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BRIEF REPORT

Treatment with Calcimimetic (Cinacalcet) Alters Epoetin Dosage Requirements in Dialysis Patients: Preliminary Report

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Abstract

Background: Secondary hyperparathyroidism (SHPT), known complication of chronic renal failure, in addition to effects on bone and cardiovascular systems, is associated with reduced response to erythropoietin (EPO). Calcimimetics such as cinacalcet are the latest generation of drugs used in the treatment of SHPT. Few studies have evaluated the effect of cinacalcet on anemia associated with SHPT in dialysis patients, while no study has compared this cinacalcet effect with that of vitamin D analogs such as paricalcitol. *Patients and methods*: Using a retrospective chart-based review of dialysis patients' records to identify patients being treated with either cinacalcet or paricalcitol alone, matched for the same EPO treatment, which had been followed for 1 year, we have evaluated the effect of cinacalcet on anemia compared to that of paricalcitol. *Results*: Ten patient records were found that fit the criteria, five treated with cinacalcet (Group 1) and five treated with paricalcitol (Group 2), all treated with the same dose of darbepoetin. Darbepoetin dosage was the only parameter that significantly changed between groups, decreasing in Group 1 (−33%, $p = 0.009$) while remaining unchanged in Group 2. PTH-level reduction, which was significant versus baseline in both groups, although not statistically different between groups, was higher with cinacalcet. *Conclusion*: The combination of lower EPO dose in cinacalcet-treated patients compared with paricalcitol-treated patients, along with good SHPT control is a novel information and might have considerable benefits in dialysis patients not only preventing bone (fractures) and cardiovascular system (calcifications) damages but also in terms of cost savings via a reduction of EPO dosage.

Keywords: Cinacalcet, hyperparathyroidism, erythropoietin, dialysis

INTRODUCTION

Secondary hyperparathyroidism (SHPT) is a known complication of chronic renal failure (CRF) that presents as parathyroid hyperplasia accompanied by an increased synthesis and secretion of parathyroid hormone (PTH). The main factors triggering SHPT are CRF-related deficiency of 1,25-vitamin D, hyperphosphoremia, and hypocalcemia.[1]

Until recently, SHPT treatment was based on the use of the active metabolites of vitamin D along with calcium-based phosphate binders.[2] This treatment however leads to an increased calcium balance with a negative impact on cardiovascular risk[3,4] leading to suggestions that dialysis patients require more intensive control of not only PTH and phosphate but calcium levels as well.[5] Moreover, SHPT, in addition to its known effects on the bone and cardiovascular system, is associated with a reduced response to erythropoietin (EPO).[6] This lack of response is the result of increased red blood cell fragility,[7] direct inhibitory effects of PTH on EPO synthesis and erythroid progenitors, and indirectly through bone marrow fibrosis.[8,9]

Calcimimetics (cinacalcet), the latest generation of drugs in this field although highly efficient on PTH suppression,[10] has few evaluations as to its effect on anemia associated with SHPT in dialysis patients; in particular, no study has compared in dialysis patients the effect of cinacalcet on anemia associated with SHPT with that of the traditional treatment with vitamin D

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analogs such as paricalcitol. This study was undertaken to evaluate, in a pilot fashion, the effects on anemia in dialysis patients undergoing treatment for SHPT who were treated with cinacalcet as compared to matched patients treated with vitamin D analog (paricalcitol). To approach this question, a retrospective chart-based review of dialysis patients' records was done to identify those being treated with either cinacalcet or paricalcitol alone, matched for the same EPO treatment using the same kind of EPO and who had been followed for 1 year.

PATIENTS AND METHODS

Patient records from the Division of Nephrology at the University Hospital of Padova, which draws from a predominantly northern Italian urban population, were examined to identity suitable patients. Inclusion criteria included patients of either gender with chronic dialysis treatment exceeding 1 year, a diagnosis of and treatment for SHPT with either cinacalcet or paricalcitol along with the same EPO-based treatment using the same type of EPO, who have been followed for 1 or more years with well-documented clinical and biochemical data. Exclusion criteria included diabetes, chronic obstructive pulmonary diseases, heart failure, cancer, and hospitalizations.

The study was approved by our institutional authorities and informed consent was obtained by all the study participants.

STATISTICAL ANALYSIS

The qualifying records were analyzed with final stratification of the patients into the two comparison groups being based on the use of either cinacalcet or paracalcitritrol. The results for the quantitative variables are summarized as mean ± SD. Within-group comparisons were conducted using a repeated measures ANOVA and the between-group comparisons were done using ANOVA. A p-value less than 0.05 was considered significant.

RESULTS

Ten patient records were found that fit the criteria, three females and seven males, mean age 65.9 ± 14.11 years, undergoing chronic bicarbonate dialysis treatment, 210–240 min, three times a week. Five patients were being treated with cinacalcet (two females and three males, Group 1) and five were being treated with paricalcitol (four males and one female, Group 2).

The etiopathology of the CRF was nephroangiosclerosis for six patients, primary glomerulonephritis for two, obstructive nephropathy for one, and unknown for one.

All patients were being treated with darbepoetin α, whose average weekly dose at baseline was 70 ± 26 μg in Group 1 and 68 ± 10 μg in Group 2 with no difference between groups, and phosphate binders. Patients' blood pressure ranged from 134/84 to 154/92 mmHg and anti-hypertensive treatment included calcium channel blockers, ACE inhibitors, and α-blockers. The patients' general biochemical characteristics, which did not differ by patient group are presented in Table 1.

The weekly dosage for cinacalcet was 212.6 ± 60 mg, and for paricalcitol 15 ± 5 μg. Both dosages remained essentially unchanged with only minimal adjustments throughout the year of follow-up treatment. Treatment with phosphate binders was comparable between the two groups: standard mean weekly therapy of: $CaCO_3$ 12.6 ± 3.13 g—Sevelamer 34,200 ± 13,458 mg in Group 1; $CaCO_3$ 15.87 ± 3 g—Sevelamer 33,600 ± 14,093 mg in Group 2. These also remained essentially unchanged throughout the year of follow-up treatment.

Over the course of the study, EPO dosage was adjusted to maintain hemoglobin between 11 and 12 g/dL. There were no significant differences between groups in terms of Kt/V values throughout the study (mean Kt/V ratio at the beginning of the study was 1.32 ± 0.23 (Group 1) and 1.36 ± 0.22 (Group 2)). As shown in Table 1, PTH levels were reduced after 1 year of treatment compared to baseline in both groups (621.6 ± 132 vs. 405 ± 50 pg/mL, $p = 0.005$, for the patients treated with cinacalcet; and 590 ± 165.4 vs. 478 ± 81.3 pg/mL, $p = 0.048$, for those treated with paricalcitol) and, although they did not change between groups over the course of the treatments, PTH-level reduction was higher with cinacalcet. Moreover, albumin, CRP, and ferritin as markers for malnutrition and inflammation, respectively, did not differ at baseline and throughout the study (data not shown).

Of the parameters assessed throughout the course of the treatment, only EPO dosage exhibited a statistically significant treatment-related change between groups. Weekly Darbepoetin dosage at baseline, in fact, did not differ between the groups (70 ± 26 vs. 68 ± 10 μg, respectively, and then, as noted in Table 1, significantly decreased in Group 1 to 48 ± 24 μg (−33.14%, $p = 0.009$ vs. baseline) while in Group 2 Darbepoetin dose remained unchanged (68 ± 10 μg vs. 65 ± 16 μg, −5.04%, $p =$ ns vs. baseline).

The reduction of Darbepoetin dosage in Group 1 significantly differed compared with Group 2 (−33.14 ± 16.1 vs. −5.04 ± 9.84, $p = 0.01$).

DISCUSSION

A recent open multicenter study was conducted on hemodialyzed patients with SHPT who were randomized to receive conventional therapy (184 patients) or cinacalcet (368 patients): in addition to the expected greater reduction of PTH in patients taking cinacalcet in comparison with those on conventional therapy (77% vs. 22%), the most important finding was that

Table 1. Biochemical markers of hemodialysis patients at baseline and after 1 year of follow-up.

Parameters	Group 1			Group 2		
	Baseline	After 1 year of follow-up		Baseline	After 1 year of follow-up	
Ca (mg/dL)	9.01 ± 0.73	8.55 ± 0.70	ns	9.11 ± 0.80	9.01 ± 0.80	ns
P (mg/dL)	5.8 ± 1.82	4.94 ± 1.99	ns	5.9 ± 1.79	5.12 ± 1.22	ns
PTH (pg/mL)	605 ± 150	405.11 ± 50[a]	$p = 0.005$	590 ± 165	478 ± 81[a]	$p = 0.048$
Hb (g/dL)	11.24 ± 1.31	12 ± 1.19	ns	11.04 ± 1.39	11.59 ± 1.38	ns
Ht (%)	34.68 ± 3.82	36.19 ± 2.05	ns	34.35 ± 4.45	35.5 ± 2.12	ns
Darboepoetin (μg)	70 ± 26	48 ± 24[a]	$p = 0.009$	68 ± 10	65 ± 16	ns
Reduction of Darbo dose (%)		-33.14 ± 16.1[b]	$p = 0.01$		-5.04 ± 9.84	

Note: [a]versus baseline.
[b]Group 1 versus Group 2.

patients who had failed to respond to conventional therapy achieved the K/DOQI targets on cinacalcet.[10]

The use of calcimimetics is usually combined with vitamin D treatment except in the case of hypercalcemic patients with high PTH levels, who can use calcimimetics alone.[11–14] Paricalcitol was the first vitamin D analog to be approved for the treatment of SHPT.

Brancaccio and coworkers[15] reviewed the mechanisms linking elevated PTH level to anemia in patients with CRF. These mechanisms may involve a direct toxic effect of PTH on the synthesis of endogenous EPO[16] and on the production and survival of red blood cells through a direct toxic effect on the erythroid progenitors.[17–19] In addition, the effect of PTH on anemia may be indirectly through the induction of an osteitis fibrosa that leads to the substitution of the erythron elements with fibrotic tissue.[20] Rao et al.[21] demonstrated a link between the extent of fibrosis and the dose of EPO needed to maintain adequate hematocrit levels in a population of 18 patients on hemodialysis. The role of PTH in the noted negative effects on hematopiesis has also been suggested by the rise in hemoglobin levels upon parathyroidectomy in patients on dialysis.[22,23] More recent studies have confirmed the role of PTH as a risk factor of resistance to EPO therapy[24,25] and SHPT as one of the main conditions responsible for poor responsiveness to EPO.[6] However, to the best of our knowledge, very few studies have been published documenting the effect of SHPT management on hematopoesis comparing the latest-generation medications (cinacalcet) and vitamin D analogs such as paricalcitol. One study by Viana and coworkers,[26] in 2007, retrospectively investigated the influence of cinacalcet use on the anemia in 28 patients on hemodialysis and found a statistically significant increment in these patient's hemoglobin levels after 9 months of treatment with no adjustments made in the EPO dose. Torres et al.[27] have sought to document the effectiveness of cinacalcet but did not compare it to Vitamin D analogs such as paricalcitol. Conversely, Matias and coworkers[28] have shown that the addition of cholecalciferol treatment to SHPT therapy in CRF patients using paracalcitol, sevelamer, and darbepoetin reduced darbepoetin use with no changes in hemoglobin levels.

Our study showed that treatment of SHPT with cinacalcet in dialysis patients produced a decline in the dosage of darbepoetin compared to no change in the dosage of darbepoetin in dialysis patients treated for SHPT with paracalcitol. The lack of change in EPO upon treatment with paracalcitol differs in the current study from that reported by Capuano and coworkers[29] who reported in 12 SHPT dialysis patients that paracalcitol resulted in decreased EPO doses, but, again, they did not compared paricalcitol to cinacalcet. In addition and contrary to the study of Capuano et al., in our study no increase in serum calcium level was observed both in the patients treated with paricalcitol and in those treated with cinacalcet. Increased serum calcium level upon paricalcitol treatment had been, in fact, considered by Capuano et al. as independent additional factor to the reduction of PTH for ameliorating erythropoiesis, therefore determining the reduced dose of EPO upon paricalcitol treatment they observed.[29]

The other risk factors potentially implicated in a hyporesponsiveness to EPO were not altered in our study as there were no changes in iron status (ferritin), inflammation (PCR), malnutrition (albumin), or inadequate dialysis (Kt/V).

In conclusion, the current study found that using cinacalcet in the treatment of SHPT in dialysis patients resulted in a lower EPO dose needed along with good SHPT control in those treated with this calcimimetic. This finding is novel information regarding the behavior of cinacalcet with respect to EPO resistance. The combination of better SHPT control with reduced required EPO dosage offered by cinacalcet might have considerable benefits in dialysis patients in terms not only of preventing damage to bones (fractures) and the vascular system (calcifications) but also in terms of cost savings; thanks to a reduction of the dosage of EPO needed. All this suggests that these preliminary results coming from a retrospective chart-based review evaluation of a small number of patients should serve as a useful working hypothesis for further studies with a larger number of patients enrolled from different dialysis

units as well as for extended study duration to allow the benefit of SHPT treatment with cinacalcet on erythropoiesis and reduction of EPO dosage in dialysis patients to be conclusively demonstrated.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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