ORIGINAL ARTICLE

Treatment of secondary hyperparathyroidism with paricalcitol with or without cinacalcet in hemodialysis patients

Jacek Zawierucha[1], Jolanta Małyszko[2], Jacek S. Małyszko[3], Tomasz Prystacki[4], Wojciech Marcinkowski[4], Teresa Dryl-Rydzyńska[1]

1 Fresenius Medical Care Polska S.A., Poznań, Poland
2 Second Department of Nephrology and Hypertension with Dialysis Unit, Medical University of Bialystok, Poland
3 Department of Nephrology with Dialysis Unit, Medical University of Bialystok, Poland
4 Fresenius Nephrocare Polska Sp. z o.o., Poznań, Poland

KEY WORDS

cinacalcet, hemodialysis, hyperparathyroidism, paricalcitol, vitamin D analogues

ABSTRACT

INTRODUCTION Secondary hyperparathyroidism (SHPT) is a common hormonal disorder associated with chronic kidney disease (CKD). The treatment of SHPT should lead to a reduction in parathormone concentrations by calcimimetics or active vitamin D administration and stabilization of calcium and phosphate metabolism. In the event of failure of conservative treatment, complete or partial parathyroid resection should be considered.

OBJECTIVES The aim of the study was to assess the beneficial effects of a combination treatment with paricalcitol and cinacalcet in comparison with paricalcitol alone.

PATIENTS AND METHODS A total of 64 hemodialyzed patients (mean [SD] age, 58 [16] years) with inadequate control of serum parathyroid hormone levels were treated with intravenous paricalcitol, while 16 patients simultaneously received oral cinacalcet. Laboratory tests (intact parathormone [iPTH], calcium, phosphorus) were performed on a monthly basis. In the study, iPTH, calium, phosphorus, and alkaline phosphatase levels were assessed at baseline and after 24 weeks of treatment with paricalcitol alone or in combination with cinacalcet.

RESULTS In both groups, a significant decrease in the iPTH level was observed. Although paricalcitol affects calcium levels, no hypercalcemia was observed. The combination treatment did not result in a significant lowering of iPTH levels in comparison with paricalcitol alone.

CONCLUSIONS Treatment of SHPT with intravenous paricalcitol in patients on hemodialysis is effective and has a good safety profile. The combination of paricalcitol and cinacalcet does not improve the outcomes. Moreover, the combined treatment does not affect calcium and phosphorus concentrations. The cost-effectiveness of therapy should also be considered.

Correspondence to:
Prof. Jolanta Małyszko, MD, PhD, II Klinika Nefrologii z Oddziałem Leczenia Nadciśnienia Tętniczego i Pododdziałem Dializoterapii, Uniwersytet Medyczny w Białymstoku, M. Skłodowskiej-Curie 24A, 15-276 Białystok, Poland, phone: +48 85 8317872, email: jolmal@poczta.onet.pl
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INTRODUCTION With progressive renal impairment and worsening of renal excretory function, the disorders of calcium and phosphorus metabolism become more severe. The increasing reduction of glomerular filtration results in lower phosphate excretion and, consequently, hyperphosphatemia. Phosphorus anions bond serum calcium cations, which leads to a reduction of ionized calcium levels. At the same time, a sustained high phosphate level inhibits vitamin D_3 synthesis. The disorders of calcium and phosphorus metabolism, secondary hyperparathyroidism (SHPT), bone abnormalities, and vascular calcification in patients with chronic kidney disease (CKD) are the components of chronic kidney disease–mineral bone disorder (CKD-MBD).[1-3] This systemic disorder significantly contributes to the morbidity and mortality of patients with CKD.[4-6]

SHPT (intact parathyroid hormone [iPTH] level >300 pg/ml) is diagnosed in 30% to 49% of dialyzed patients in Europe and even in 54% of those in the United States and Canada).[7] The diagnosis

of SHPT is based on regular biochemical measurements of serum iPTH, calcium, phosphate, and alkaline phosphatase levels. Additionally, vitamin D concentrations can be measured. The criteria for diagnosing SHPT are primary hypocalcemia and elevated iPTH levels. Additionally, imaging studies may reveal parathyroid hyperplasia.

According to the latest Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, a limitation of dietary phosphate intake (ie, phosphate binders) is recommended in the treatment of hyperphosphatemia alone or in combination with other treatments in CKD stages 3A to 5D (dialysis) (level of evidence 2D meaning "we suggest"; very low grade).[8] Moreover, a restriction of the dose of calcium-based phosphate binders is also recommended (level of evidence 2B meaning "we suggest"; moderate grade). The KDIGO guidelines recommend calcimimetics, calcitriol, or vitamin D analogues, or a combination of calcimimetics with calcitriol or vitamin D analogues (level of evidence 2B) to lower iPTH levels in patients on dialysis.[8] In the case of weak or the lack of effects of pharmacological treatment, partial or total parathyroidectomy should be considered.

Data on the comparison of different treatments of SHPT are scarce and generally limited to studies on the effectiveness of different vitamin D analogues and vitamin D receptor analogues. As calcimimetics and vitamin D receptor analogues exert opposite effects on serum calcium levels, it might be reasonable from the clinical standpoint to assess the simultaneous administration of these 2 compounds on iPTH and serum calcium and phosphate levels. Considering all these data and the possibility of combining 2 drugs in a single therapeutic regimen, the aim of this study was to evaluate the effectiveness of treatment of SHPT in patients on hemodialysis who received either intravenous paricalcitol or a combination of intravenous paricalcitol and oral cinacalcet.

PATIENTS AND METHODS

A total of 64 hemodialyzed patients (mean [SD] age, 58 [16] years) with SHPT (iPTH >500 pg/ml) were treated with intravenous paricalcitol for 24 weeks. The mean (SD) dose of paricalcitol at baseline was 7.3 (3.3) μg/dialysis. The dose was modified on a monthly basis after laboratory checks. The mean (SD) dose of paricalcitol in weeks 20 to 24 of treatment was 6.0 (4.0) μg/dialysis. Sixteen patients simultaneously received oral cinacalcet at a mean (SD) dose of 0.6 (0.3) mg/kg bw/d. The cinacalcet dose was maintained during the study. Hyperphosphatemia was controlled with phosphate binders in 40% of the patients. Calcium-containing phosphate binders were used by 27 patients.

We evaluated changes in iPTH and alkaline phosphatase levels during the 24-week follow-up, as well as assessed the safety profile of both therapies, especially with regards to the effects on calcium and phosphorus metabolism. The baseline clinical and demographic characteristics of the study groups are shown in TABLE 1.

Statistical analysis The results were analyzed using the Statistica 13.0 computer software (Tulsa, Oklahoma, United States). Variables with normal distribution were assessed using the Shapiro–Wilk test. The analysis of variance (ANOVA), the Mann–Whitney rank sum test, or the *t* test was used to compare the differences between the groups. Normally distributed variables were reported as means and SD, and nonnormally distributed variables, as medians and quartiles. As these were real-life data gathered when the therapeutic program with paricalcitol became available, the power calculation was not performed. We collected all the available data possible. In patients treated with cinacalcet without significant lowering of iPTH levels, paricalcitol was added. In those without hypercalcemia, paricalcitol was introduced for SHPT treatment. A *P* value of less than 0.05 was considered significant. The intragroup comparisons were performed with the nonparametric Friedman's ANOVA by ranks and Wilcoxon single-rank tests.

RESULTS

We observed significant changes in iPTH levels in both study groups. Alkaline phosphatase activity decreased in both groups, but the change was not significant (TABLE 2). KDIGO targets (iPHT <300 pg/ml) were achieved during the 24-week treatment by 29 patients (45%). In all patients, the elevated serum level of total calcium was observed; however, only 1 patient had severe hypercalcemia (>17 mg/dl) (TABLE 3). None of the patients were excluded during the follow-up.

Treatment of SHPT with intravenous paricalcitol and with the combination of intravenous paricalcitol and cinacalcet was shown to be effective and safe. There were no differences in the efficacy and safety profile between the groups; however, the elevated serum phosphorus level in the combination-treatment group was observed (TABLE 3).

DISCUSSION

The efficacy and safety profile of intravenous paricalcitol in the treatment of SHPT has been documented in a number of clinical trials and observational studies. Several studies showed a significant reduction in iPTH levels and revealed an increase in serum calcium levels during treatment of SHPT with paricalcitol.[9-17] Izquerdo et al[11] and Fernstrom et al[14] reported a significant increase in serum calcium levels. However, other studies did not reveal significant changes for this parameter.[10,17,18]

As an effective antiparathyroid hormone agent, cinacalcet has been the subject of several studies.[18-21] Patients who received the selective vitamin D receptor activator paricalcitol while undergoing long-term hemodialysis showed a lower number of hospitalizations and hospital days per year and a significant survival benefit compared with those who received calcitriol.[9,10] They also had fewer episodes of hyperphosphatemia compared with patients receiving doxercalciferol,[11-13]

TABLE 1 Baseline clinical and demographic characteristics of the study groups.

Characteristics		All patients (n = 64)	Paricalcitol (n = 48)	Paricalcitol + cinacalcet (n = 16)	*P* value
Demographic and clinical data					
Age, y	Mean (SD)	58 (16)	61 (15)	48 (14)	0.001
Sex, %	Female	36	42	19	<0.001
	Male	54	58	81	<0.001
Duration of dialysis, mo	Median	50.5	46	53	0.3
	Quartile 1	30	15.25	38.75	
	Quartile 4	345	345	219	
Use of phosphate binders, %	Total	40	45	38	0.3
	Calcium-containing only	33	40	25	0.02
	Sevelamer only	0	0	0	NA
	Combination of calcium--containing and sevelamer	7	5	13	0.04
	Other	0	0	0	NA
Paricalcitol dose, µg/dialysis					
Initial dose	Median	6.15	6.15	5.8	0.3
	Quartile 1	5	5	4.9	
	Quartile 4	15	15	15	
Week 24	Median	5	4.6	9.2	0.3
	Quartile 1	3.5	3.1	5	
	Quartile 4	20	20	17.3	
Cinacalcet dose, mg/kg bw/d					
Initial dose	Mean (SD)	–	–	0.6 (0.3)	NA
Week 24	Mean (SD)	–	–	0.6 (0.3)	NA

Abbreviations: NA, not available

TABLE 2 Intact parathyroid hormone (iPTH) and alkaline phosphatase levels after 24-week treatment

	iPTH, pg/ml				Alkaline phosphatase, ng/ml			
	Baseline	Week 24	Percent change	*P* value	Baseline	Week 24	Percent change	*P* value
All patients (n = 64)								
Median	784.5	319.5	–55 (32)	0.001	116	80	–23 (26)	0.1
Quartile 1	640	170.25			83.25	66.5		
Quartile 4	2718	1843			2501	1397		
Paricalcitol (n = 48)								
Median	752.5	237.5	–59 (32)	0.001	113	79	–21 (24)	0.2
Quartile 1	632.5	148.25			83.25	64.75		
Quartile 4	2718	1843			1899	1397		
Paricalcitol + cinacalcet (n = 16)								
Median	949	418.5	–46 (34)	0.001	129	91	–25 (33)	0.2
Quartile 1	703.75	309.5			98	68		
Quartile 4	2224	1485			2501	1007		

as well as of hypercalcemia compared with patients receiving calcitriol.[14] As a result, paricalcitol has become the preferred vitamin D receptor activator for SHPT.

Cinacalcet, a calcimimetic agent, is also effective in reducing iPTH levels and has the additional effect of reducing calcium and phosphate levels. Beside the lowering iPTH effect, the hypocalcemic activity of cinacalcet was also reported.[19-21]

There are scarce comparative data for paricalcitol and cinacalcet. In the TARGET study,[22] which included 444 hemodialyzed patients with moderate to severe SHPT (mean serum biointact PTH level >160–430 pg/ml; iPTH, approximately 300–800 pg/ml or ng/l), cinacalcet was titrated (30–180 mg/d) during an 8-week dose--titration phase to achieve biointact PTH levels of 160 pg/ml or lower (iPTH, approximately 300 pg/ml or ng/l), and the efficacy was assessed over

TABLE 3 Serum calcium and phosphate levels after 24-week treatment in the study groups

Study groups	Serum calcium, mg/dl				Serum phosphate, mg/dl			
	Baseline	Week 24	Percent change	*P* value	Baseline	Week 24	Percent change	*P* value
All patients (n = 64)	8.7 (0.9)	9.7 (1.3)	12.2 (19.9)	0.001	5.4 (1.5)	6.1 (1.6)	20.1 (41.9)	0.003
Paricalcitol (n = 48)	8.7 (0.9)	9.6 (1.3)	10.9 (21.6)	0.001	5.3 (1.6)	5.9 (1.5)	–6.2 (28.7)	0.04
Paricalcitol + cinacalcet (n = 16)	8.6 (0.6)	10.0 (1.0)	16.3 (12.8)	0.001	5.6 (1.2)	7.0 (1.5)	27.1 (29.8)	0.004

Data are presented as mean (SD).

8 weeks. At week 2 of the study, participants receiving vitamin D sterols had the doses titrated to the equivalent of 2 μg of paricalcitol 3 times a week or 6 μg/wk. Block et al[22] concluded that the percentage of patients with the values of biointact PTH, of the calcium × phosphorus product, and of both biointact PTH and calcium × phosphorus product within the target range during the assessment phase did not differ between patients who received cinacalcet with vitamin D sterols and those who received cinacalcet alone. However, the authors did not assess the cost of this therapy.

In the FARO-2 study,[23] intravenous paricalcitol significantly increased the percentage of patients at target for the combined endpoint of iPTH, calcium, and phosphate ($P = 0.001$), whereas the groups receiving intravenous calcitriol and a combination of intravenous paricalcitol with cinacalcet were not analyzed owing to a small number of patients.

In a retrospective study, Schumock et al[24] compared the rates of parathyroidectomy in patients with SHPT treated with paricalcitol or cinacalcet. They found that a long-term treatment with paricalcitol was associated with fewer parathyroidectomies when compared with cinacalcet. It was unclear why patients who received cinacalcet were more likely to experience parathyroidectomy compared with those who received paricalcitol. The paricalcitol group appeared to be sicker, to have more comorbidities, and to have a shorter time from the start of hemodialysis to the start of the index drug treatment, while patients in the cinacalcet group were more likely to be female. Even when these and other risk factors were adjusted for in the final analysis, the risk of parathyroidectomy was substantially higher in the cinacalcet group.[24]

In the randomized IMPACT SHPT study,[25-27] paricalcitol was compared with cinacalcet in terms of the effect on a reduction in iPTH levels as well as changes in serum calcium and phosphorus levels, alkaline phosphatase activity, and fibroblast growth factor-23 concentrations. In the case of a reduction in iPTH levels, paricalcitol was more effective than cinacalcet during the 28-week follow-up. The mean reduction of iPTH concentrations was significantly greater in the case of paricalcitol, as was the percentage of patients who achieved iPTH levels ranging from 150 to 300 pg/ml.[25-27]

Both agents have a good safety profile and can be used successfully in the management of SHPT. An intravenous administration of paricalcitol seems to be preferable in hemodialyzed patients with vascular access. Cinacalcet as an oral formulation should only be recommended for patients with earlier stages of CKD and those with CKD stage 5 treated with peritoneal dialysis. Adding cinacalcet to the SHPT treatment protocol with intravenous paricalcitol can help reduce hypercalcemic activity of paricalcitol; however, we did not confirm this in our study. In addition, on the basis of dosing and effectiveness data from the IMPACT SHPT study, Sharma et al[28,29] found that a regimen with intravenous paricalcitol was more cost-effective than cinacalcet plus low-dose vitamin D in the management of iPTH levels in patients with SHPT requiring hemodialysis. Their results suggest that the paricalcitol-based regimen is more cost-effective than the cinacalcet one, and this may mean both improved outcomes for patients and reduced costs for health care providers and payers.

Chertow et al,[30] in an open-label 16-week clinical trial, assessed the effects of a combination of low-dose active vitamin D derivatives and cinacalcet on mineral metabolism in hemodialyzed patients with normal iPTH levels (80–160 pg/ml) but elevated calcium × phosphorus product (>55 mg^2/dl^2), who received paricalcitol at a dose of more than 6 μg/wk (or an equipotent dose of an alternative active vitamin D derivative). At the start of the study, active vitamin D derivatives were reduced to a mean equivalent dose of paricalcitol of 6 μg/wk, and cinacalcet was titrated from 30 mg/d to a maximum possible dose of 180 mg/d. The authors concluded that a combination of low-dose active vitamin D derivatives and cinacalcet improved control of mineral metabolism.

On the other hand, in a post-hoc analysis of the ADVANCE study,[31] progression of coronary artery calcification was compared between 70 protocol-adherent participants given cinacalcet and low doses of vitamin D, as specified in the study protocol, and 120 controls given vitamin D sterols. The study protocol stated specifically that the dose of vitamin D was not to exceed the amount equivalent to 6 μg/wk of intravenous paricalcitol among those receiving cinacalcet. Subjects assigned to the control group were treated with higher, varying doses of vitamin D sterols administered intravenously during

thrice-weekly hemodialysis procedures or orally every day. The authors found that the progression of coronary artery calcification was attenuated among cinacalcet-treated subjects with SHPT given low doses of vitamin D per protocol compared with controls in whom SHPT was treated with higher doses of vitamin D sterols alone after 52 weeks.

Our study has several limitations. First, the sample size was small, but in the FARO-2 study,[23] the combination-therapy group was also too small for the analysis. Intravenous paricalcitol, as well as the combination of 2 drugs, has not been available in dialysis units until recently. Nowadays, we have an opportunity to assess the effect of this therapy on clinical parameters and also on the costs of therapy. In our pilot study, we analyzed the results of a 3-month paricalcitol treatment of 36 hemodialyzed patients with SHPT (serum iPTH level >500 pg/ml), including 11 patients who additionally received cinacalcet. The results showed a significant reduction in iPTH and alkaline phosphatase levels in the whole group.[32]

The results of the EVOLVE trial were controversial.[33] The unadjusted primary composite endpoint showed a nonsignificant reduction (hazard ratio, 0.93; P 1/4 = 0.112) with cinacalcet use.[33] In a recent subanalysis of the EVOLVE trial,[34] blood calcification propensity was independently associated with the primary composite endpoint, all-cause mortality, myocardial infarction, peripheral vascular events, and improved risk prediction. However, due to a subsequent series of secondary and post hoc publications of the EVOLVE trial,[35-37] KDIGO decided not to prioritize any iPTH-lowering treatment at this time, because calcimimetics, calcitriol, or vitamin D analogues are all acceptable first-line options in patients with CKD stage 5D (dialyzed). In principle, this recommendation was supposed to be maintained as it was in the previous set of the KDIGO guidelines from 2009.[38] However, the optimal level of iPTH was not established.[8] Both ADVANCE[31] and EVOLVE[34] trials assessed the effects of cinacalcet on cardiovascular calcification and the risk of cardiovascular events and mortality, respectively. Although the primary analysis of both trials did not reveal significant effects of cinacalcet, the benefit of cinacalcet was suggested in the subanalyses which accounted for the potential limitations of the trials.

Our study was too short to allow the assessment of long-term cardiovascular risk in the studied population or the relationship between the therapy and cardiovascular events. Moreover, we did not study vitamin K levels reported to affect vascular calcifications in patients on hemodialysis[39] but not in nondialyzed patients.[40] As many healthy individuals[39] as well as dialyzed patients[41] are vitamin-D deficient, vitamin D should be supplemented first. As reported, correction of 25(OH)D deficiency in patients on hemodialysis was associated with better SHPT control with lower doses of vitamin D analogues.[42] In addition, the GC polymorphism was associated with plasma 25(OH)D levels in this population.[43] On the other hand, vitamin D pathway genes were not associated with survival probability of patients on renal replacement therapy.[44]

In our study, we investigated a real-life treatment of SHPT in hemodialysed patients on intravenous paricalcitol and the combination of intravenous paricalcitol and oral cinacalcet. We conclude that treatment of SHPT with intravenous paricalcitol in these patients is effective and has a good safety profile. The combination therapy of paricalcitol and cinacalcet does not improve the efficacy; however, the possibility effect of cinacalcet on reducing vascular calcification requires further studies. Also, the combined treatment does not affect calcium and phosphate concentrations. However, it is possible to combine cinacalcet and paricalcitol, especially in the case of hypocalcemia (the Polish National Health Fund also allows to combine the 2 therapeutic regimens), but the decision making should be guided primarily by the cost-effectiveness of therapy.

Contribution statement JZ contributed to study design, statistical analysis, data collection, data interpretation, and manuscript draft. JM contributed to study design, statistical analysis, data interpretation, manuscript draft, and the final revision of the manuscript. JSM contributed to data interpretation. WM collected the data. TP and TD-R approved the final version of the manuscript.

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