitamin D therapy

	Paricalcitol (n = 10)	Calcitriol (n = 10)	P value
Age, *years* *	63±13	64±12	ns
Male, *n* (%)	5 (50)	5 (50)	ns
Duration of HD, *years**	4±2	4±2	ns
Causes of ESKD			
Hypertension	3	3	
Diabetes	2	3	
ADPKD	2	1	
Glomerulonephritis	1	2	
Others	2	1	
Laboratory values*			ns
sCreat (umol/L)	824	817	
sUrea (mmol/L)	22.4	20.8	
hsCRP (mg/L)	3.26	3.51	
sAlb (g/L)	40.5	39.0	
Leuc (G/L)	7.0	6.0	
PMN (%)	70.4	63.1	
Ly (%)	20.3	23.8	

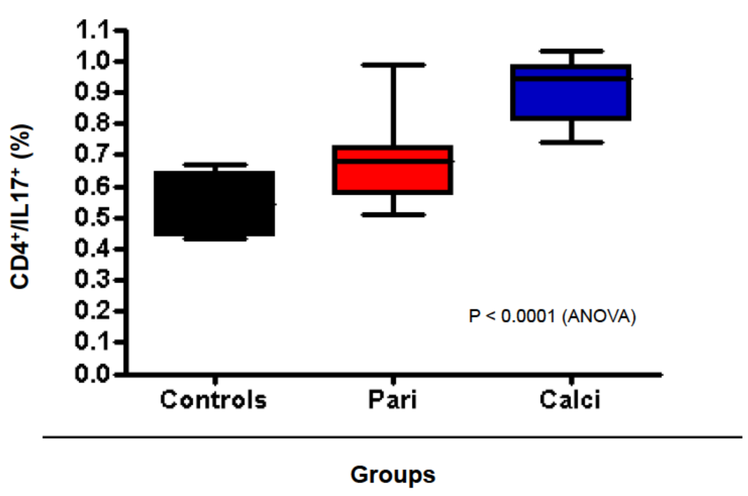
	Paricalcitol (n = 10)	Calcitriol (n = 10)	P value
Calcium (mmol/L)*	2.18±0.11	2.21±0.13	ns
Phosphorus (mmol/L)*	1.36±0.16	1.38±0.15	ns
Parathyroid hormone (pg/ml)*	453±173	449±188	ns
Alkaline phosphatase (U/liter)*	122±52	124±45	ns
Hemoglobin (g/L)*	110±5	112±6	ns
Kt/V*	1.43±0.21	1.45±0.26	ns
HBs Ag (neg.)	neg.	neg.	
Anti-HBs (< 10 UI/L)*	3.21±3.98	3.28±4.08	ns
Anti-HBc (neg.)	neg.	neg.	

*mean SD; ESKD: end-stage kidney disease; ADPKD: autosomal dominant polycystic kidney disease

Circulating Tregs numbers (T0+12 m)

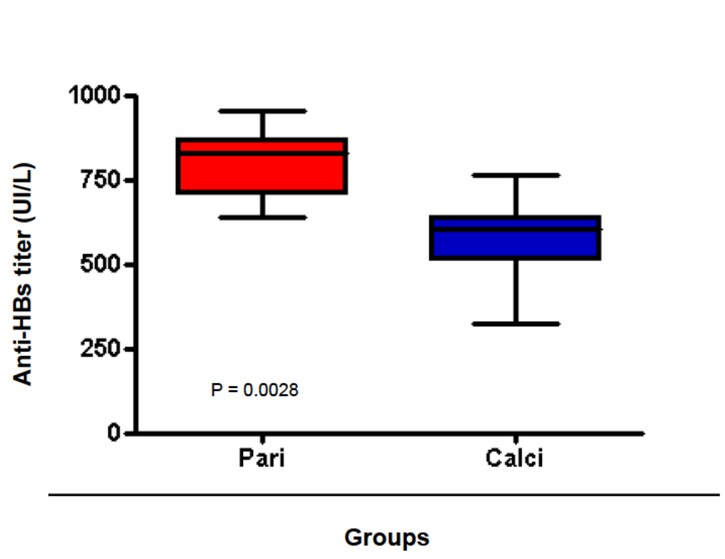


IL-17-positive CD4 T cells in PBMCs (T0+12 m)

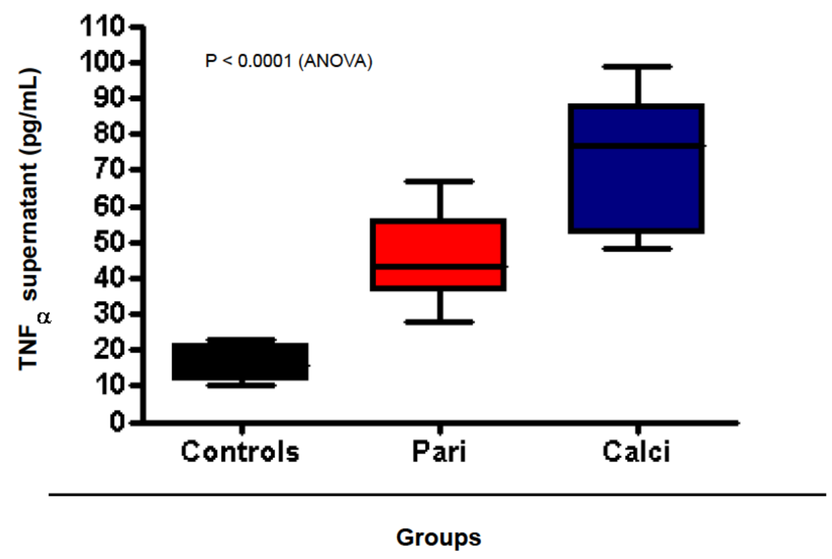


Controls: healthy HB vaccinated subjects with normal kidney

Anti-HBs titer by group at the end of the study (T0+12 m)



TNFα supernatant concentrations after HB vaccination



Controls: healthy HB vaccinated subjects with normal kidney

Summary and Conclusions

A better neutralization of Th17 *in vivo* with paricalcitol reveals that paricalcitol inhibits micro-inflammatory process mainly in a Tregs-dependent manner but also partly because of a decrease in Th17 number and function. These findings suggest that systemic immune modulation by paricalcitol may be a potentially valuable therapeutic approach against micro inflammation and to improve immune response in stage 5D CKD patients.

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