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NEPHROLOGY - ORIGINAL PAPER

Treatment of secondary hyperparathyroidism with paricalcitol in patients with end-stage renal disease undergoing hemodialysis in Turkey: an observational study

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Abstract

Objective To evaluate monthly percentage changes of intact parathyroid hormone (iPTH) and other major bone marker levels in patients with secondary hyperparathyroidism (SHPT) undergoing hemodialysis (HD) and receiving paricalcitol.

Methods A total of 493 (F/M 244/249) adult patients with SHPT who were undergoing HD in 22 HD units and receiving paricalcitol treatment, with iPTH > 300 mg/mL, adjusted serum levels of calcium (Ca) < 10.2 mg/dL, and serum levels of inorganic phosphorus (iP) < 6 mg/dL were included in this multi-center, national, prospective, observational study. Data regarding efficacy, safety, and adverse events of paricalcitol treatment were collected during a 12-month follow-up period through monthly visits along with serum iPTH, Ca, iP, alkaline phosphatase (ALP) and other required biochemistry tests as necessary. Mortality data until 6 months after the end of the study were also investigated.

Results The mean age was 58.3 ± 15.8 years and the mean duration of HD was 6.2 ± 5.5 years, respectively. As of 12th month, mean iPTH values decreased from 646 ± 424 pg/mL to 473 ± 387 pg/mL ($p < 0.001$); no statistically significant changes were observed in Ca levels ($p > 0.05$). Serum ALP levels also significantly decreased ($p = 0.001$) and serum phosphorus levels significantly increased ($p < 0.001$) during the study observation period. Reasons for early terminations were being lost to follow-up ($n = 119$, 24.1%), hyperphosphatemia (iP > 6 mg/dL, $n = 108$, 21.9%), low iPTH levels (iPTH < 150 mg/dL, $n = 97$, 19.7%), and withdrawal of consent ($n = 41$, 8.3%). In total 32 patients (6.5%) were prematurely terminated the study with hypercalcemia (Ca > 10.2 mg/dL). 46.9% of those hypercalcemic patients had other anomalies with iP and iPTH levels along with hypercalcemia.

Conclusion Paricalcitol treatment, resulted in successful iPTH control. In approximately 6.5% of the patients paricalcitol treatment was discontinued since Ca levels reached > 10.2 mg/dL in those patients. No unfavorable effects on serum phosphorus and Ca–phosphorus (Ca × P) product were observed.

Keywords Paricalcitol · Chronic kidney disease · End-stage renal disease · Hemodialysis · Hyperparathyroidism

Introduction

High mortality rates are one of the major problems among patients with chronic kidney disease (CKD) who were undergoing hemodialysis (HD). Patients with CKD have a markedly increased incidence of cardiovascular events and cardiovascular disease (CVD) mortality compared with their age-matched counterparts in the general population [1] and the leading cause of death in patients with CKD is CVD, regardless of whether there is progression to end-stage renal disease [2–4].

Patients with CKD are also affected by mineral and bone disorder, which eventually results in abnormalities in serum calcium (Ca), inorganic phosphorus (iP), and intact

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parathyroid hormone (iPTH) levels and many other organ systems. Higher rates of serum Ca, iP and iPTH levels are associated with an increased risk of cardiovascular-related mortality [5, 6]. The majority of patients undergoing HD also become deficient in 1,25-dihydroxycholecalciferol (calcitriol) in time [7, 8]. The reduction of calcitriol levels due to HD is a well-known causal factor in the pathogenesis of secondary hyperparathyroidism (SHPT), which is associated with poor clinical outcomes of patients with CKD [9, 10].

On the other hand, treatment attempts of such patients with exogenous administration of calcitriol and other vitamin D metabolites may result in hypercalcemia, which potentially contributes in an increased risk of morbidity and mortality. To overcome this problem, several synthetic vitamin D receptor activators (VDRA) have been developed [11–13]. The accumulated data shows that occurrence rates of hypercalcemia and hyperphosphatemia are higher with calcitriol treatment when compared with selective VDRA (paricalcitol) treatment [12]. This effect may be attributed to a lesser bone resorption and intestinal absorption of Ca and iP, which may translate into a reduced risk of vascular calcifications and hence cardiovascular events. The use of selective VDRA (sVDRA, paricalcitol in this study), has shown to result in improvements in the survival of patients undergoing HD [14–16].

Country-based available information on results of paricalcitol treatment in Turkey was limited. Therefore, we planned this observational study to describe safety and efficacy of paricalcitol treatment in our country. With this study, we selectively observed iPTH levels during a 12-month of follow-up period and aimed to find out the percentage change in monthly iPTH levels among patients with SHPT who were undergoing HD and receiving paricalcitol treatment. The secondary objectives were: (1) to observe changes in commonly-assessed biochemical parameters for bone and mineral metabolism [Ca, iP, and alkaline phosphatase (ALP)]; (2) to evaluate routinely-checked follow-up parameters such as albumin, hemoglobin levels and dialysis adequacy (Kt/V); and (3) to collect and evaluate adverse event and mortality data to establish the country-based safety profile of paricalcitol use in routine clinical practice. The study was designed in an exploratory nature.

Subjects and methods

Study design, study size and subjects

This study was designed as an open-label, prospective, multi-central, post-marketing observational study. The inclusion criteria were: (1) adult male or female patients with stage 5 CKD and SHPT undergoing HD; (2) patients who are eligible for paricalcitol treatment according to the local label and reimbursement regulations (iPTH levels > 300 pg/mL, serum Ca levels < 10.2 mg/dL, and serum iP levels < 5 mg/dL); (3) patients who provided consent and signed the informed consent form; and (4) patients with diabetes mellitus or hypertension who have been receiving optimal and persistent treatment regimen. Classification of CKD was performed according to the K/DOQI guidelines [17]. After consenting and screening evaluations at baseline, follow-up period was initiated for eligible patients. If paricalcitol treatment was interrupted for any reason, patients were discontinued and the reason for discontinuation was recorded. Since this was an observational study, patient treatments were left to the discretion of the treating physician who was regularly seeing patients with CKD when receiving HD. Dosing regimen for paricalcitol, including the starting dose and dose adjustments, were chosen by the treating physician according to the local label which require the dose to be adjusted according to iPTH levels. Paricalcitol treatment was discontinued when Ca levels reached > 10.2 mg/dL and iP levels reached > 6 mg/dL according to local regulations of Ministry of Health of Turkey. Paricalcitol was administered intravenously and the protocol did not limit the paricalcitol dose during initiation or follow-up period.

Patients who met inclusion criteria were enrolled to the study and treatment was followed up for 12 months with monthly intervals. Patients were called 6 months after the last visit or early study termination, to collect survival data. The required data were entered into the CRFs using the patient's medical records as source data. Regular site monitoring visits were conducted and recorded data were verified during these visits. All eligible patients were included in the statistical analysis. In addition, patient data were evaluated on the basis of the "last observation carried forward" (LOCF) method.

Safety evaluations

Safety variables were defined as "adverse events" (AE) and "serious adverse events" (SAE), which were reported throughout the study period. Other safety variables were defined as persistently elevated Ca, iP, and Ca × P values. Regarding clinical terms, hypercalcemia was defined as two consecutive elevated serum Ca (Ca > 10.2 mg/dL), hyperphosphatemia was defined as two consecutive elevated iP (iP > 6.0 mg/dL), and elevated Ca × P product was defined as two consecutive elevated Ca × P > 55 mg^2/dL^2. Increased levels for Ca, iP, and Ca × P resulted in treatment cessation and patients with increased levels were dropped-out of the study due to applicable reimbursement criteria in Turkey for paricalcitol treatment, as specified in the study protocol. Thus, such increases were not recorded as patients were dropped from the study as per the study protocol.

Efficacy evaluations

iPTH levels were assessed as the only efficacy criteria. The study protocol intended to collect iPTH levels at baseline and at all follow-up visits until patient drop-out from the study, either due to treatment cessation or any other reason, such as an investigator-patient decision to withdraw the patient from the study. If paricalcitol treatment was interrupted for any reason, patients were discontinued and the reason for discontinuation was recorded. Paricalcitol treatment was given in accordance with the treating physician's decision and the applicable "summary of product characteristics" (SmPC) in Turkey. No interventions were made to the treatment, patient discontinuance, or to the follow-up decisions of the treating physicians.

Survival evaluations

Survival was evaluated with a telephone call 6 months after the patients' last visit.

Statistical analysis

Previous publication on the effects of VDRA agents, in controlling parathyroid hormone levels in HD patients indicate a reduction in serum iPTH levels between 10 and 12%. Considering this positive effect into calculation and estimating a decrease of minimum 9.5% in iPTH levels after a minimum of 6 months treatment, with a power of 95% and with an error rate of 5% (alpha), a minimum of 447 patients would be enrolled into the study. Due to the nature of the dialysis patients and/or end-stage renal failure, a minimum of 15% lost-to-follow-up patients was expected, thus, approximately 510 patients were planned to be enrolled. Therefore, this study was planned as a post-marketing observational study that would enroll approximately 510 patients at 22 sites throughout Turkey.

For numeric variables, descriptive statistics are provided as mean, median, standard deviation, minimum and maximum values. For categorical values descriptive statistics are provided with frequencies and percentages. Whenever applicable, implementing of actual values and/or LOCF methods were used. Missing values were not completed through any assumptions and were double-checked through data queries whenever applicable, otherwise they were either confirmed as missing data or replacement data were provided by the treating physicians. All analyses were performed using SPSS version 20 (IBM SPSS Inc., Chicago, IL, USA).

Results

After ethics committee and regulatory authority approvals, patients were enrolled in 22 dialysis centers in Turkey. All eligible patients have signed written informed consent forms and were consequently enrolled in the study.

Baseline clinical characteristics

A total of 493 patients were enrolled in the study and were intended to be followed up for 12 months. However, 421 patients (85.4%) were dropped out and only 72 patients attended all planned follow-up visits. Disposition of patients with the reason of withdrawal is provided in Table 1.

Male patients formed 50.5% of the total population and the mean age at enrolment was 58.3 ± 15.8 years. The patients were aged between 18 and 92 years with a median age of 60 years. The majority of patients had been undergoing HD (71.4%) for a minimum 2 years at enrolment, and approximately two-thirds had undergone HD for more than 3 years (59.2%). At baseline patients used pre-medications which were Ca containing phosphate binders ($n = 53$), active vitamin D (as 1,25-dihydroxycholecalciferol or 25 hydroxycholecalciferol) ($n = 393$), and non-calcium containing phosphate binders ($n = 365$). Phosphate binders as a whole, have been used by 95.1% of the patients at baseline. Erythropoietin and related agents were used as necessary under local regulations of Ministry of Health of Turkey. The

Table 1 Disposition of patients and reason of withdrawal

	N	%
Enrolled	493	100.00
Completed the study	72	14.60
Withdrawn from follow-up	421	85.40
Lost to follow-up	119	24.14
Hyperphosphatemia[a] (iP > 6 mg/dL)	91	18.46
Low iPTH levels[b] (< 150 pg/ml)	82	16.63
Withdrawn consent	41	8.32
Reimbursement issue	28	5.68
Adverse events	20	4.06
Hypercalcemia[c] (Ca > 10.2 mg/dL)	32	6.49
Ca > 10.2 mg/dL	17	3.45
Ca > 10.2 mg/dL and iP > 6 mg/dL	8	1.62
Ca > 10.2 mg/dL and iPTH < 150 pg/mL	6	1.22
Ca > 10.2 mg/dL and iPTH < 150 pg/mL and iP > 6 mg/dL	1	0.20
iPTH < 150 pg/mL and iP > 6 mg/dL	8	1.62

[a]Total number of patients with hyperphosphatemia = 108 (21.91%)

[b]Total number of patients with low iPTH levels = 97 (19.68%)

[c]Total number of patients with hypercalcemia = 32 (6.49%)

patient population had a high rate of comorbidities (87%), with almost half (49.5%) of the patients having two or more co-morbid medical conditions at the time of enrolment. ALP, albumin, hemoglobin, as well as Kt/V ratios were the main safety parameters.

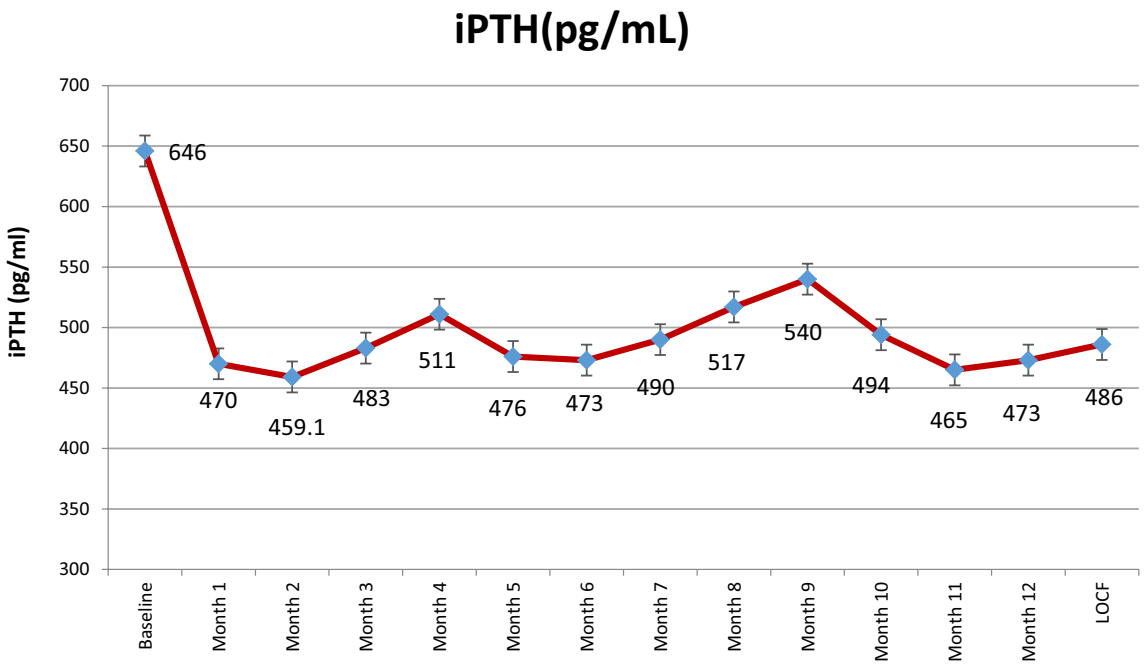
Main results

Following initiation of treatment a significant reduction in iPTH levels was observed. Figure 1 shows the significant decrease ($p < 0.001$) in iPTH levels and it's fluctuation within normal range (150–600 pg/mL) according to the KDIGO criteria [18]. After the initial fall, iPTH levels remained within the range of 450–550 pg/mL levels throughout the study (Fig. 1). Due to the large number of patients who did not complete the study, a sensitivity analysis was conducted using two different methods. In the first method, missing values were imputed using the worst iPTH levels (imputed dataset) whereas in the second method, patients who have a missing iPTH value in any visit were excluded from the analysis (missing excluded dataset). A statistical significance ($p < 0.001$) was obtained in both datasets when mean baseline iPTH value was compared to mean values of other study visits. Additionally, change from baseline to 12th month visit was also significant for both datasets ($p < 0.001$ for the imputed dataset and $p = 0.006$ for the missing excluded dataset).

The secondary objectives of this study mainly focused on levels of serum Ca, iP, Ca × P, and ALP as the main bone and mineral metabolism predictors and their levels of change during treatment with paricalcitol treatment. Mean values of these parameters are presented in Table 2. Serum Ca levels remained within normal ranges throughout the study with only a slight but statistically significant increase from the baseline level of 8.80–8.93 mg/dL, again remaining within normal limits, for the LOCF analysis group ($p = 0.001$, $n = 471$, Fig. 2).

A slight but significant increase was observed in mean serum iP levels (Table 2). Baseline mean iP was 4.72 (± 0.89) mg/dL and at 12th month visit this level was increased to 5.18 (± 1.17) mg/dL (baseline to LOCF, $p < 0.001$, $n = 471$). Even though this slight increase was significant, iP levels remained within normal limits during the course of the study.

Serum Ca × P levels were also recorded in patients with CKD treated with HD. At baseline visit Ca × P levels were 41.5 (± 8.6) mg^2/dL^2 and increased to 46.1 (± 11.2) mg^2/dL^2 at 12th month visit (Table 2). This increase was not



- Baseline to 1st month, p<0.001 (n=464)
- Baseline to 12th month, p<0.001 (n=72)
- Baseline to LOCF, p<0.001 (n=84)

Fig. 1 iPTH (pg/mL) levels and changes compared with baseline during the follow-up period

Table 2 Mean (±SD) laboratory parameters by study visit

	iPTH (pg/mL)	Ca (mg/dL)	P (mg/dL)	Ca×P (mg^2/dL^2)	ALP (U/L)	Albumin (g/dL)	Hb (g/dL)	Kt/V
Baseline	646±424 (*n*=493)	8.80±0.69 (*n*=493)	4.72±0.89 (*n*=493)	41.5±8.6 (*n*=493)	170.4±153.2 (*n*=492)	4.0±0.5 (*n*=493)	11.3±1.3 (*n*=491)	1.6±0.3 (*n*=491)
1st visit	470±393 (*n*=464)	8.94±0.81 (*n*=458)	5.02±1.21 (*n*=458)	44.8±11.8 (*n*=458)	164.1±144.8 (*n*=455)	4.0±0.5 (*n*=456)	11.3±1.4 (*n*=437)	1.6±0.3 (*n*=437)
2nd visit	459±394 (*n*=367)	8.90±0.87 (*n*=368)	5.06±1.30 (*n*=368)	44.8±12.1 (*n*=368)	164.1±152.6 (*n*=365)	4.0±0. 5 (*n*=368)	11.4±1.6 (*n*=367)	1.5±0.3 (*n*=347)
3rd visit	483±355 (*n*=275)	8.86±0.85 (*n*=276)	5.08±1.16 (*n*=276)	45.1±11.2 (*n*=276)	167.2±160.3 (*n*=276)	4.1±2.3 (*n*=276)	11.4±1.6 (*n*=276)	1.6±0.3 (*n*=254)
4th visit	511±402 (*n*=232)	8.84±0.90 (*n*=232)	5.04±1.19 (*n*=232)	44.5±11.6 (*n*=232)	167.0±153.5 (*n*=231)	4.1±1.8 (*n*=231)	11.4±1.6 (*n*=231)	1.6±0.3 (*n*=217)
5th visit	476±391 (*n*=209)	8.78±0.74 (*n*=209)	5.07±1.17 (*n*=209)	44.5±10.8 (*n*=209)	169.7±148.9 (*n*=206)	4.1±0.9 (*n*=209)	11.5±1.5 (*n*=209)	1.5±0.3 (*n*=192)
6th visit	473±365 (*n*=180)	8.76±0.74 (*n*=179)	4.96±1.16 (*n*=179)	43.6±11.3 (*n*=179)	170.3±171.8 (*n*=180)	4.1±0.4 (*n*=178)	11.5±1.5 (*n*=178)	1.5±0.4 (*n*=162)
7th visit	490±397 (*n*=152)	8.90±0.81 (*n*=153)	4.91±1.14 (*n*=153)	43.8±11.5 (*n*=153)	168.8±162.3 (*n*=152)	4.0±0.4 (*n*=153)	11.6±1.4 (*n*=152)	1.6±0.3 (*n*=126)
8th visit	517±409 (*n*=131)	8.87±0.86 (*n*=131)	5.10±1.44 (*n*=131)	45.2±13.3 (*n*=131)	167.4±141.7 (*n*=130)	4.1±0.4 (*n*=131)	12.3±8.2 (*n*=131)	1.6±0.3 (*n*=107)
9th visit	540±444 (*n*=117)	8.88±0.82 (*n*=116)	5.14±1.23 (*n*=116)	45.6±11.7 (*n*=116)	158.5±129.7 (*n*=115)	4.1±0.5 (*n*=117)	11.4±1.6 (*n*=116)	1.6±0.3 (*n*=88)
10th visit	494±380 (*n*=97)	8.86±0.75 (*n*=97)	5.03±1.12 (*n*=97)	44.5±10.3 (*n*=97)	157.4±149.7 (*n*=97)	4.2±0.6 (*n*=96)	11.7±1.4 (*n*=97)	1.5±0.3 (*n*=98)
11th visit	465±404 (*n*=84)	8.85±0.71 (*n*=84)	5.04±1.25 (*n*=84)	44.4±12.1 (*n*=84)	152.7±149.6 (*n*=83)	4.3±0.7 (*n*=84)	11.8±1.4 (*n*=83)	1.5±0.3 (*n*=68)
12th visit	473±387 (*n*=72)	8.88±0.78 (*n*=72)	5.18±1.17 (*n*=72)	46.1±11.2 (*n*=72)	143.8±143.5 (*n*=72)	4.5±1.1 (*n*=72)	11.7±1.7 (*n*=71)	1.5±0.3 (*n*=65)

Normal limits: iPTH ≤ 300 (pg/mL), Ca ≤ 10.2 mg/dL, *p* ≤ 5.5 mg/dL, Ca × P ≤ 55 mg^2/dL^2, ALP: 25–100 U/L, albumin: 3.5–5.5 g/dL, Hb: 13.8–17.2 g/dL, male; 12–15.6 g/dL, female, Kt/V: ≥ 1.2

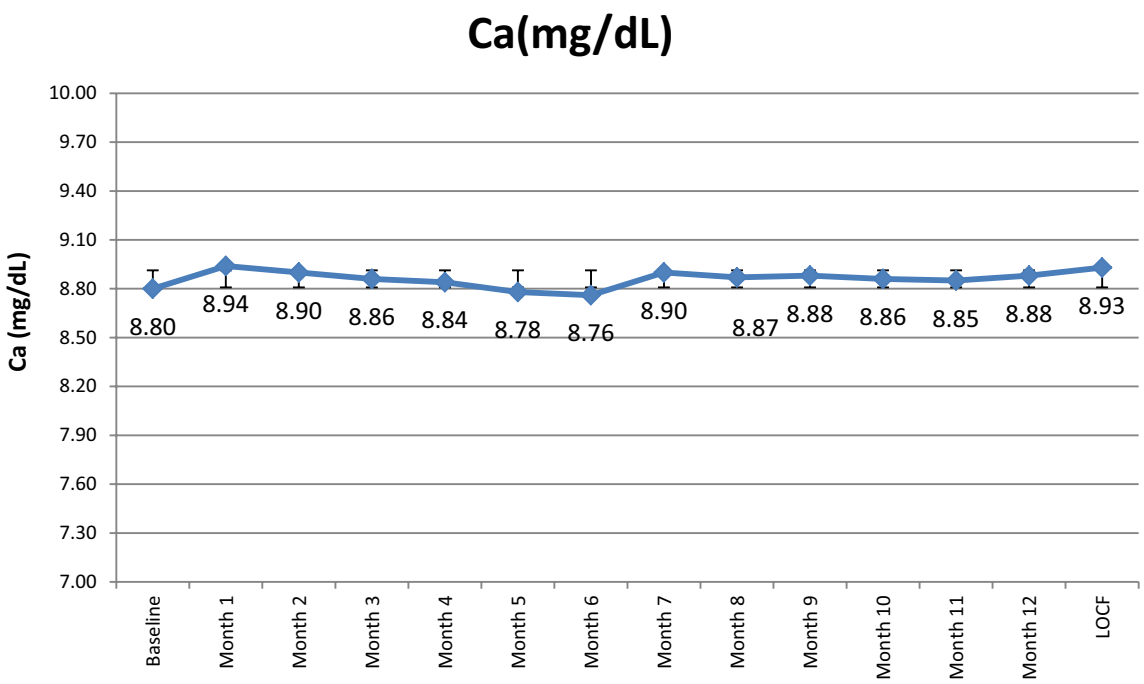
statistically significant however a significant increase was observed between baseline and LOCF values (41.5 vs. 45.4 mg^2/dL^2, $p < 0.001$, Fig. 3). An important finding of the study was that the mean serum Ca × P levels remained below the critical threshold level of 55 mg^2/dL^2 at all visits, which indicates a successful treatment outcome during the study (Fig. 3).

We also collected data on HD efficiency criteria such as the Kt/V ratio, albumin levels, as well as ALP, which is an indicator of bone turnover during SHPT. There were no changes in the Kt/V ratio throughout the study visits, but serum ALP levels significantly decreased during the same period ($p = 0.001$). Serum albumin levels have increased significantly ($p = 0.003$) and stayed over 4 mg/dL at all visits, which indicates that patients were not in malnutrition during the treatment period (Table 2). On the other hand, no significant changes in required paricalcitol dosage was observed during the study and mean dose in micrograms are shown in Table 3.

Reason for early termination of the treatment was questioned at the end of the follow-up period. Most frequent reason of early terminations were lost to follow-up ($n = 119$, 24.1%), hyperphosphatemia (iP > 6 mg/dL, $n = 108$, 21.9%), low iPTH levels (iPTH < 150 mg/dL, $n = 97$, 19.7%), and withdrawal of consent ($n = 41$, 8.3%). In total, 32 patients (6.5%) were prematurely terminated the study with hypercalcemia (Ca > 10.2 mg/dL). 46.9% of those hypercalcemic patients had other anomalies with serum iP and iPTH levels along with hypercalcemia. These and further details for reason of early termination are provided in Table 1.

Additionally, a survival analysis was conducted. Among 493 enrolled patients 440 patients (89.2%) were called out and results revealed that 84.8% of the patients were alive at the 18th month telephone interview.

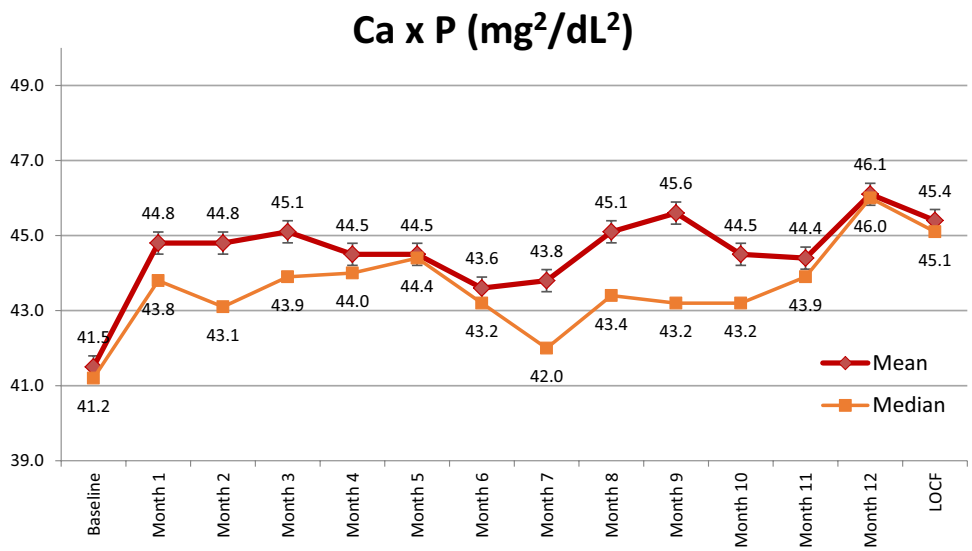
During the study, AE and SAE were recorded as per the study protocol. There were 25 (5.1% of all patients) SAEs and one non-SAE reported. The only non-SAE was a minor diagnostic intervention. Fifteen patients died of complications of the reported SAEs. The majority of patients who presented with a SAE had more than three comorbidities and most deaths were evaluated as a result of CKD and its cardiovascular complications. No SAEs were considered related to treatment. A complete list of the SAEs that occurred during the study, along with physician-reported



- Baseline to 12th month, p= 0.058 (n=71)
- Baseline to LOCF, Wilcoxon test, p= 0.001 (n=471)

Fig. 2 Serum calcium levels and changes compared with baseline during the follow-up period

Fig. 3 Mean serum calcium × P (mg^2/dL^2) levels and changes compared with baseline during the follow-up period



- Baseline to LOCF, Wilcoxon test, p<0.001(n=471)

terms, related Medical Dictionary for Regulatory Activities (MedDRA) coded terms, outcomes and relationship to paricalcitol treatment, are presented in Table 4.

Table 3 Paricalcitol doses (mcg) at monthly visits

	N	Mean ± SD	Median (min–max)
Baseline	492	71.4 ± 42.2	60 (5–300)
1st visit	442	71.8 ± 52.9	60 (5–480)
2nd visit	359	69.8 ± 51.4	60 (5–480)
3rd visit	269	69.2 ± 58.5	60 (5–320)
4th visit	227	72.4 ± 65.2	60 (5–380)
5th visit	206	72.6 ± 62.7	60 (5–320)
6th visit	175	77.8 ± 91.7	60 (5–960)
7th visit	148	88.6 ± 103.3	60 (5–690)
8th visit	130	94.1 ± 110.6	60 (5–960)
9th visit	109	97.2 ± 119.2	60 (5–960)
10th visit	95	94.0 ± 123.4	60 (10–960)
11th visit	84	83.9 ± 120.9	60 (20–960)
12th visit	72	56.5 ± 46.0	40 (20–240)

$n = 72$, Wilcoxon signed-rank test $p = 0.827$

Changes in paricalcitol doses, baseline to 12th visit, were not statistically significant

Discussion

SHPT frequently occurs in patients with CKD undergoing HD. SHPT manifests with high serum parathyroid hormone level, which is an early and major complication of CKD. High iPTH levels result in increased bone remodeling, which leads to loss of bone density and structural integrity with a loss of bone mineral, and an increase in the mobilization of Ca and phosphorus from the bone.

Paricalcitol in patients with CKD and SHPT reduces circulating iPTH levels by inhibiting parathyroid cell proliferation, and decreases iPTH synthesis and secretion, with minimal impact on Ca and phosphorus levels. Besides the correction of abnormal iPTH levels, normalization of circulating serum Ca and phosphorus levels, paricalcitol corrects the chronic kidney disease mineral bone disease (CKD-MBD) and probably helps in maintaining bone volume.

The results of this observational, non-interventional exploratory study provide two major outcomes by showing a significant decrease in iPTH levels and a minimal effect on Ca and phosphorus levels during paricalcitol treatment in patients with CKD. Olaizola et al. [19] studied effectiveness

Table 4 Serious adverse events

Reported term[a]	Preferred term (MedDRA coding)	*N* = 493	Outcome	Related to study drug
Respiratory arrest	Respiratory failure	1	Death	No
Mitral insufficiency	Mitral valve disease	1	Not recovered	No
Cardiovascular insufficiency	Heart failure, cardiac arrest	3	Death	No
Cardiac embolism	Cardiac disorders, embolism	1	Death	No
Cardiopulmonary arrest	Cardiac arrest	1	Death	No
Infection	Kidney infection	3	Death	No
Stomach bleeding	Gastric hemorrhage	1	Recovering	No
Dyspnea, fever	Dyspnea and fever	1	Recovering	No
Parathyroidectomy	Surgical and medical procedures; Parathyroidectomy	2	Recovered	No
Cardiopulmonary arrest	Cardiac arrest	1	Death	No
Pneumonia	Lung infection	1	Death	No
Leucopenia	Anemia	1	Recovering	No
Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease	1	Not known	No
Acid in the abdomen, splenomegaly	Ascites	1	Not recovered	No
Chronic obstructive pulmonary disease, acute bronchitis	Chronic obstructive pulmonary disease, acute bronchitis	1	Not known	No
Coldness in lower extremities, acute arterial occlusion	Visceral arterial ischemia	1	Death	No
Myocardial infarction	Myocardial infarction	1	Death	No
Catheter infection	Catheter-related infection	1	Death	No
Dysfunctional uterine bleeding	Chronic kidney disease, surgical and medical procedures	1	Recovered	No
Infection	Uterine hemorrhage	1	Recovered	No

N number of patients experiencing at least one serious adverse event

[a]Renal transplantation was performed in three patients however these patients were not included in the statistical analysis

and safety of a 6-month treatment with paricalcitol in patients on HD with SHPT. Similar to our study results, they reported a significant decrease in iPTH levels when compared to baseline. These results suggest that paricalcitol has a significant effect on iPTH reduction in patients with CKD.

Ca and P have crucial effects on arterial calcifications as demonstrated by in vitro studies conducted by Giachelli et al. [20, 21]. High serum P levels are also associated with CKD progression in addition to vascular calcification [22, 23]. Even though an increase was observed both in serum Ca and P levels towards the end of the study, serum Ca and P levels remained within normal ranges throughout the whole study and did not suggest an increased risk of high Ca × P related vascular calcification in CKD patients. Various results are reported in other studies. There was no significant increase in mean serum P levels throughout the study of Olaizola et al. [19] however; there was a significant increase in mean serum Ca levels. In another study, mean Ca and phosphorus levels did not change over the 16 months of paricalcitol therapy similar to our study [24]. Although Ca × P levels have increased towards the end of the study, this increase was again, within normal limits and it was considered as related to nutritional changes in patients. Similarly, Olaizola et al. [19] did not report a significant difference in Ca × P levels and in their study, mean Ca × P levels have ranged between 44.4 and 50.1 mg^2/dL^2 during a follow-up period of 6 months.

Paricalcitol treatment might be interrupted due to high Ca and P levels and treatment discontinuation was a reason of withdrawal in our study. Due to high withdrawal rate, we evaluated number of patients with hypercalcemia and/or hyperphosphatemia within withdrawn patients. In our study, only 6.5% of the patients terminated paricalcitol treatment due to hypercalcemia and this ratio was considered similar to other published study reports. Coyne et al. [25] reported an incidence rate of 3.2% in their study which included analysis of 281 patients with diabetic nephropathy. In another multicentral study, which enrolled 110 stage 3–4 CKD patients, the same investigator reported hypercalcemia and hyperphosphatemia rates as 5.7% and 40%, respectively [26].

Hemoglobin and albumin levels are good indicators of general health status, as well as nutritional adequacy. Additionally, albumin plays an important role while adjusting Ca levels. Serum albumin levels were shown to be increasing during the follow-up period indicating a good nutritional and general health status. Hemoglobin levels were also remained within desired range. Although there were no changes in the Kt/V ratio, serum ALP levels have significantly decreased during the follow-up period. Therefore, serum ALP results indicated a change towards normal levels. On the other hand, since this is a cardiovascular risk factor, reduction was considered as a positive sign [27]. Similar results were reported in another study evaluating paricalcitol treatment in dialysis patients with calcitriol-resistant SHPT. Results obtained from that study indicated that ALP levels significantly decreased at 16 months when compared to baseline values [24].

During this study, the doses of paricalcitol used were recorded at each visit and thus collected on a monthly basis. The evaluation of mean paricalcitol doses showed a fluctuating trend during all visits, but with no significant changes throughout the follow-up period. With the exception of the 12th visit (40 mg, $n = 72$), the median paricalcitol dose was found as 60 mg at all visits.

The survival analysis, which was conducted through a telephone interview 6 months after the patients' last visit indicated a survival of 84.8%. Teng et al. [28] reported similar survival rates in their historical cohort study, in which they evaluated survival rates in 29,000 patients receiving HD either with paricalcitol or calcitriol. According to their results, survival rates were approximately 85% for 1 year and 73% for 2 years.

The majority of recorded AE were SAEs, mostly due to end-stage chronic renal failure, requiring continuous HD treatment. The high comorbidities may also account for severe and serious nature of some AE recorded. There was no indication of a relationship with paricalcitol treatment, and half of the patients were reported as deceased due to an adverse event. Paricalcitol treatment was well tolerated with a low incidence of SAEs. In line with the fact that CKD is a chronic and severe illness, the occurrence of SAEs and deaths were evaluated as low and related to the patients' underlying medical conditions.

The major limitation of this study was the low number of patients during the follow-up period. Although the number of patients at baseline was relatively high ($n = 493$), a larger sample size might have provided more statistical power as high drop-out rate (85.4%) resulted in not attaining statistical significance in some of the evaluated parameters. However, due to high drop-out rate, a sensitivity analysis was conducted for the primary outcome (iPTH levels) and results obtained from the sensitivity analysis were in accordance with the initial study results. The country re-imbursement rules had a great impact on these low numbers of follow-up patients because patients who reach target iPTH or P levels were forced to stop paricalcitol treatment, and were consequently dropped out from the study. More than a quarter of the study population terminated the study prematurely due to reimbursement issues. CKD-MBD markers of patients who discontinued the study were of critical importance. In our study, high Ca × P was not the main causes of discontinuation. Additionally, as no control group was allocated for this study, it carried a major bias with an obvious shortfall of one arm studies. Furthermore, the selected sites were not geographically representative of Turkey, but the data obtained

were sufficient to provide initial scientific conclusions on paricalcitol treatment in SHPT during HD.

Conclusion

Based on the results of this study, a decrease of iPTH compared with baseline was achieved in almost all patients enrolled in this study. This effect occurred mostly in the first 2 months.

With regards to the safety of paricalcitol treatment it was concluded that paricalcitol was well tolerated with a low incidence of SAE. Considering the severity of baseline medical conditions of enrolled patients, the percentage of SAEs and deaths observed were low and due to underlying medical conditions of the patients.

Thus, the overall results of this PMOS performed in a selected Turkish population of patients with CKD undergoing HD were in line with other published data published in the literature.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Daly C (2007) Is early chronic kidney disease an important risk factor for cardiovascular disease A background paper prepared for the UK consensus conference on early chronic kidney disease. Nephrol Dial Transplant 22(Suppl. 9):19–25
2. Perazella MA, Khan S (2006) Increased mortality in chronic kidney disease: a call to action. Am J Med Sci 331(3):150–153
3. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX (2006) Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol 17(7):2034–2047 **(Epub 2006 May 31)**
4. Hajhosseiny R, Khavandi K, Goldsmith DJ (2013) Cardiovascular disease in chronic kidney disease: untying the Gordian knot. Int J Clin Pract 67(1):14–31
5. Foley RN, Parfrey PS, Sarnak MJ (1998) Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 32(Suppl 3):S112–S119
6. Abe M, Okada K, Soma M (2013) Mineral metabolic abnormalities and mortality in dialysis patients. Nutrients. 5(3):1002–1023. https://doi.org/10.3390/nu5031002
7. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM (2004) Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 15:2208–2218
8. Bansal B, Bansal S, Mithal A, Kher V, Marwaha R (2012) Vitamin D deficiency in hemodialysis patients. Indian J Endocrinol Metab 16(2):270–273. https://doi.org/10.4103/2230-8210.93749
9. Slinin Y, Foley RN, Collins AJ (2005) Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: the USRDS waves 1, 3, and 4 study. J Am Soc Nephrol 16:1788–1793
10. Drechsler C, Pilz S, Obermayer-Pietsch B, Verduijn M, Tomaschitz A, Krane V et al (2010) Vitamin D deficiency is associated with sudden cardiac death, combined cardiovascular events, and mortality in haemodialysis patients. Eur Heart J 31:2253–2261
11. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B et al (2005) Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol 16:520–528
12. Ogawa T, Kyono A, Sato M, Sugimoto H, Otsuka K, Nitta K (2012) Vitamin D receptor agonist supplementation and suppression of inflammation may have advantage for all-cause mortality in hemodialysis patients. Clin Exp Nephrol 16:779–785
13. Ketteler M, Martin KJ, Wolf M, Amdahl M, Cozzolino M, Goldsmith D, Sharma A, Marx S, Khan S (2012) Paricalcitol versus cinacalcet plus low-dose vitamin D therapy for the treatment of secondary hyperparathyroidism in patients receiving haemodialysis: results of the IMPACT SHPT study. Nephrol Dial Transplant 27(8):3270–3278
14. Brancaccio D, Cozzolino M, Cannella G, Messa P, Bonomini M, Cancarini G et al (2011) Secondary hyperparathyroidism in chronic dialysis patients: results of the Italian FARO survey on treatment and mortality. Blood Purif 32:124–132
15. Messa P, Cozzolino M, Brancaccio D, on behalf of the FARO Study Group et al (2015) Effect of VDRA on survival in incident hemodialysis patients: results of the FARO-2 observational study. BMC Nephrol 16:11
16. Vervloet MG, Twisk JWR (2009) Mortality reduction by vitamin D receptor activation in end-stage renal disease: a commentary on the robustness of current data. Nephrol Dial Transplant 24:703–706. https://doi.org/10.1093/ndt/gfn492
17. National Kidney Foundation (2002) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 39(suppl 1):S1–S266
18. KDIGO (2017) Clinical practice guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. Kidney Int Suppl 2017(7):1–59
19. Olaizola I, Caorsi H, Fajardo L, Ferreiro A, Campistrus N, Dolinsky D, Petraglia A, Ambrosoni P (2016) Effectiveness and safety of a 6-month treatment with paricalcitol in patients on

hemodialysis with secondary hyperparathyroidism. J Bras Nefrol 38(3):302–312
20. Giachelli CM (2003) Vascular calcification: in vitro evidence for the role of inorganic phosphate. J Am Soc Nephrol 14:S300–S304
21. Giachelli CM (2004) Vascular calcification mechanisms. J Am Soc Nephrol 15:2959–2964
22. Stubbs JR, Liu S, Tang W, Zhou J, Wang Y, Yao X et al (2007) Role of hyperphosphatemia and 1,25-dihydroxyvitamin D in vascular calcification and mortality in fibroblastic growth factor 23 null mice. J Am Soc Nephrol 18:2116–2124
23. Silver J, Rodriguez M, Slatopolsky E (2012) FGF23 and PTH-double agents at the heart of CKD. Nephrol Dial Transplant 27:1715–1720
24. Llach F, Yudd M (2001) Paricalcitol in dialysis patients with calcitriol-resistant secondary hyperparathyroidism. Am J Kidney Dis 38:S45–S50
25. Coyne DW, Andress DL, Amdahl MJ, Ritz E, de Zeeuw D (2013) Effects of paricalcitol on calcium and phosphate metabolism and markers of bone health in patients with diabetic nephropathy: results of the VITAL study. Nephrol Dial Transplant 28(9):2260–2268
26. Coyne DW, Goldberg S, Faber M, Ghossein C, Sprague SM (2014) A randomized multicenter trial of paricalcitol versus calcitriol for secondary hyperparathyroidism in stages 3-4 CKD. Clin J Am Soc Nephrol 9(9):1620–1626
27. Regidor DL, Kovesdy CP, Mehrotra R et al (2008) Serum alkaline phosphatase predicts mortality among maintenance hemodialysis patients. J Am Soc Nephrol 19(11):2193–2203
28. Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, Thadhani R (2003) Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. N Engl J Med 349(5):446–456