FAVORABLE EFFECT OF PARICALCITOL ON ERYTHROPOIESIS IN PATIENTS WITH CHRONIC KIDNEY DISEASE UNDERGOING HEMODIALYSIS

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Introduction

The highly prevalent anemia among the patients with chronic kidney disease (CKD) increase their morbidity and mortality [1,2]. Decreased endogenous production of erythropoietin, the main regulator of erythropoiesis, contributes to the development of renal anemia[3].
Impaired synthesis of calcitriol ($1,25(OH)_2D_3$), the active form of vitamin D, appears early during the course of CKD, leading to secondary hyperparathyroidism (SHPT)[4]. Since nuclear receptor of vitamin D (VDR) has a widespread tissue presence, vitamin D exerts a variety of autocrine or paracrine effects beyond the regulation of minerals' metabolism[5]. Administration of active vitamin D in patients undergoing chronic hemodialysis (HD) improved renal anemia and reduced the needs for rHuEPO in previous clinical studies[6,7].
Paricalcitol ($19\text{-nor-}1,25(OH)_2D_2$) is a third-generation analog of vitamin D, indicated for the treatment of SHPT in CKD[8]. We presumed that in the context of vitamin's D pleiotropic effects, paricalcitol could present a favorable effect on renal anemia. This effect has not been studied yet.

Purpose of the study

Evaluation of the effect of paricalcitol on anemia and erythropoiesis in patients with CKD stage 5D

Discussion

Three-month administration of paricalcitol had a favorable effect on erythropoiesis in our patients. Stability of hemoglobin levels was achieved by administering significantly reduced doses of rHuEPO weekly. Moreover, a significantly increment of the percentage of reticulocytes was observed.
Paricalcitol is a vitamin D analog, effective in the treatment of SHPT9. Control of SHPT by using active vitamin D or calcimimetics has improved anemia in ESRD patients previously10,11. Patients in our study had mildly elevated serum levels of iPTH. Although there was a decrease of iPTH levels at the end of the follow-up period, they were not statistically different from the initial values. Thus, PTH-lowering effect of paricalcitol does not explain our finding.
Administration of vitamin D analog was associated with significant reduction of serum levels of the cytokine IL-6. Additionally, C-reactive protein levels were reduced, although not significantly. In ESRD inflammatory markers have been consistently associated with renal anemia and rHuEPA hyporesponsiveness12,13. Proinflammatory cytokines exert a negative effect on erythropoiesis, altering the sensitivity of the erythroid progenitor cells to erythropoietin14. Moreover, contribute to functional iron deficiency by upregulating the synthesis of hepcidin15. Our results show that paricalcitol did not interfere in iron metabolism. Mean weekly dose of administered iron remained stable ensuring sufficient circulating levels without reticuloendothelial block. Serum levels of the markers of iron transport (transferin, sTfr) were not influenced by the administration of paricalcitol.

Table 1. Demographic data and parameters of hemodialysis treatment

Patients (n)	21
Gender (M/F)	14/7
Mean age (years)	61,9 (min 30, max 81)
Primary renal disease (n)	Diabetes (4), hypertension (4), obstructive nephropathy (1), chronic GN (1), ADPKD (1), angiitis (1), Fabry disease (1), unknown (1)
Mean time on HD (months)	20,52 (min 3, max 116)
HD treatment type (n)	Classic HD (13), on-line HDF (8)
Vascular access (n)	A-V fistula (11), A-V graft (2), CVC (8)

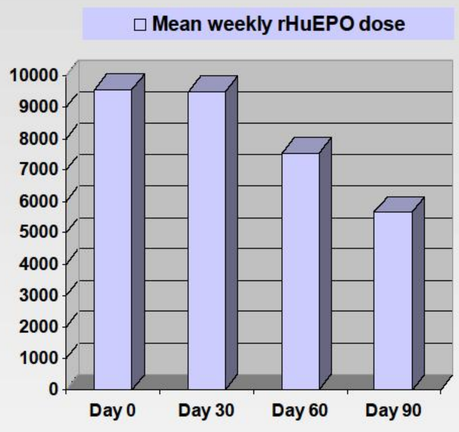
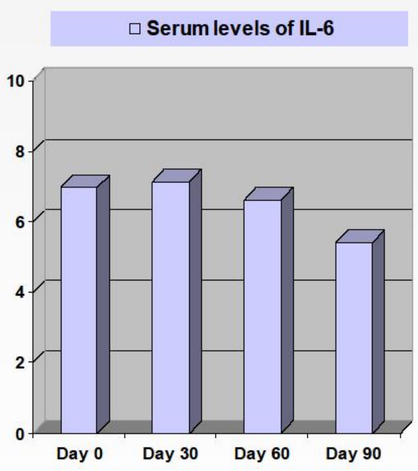


Table 2. Data analysis

	Day 0	Day 90	p value
Paricalcitol dose (μg)	5±2,5	2,8±1,5	
Hematocrit (%)	36,14±4,31	37,37±3,8	0.26
Hemoglobin (gr/dl)	11,61±1,42	11,92±1,16	0.38
Reticulocytes (%)	1,58±0,8	1,85±0,59	**0.036**
Iron (μg/dl)	90,24±48,6	77±37,2	0.24
Ferritin (ng/ml)	926,67±474,5	783±302,3	0.05
Transferin (mg/dl)	95,82±24,25	103,2±27,28	0.41
TSAT (%)	48,63±15,09	45,02±11,03	0.14
sTfr (nmol/L)	25,27±13,12	23,62±15,45	0.60
Calcium (mg/dl)	9,16±0,99	9,35±0,95	0.41
Phosphate (mg/dl)	4,77±1,19	5,44±1,04	0.05
Ca×P	43,95±12,22	52,04±12,02	**0.028**
iPTH (pg/ml)	498,3±197,7	443±280,9	0.02
CRP (mg/dl)	0,69±0,53	0,49±0,31	0.09
IL-6 (pg/ml)	6,97±3,88	5,41±2,76	**0.032**
spKt/V	1,36±0,17	1,38±0,16	0.62
Iron dose (mg/week)	157,14±77,92	154,76±77,31	0.92
EPO dose (IU/week)	9571±5065	5666±2972	**0.0003**



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Methods

Twenty one ESRD patients, fourteen men and seven women with mean age of 61,9 years, were included in the study. All patients underwent regular hemodialysis for at least 3 months. Demographic data and some parameters of dialysis treatment are shown in table 1.
Their dialysis program was in accordance with the K/DOQI guidelines regarding the duration (4 hours), the frequency (3 times/week) and the adequacy (spKt/V≥1,2). All patients had mild secondary hyperparathyroidism (iPTH 300-800 pg/ml) and efficient deposits of iron (TSAT≥20%, ferritin≥200 ng/ml), folic acid and vitamin B12. They were all treated with rHuEPO for renal anemia. Patients with chronic inflammatory disease or active inflammation, hematologic malignancy or other hematologic disease, active bleeding or tertiary hyperparathyroidism were excluded from the study.
After an initial wash-out period of 3 months, during which the use of paricalcitol or other derivative of vitamin D were stopped, administration of paricalcitol for a 3-month period followed. The initial dose of paricalcitol was calculated using the formula iPTH/120. The dose, administered intravenously at the end of each dialysis session, was adjusted accordingly to monthly variations of values of iPTH, calcium, phosphate and Ca×P. The target values were: iPTH 150-300 pg/ml, calcium <10,5 mg/dl, phosphate<6 mg/dl and Ca×P<65. Throughout the study period the adequacy of iron stores as well as the delivered dose of dialysis were insured.
Monthly during the study period hematologic tests (Ht, Hb, reticulocytes, Fe, ferritin, TSAT, soluble receptors of transferin-sTfR), parameters of mineral metabolism (calcium, phosphorus, iPTH) as well as inflammatory markers (CRP, IL-6) were measured. The mean weekly dose of rHuEPO and iron was estimated before the administration of paricalcitol and at the end of the study.
The values at the beginning of the administration of paricalcitol (day 0) and at the end of the follow-up period (day 90) were analysed using the Student's t-test for paired data. Statistical significance was set for p value <0.05.

Results

Three-month administration of paricalcitol was associated with significantly reduction of the mean weekly dose of rHuEPO (9571,43±5065 IU vs 5666,67±2972,09 IU, p<0.0003, Graphic 1). Moreover the percentage of the reticulocytes was increased significantly (1,58±0,8% vs 1,85±0,59%, p<0.036). Regarding the inflammatory markers, a significantly reduction of interleukin-6 was observed (6,97±3,88 pg/ml vs 5,41±2,76 pg/ml, p<0.032, Graphic 2). Levels of acute phase protein CRP were also decreased, although not significantly (0,69±0,53 mg/dl vs 0,49±0,31 mg/dl, p<0.09). As expected, administration of paricalcitol was associated with reduction of iPTH levels and mild increases of total calcium and phosphorus. No difference in the levels of TSAT and sTfr was observed. The results are summarized in Table 2.

Conclusions

Paricalcitol administration induced a favorable effect on erythropoiesis of patients suffering from CKD stage 5D, leading to decreased needs for rHuEPO. Since this result was associated with decreased levels of the inflammatory markers, especially of IL-6, we presume that the inflammatory modulation may constitute a possible pathophysiologic pathway.

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