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Achieving K/DOQI targets with Cinacalcet in dialysis patients with secondary hyperparathyroidism – A Portuguese observational study

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ABSTRACT

Secondary hyperparathyroidism is a common complication of chronic kidney disease. The elevated serum intact parathyroid hormone, phosphorus, calcium and calcium x phosphorus product have been independently associated with an increased relative risk of mortality. The standard therapy for secondary hyperparathyroidism, including active vitamin D analogues and phosphate binders, is often insufficient to allow patients to achieve the recommended Kidney Disease Outcomes Quality Initiative targets for bone and mineral metabolism. Randomised controlled phase III clinical studies in chronic kidney disease patients with secondary hyperparathyroidism have shown that cinacalcet treatment increases the proportion of patients achieving the recommended Kidney Disease Outcomes Quality Initiative targets for intact parathyroid hormone, phosphorus, calcium and calcium x phosphorus product.

Aims: This observational multicentre study aims to evaluate cinacalcet's ability to achieve and maintain Kidney Disease Outcomes Quality Initiative targets in a population with secondary hyperparathyroidism on chronic haemodialysis in Portugal.

Patients and Methods: Patients on chronic dialysis that received cinacalcet during a free sampling programme were enrolled. Retrospective and prospective monthly data were collected from 3 months before until 6 months after the beginning of cinacalcet treatment. Additional assessment included a 12 month evaluation of all parameters.

Results: 140 dialysis patients with secondary hyperparathyroidism were enrolled, 60% male, mean age 57.4±14.1 years. The mean intact parathyroid hormone, calcium, phosphorus, and calcium x phosphorus product values at baseline were 751.7±498.8

pg/ml, 9.7±3.8 mg/dl, 5.5±1.5 mg/dl, and 52.7±25.3 mg^2/dl^2, respectively.

After 6 months' cinacalcet treatment, 26.2%, 53.6%, 59.3%, and 81.0% of the patients achieved the Kidney Disease Outcomes Quality Initiative recommended levels for intact parathyroid hormone, calcium, phosphorus, and calcium x phosphorus product, respectively. The mean dose of cinacalcet at 6 months was 57.1±29.7 mg/day.

Conclusions: The use of cinacalcet in clinical practice is an effective option for the treatment of secondary hyperparathyroidism in chronic dialysis patients, allowing more patients to reach and maintain the Kidney Disease Outcomes Quality Initiative targets.

Key-Words:
Biochemical parameters; calcimimetics; cinacalcet; dialysis; Kidney Disease Outcomes Quality Initiative (K/DOQI); secondary hyperparathyroidism.

INTRODUCTION

Secondary hyperparathyroidism (SHPT) is common in chronic kidney disease (CKD) patients receiving haemodialysis[1]. According to previous studies and the Dialysis Outcomes and Practice Patterns Study (DOPPS), the estimated proportion of haemodialysis patients with SHPT, defined by intact parathyroid hormone (iPTH) levels higher than 300 pg/mL, ranges from 30-50%[2,3]. A majority of untreated CKD patients will develop SHPT as a result of the kidney's inability to maintain mineral homeostasis. SHPT is characterised by persistently elevated levels of parathyroid hormone (PTH) and progressive parathyroid gland hyperplasia. Parathyroid glands are responsible for maintaining calcium homeostasis through PTH action. PTH increases the release of calcium from bone and stimulates the synthesis of calcitriol, increasing calcium absorption from the gastrointestinal tract[4].

The elevated serum PTH, phosphorus (P), calcium (Ca) and calcium x phosphorus product (CaxP) associated with SHPT has been independently associated with an increase relative risk of mortality. The standard therapy for SHPT, including active vitamin D analogues and phosphate binders, is often insufficient to allow patients to achieve the recommended Kidney Disease Outcomes Quality Initiative (K/DOQI) targets for bone and mineral metabolism[5]. Randomised controlled phase III clinical studies in CKD individuals with SHPT, have shown that the use of the calcimimetic agent, cinacalcet, increases the proportion of patients achieving the recommended K/DOQI targets for iPTH, P, Ca and CaxP[6-9]. This situation usually becomes more severe as kidney function declines. Also, these alterations in bone and mineral metabolism have been associated with vascular calcification, cardiovascular disease and increased mortality risk[10-16].

The interaction between these factors is complex, and effective control of SHPT is often difficult to achieve[8,9,11,17].

Various treatment strategies are currently recommended to correct mineral metabolism and bone disease in patients with CKD[17]. Standard therapy for SHPT includes optimisation of dialysis, calcium supplementation, dietary phosphorus restriction, use of phosphate binders, and treatment with vitamin D sterols[2,17]. Until the availability of calcimimetics, surgical parathyroidectomy was usually the unique alternative to control severe SHTP.

Vitamin D sterols treatment has major direct or indirect effects on serum levels of PTH, calcium and phosphorus, and its use is frequently limited by the hypercalcaemia and hyperphosphataemia associated with this therapy[17,18]. The K/DOQI guidelines highlight the importance of controlling these levels, namely in dialysis patients with SHPT[5].

Despite the use of new medications, a significant proportion of patients routinely receiving dialysis have high plasma PTH levels, marked hypercalcaemia and hyperphosphataemia[2,17]. Attempts have been made to develop pharmacological compounds able to control the iPTH secretion without increasing Ca and P levels in these patients[7]. Cinacalcet represents a possible alternative or adjuvant to vitamin D sterols treatment[6-9]. Cinacalcet increases the sensitivity of the calcium-sensing receptor to extracellular ionised calcium, inhibits the release of PTH, lowering its levels within a few hours of administration and reduces serum calcium and phosphorus levels. This mechanism of action differs fundamentally from that

of vitamin D sterols, which diminish the transcription of the PTH gene and hormone synthesis over a period of several hours or days.

This study's main objective was to evaluate cinacalcet's ability in daily clinical practice to achieve and maintain K/DOQI targets (iPTH, Ca, P, and CaxP) in CKD stage 5 patients on chronic dialysis in Portugal, over a period of 6 months after the start of treatment.

PATIENTS AND METHODS

Study design

An observational multicentre study was conducted in 9 dialysis units in Portugal. CKD stage 5 patients on chronic dialysis receiving cinacalcet at their nephrologist's discretion were enrolled. Retrospective and prospective monthly data on patients' demographics, laboratory parameters, cinacalcet dose and frequency and other concomitant medication were collected from 3 months before until 6 months after cinacalcet treatment. Additional assessment included a 12 months evaluation of all parameters.

No other clinical visits, laboratory or diagnostic tests, other than those regularly scheduled and associated with usual normal practice were required as part of this study.

Study endpoints

The primary endpoint was the proportion of patients with iPTH>150 and <300 pg/ml, CaxP<55 mg^2/dl^2, Ca≥8.4 and <9.5 mg/dl, and P<5.5 pg/ml, 6 months after the beginning of cinacalcet treatment.

Secondary endpoints included the proportion of patients who maintained K/DOQI recommended targets at the end of the 12 month study period, and the influence of baseline characteristics such as PTH, gender, age, time on dialysis on the response to cinacalcet treatment. The effect of cinacalcet treatment on concomitant medications, namely Vitamin D and phosphate binders was also evaluated.

Statistical analysis

The statistical analysis included the description of patients' demographics and clinical characteristics considering absolute and relative frequencies for categorical variables, and mean±standard deviation (SD), and range for continuous variables.

Mean values for iPTH, Ca, P, and CaxP were calculated. Primary endpoint, meaning the proportion of patients who achieved each K/DOQI recommended targets at 6 months, and 95% confidence intervals was calculated. These analyses were also performed for the 12 month evaluation in order to assess the secondary endpoints. McNemar's test was used to compare the 6 and 12 month results.

The independent influence of age, gender and clinical variables on treatment efficacy was assessed using the chi-square test for age, and the independent sample t-test for the others, for comparisons between patients who achieved K/DOQI recommended targets and those who did not.

The over-time changes in iPTH, Ca, P, and CaxP values after cinacalcet treatment were calculated for all patients as an additional exploratory analysis.

All p-values were two-sided and those ≤0.05 were considered to indicate statistical significance. Statistical analysis was performed using SPSS software version 15.0.

Last observation was carried forward for primary endpoint variables missing data.

RESULTS

Patients

A total of 140 patients, 60.0% male, mean age 57.4±14.1 years were enrolled in the study. Fifteen percent were diabetic (19 patients), and 2.1% had undergone parathyroidectomy (3 patients). At enrolment, 47.9% of the patients were receiving intravenous calcitriol (67 patients), 42.9% oral calcitriol (60 patients), 55.7% calcium-containing phosphate binding agents (78 patients), and 81.4% sevelamer (114 patients). Mean previous time on dialysis was 4.7±4.3 years.

Table I

Evolution of the biochemical parameters evaluated during the study period

Laboratory values	-3 months	Baseline	6 months	12 months
iPTH (pg/ml)	739.1±494.6	751.7±498.8	455.3±397.3 p < 0.001	370.7±303.7 p < 0.001
Ca (mg/dl)	9.7±3.3	9.7±3.8	8.9±1.1 p = 0.021	8.7±1.2 p = 0.017
P (mg/dl)	5.5±1.5	5.5±1.5	5.0±1.3 p = 0.001	5.0±1.5 p = 0.011
Ca x P (mg^2/dl^2)	53.5±20.2	52.7±25.3	44.0±12.3 p = 0.002	43.5±14.9 p = 0.03

Laboratory values before, at baseline, and after cinacalcet treatment are given in Table I.

The mean iPTH, Ca, P, and CaxP values at baseline were 751.7±498.8 pg/ml, 9.7±3.8 mg/dl, 5.5±1.5 mg/dl, and 52.7±25.3 mg^2/dl^2, respectively.

After cinacalcet, the decreases in iPTH, Ca, P, and CaxP values were statistically significant (p<0.001) until the 4th month, when comparing each month to the month immediately prior. After that the values did not change significantly.

After 6 months of cinacalcet treatment, 26.1%, 53.6%, 59.3%, and 81.0% of the patients achieved the K/DOQI recommended levels for iPTH (150-300 pg/ml), Ca (8.4-9.5 mg/dl), P (3.5-5.5 mg/ml), and CaxP (<55 mg^2/dl^2).

At 12 months, these percentages were 39.5%, 47.0%, 65.0%, and 77.2%, respectively.

The differences between baseline, 6 and 12 month evaluations were statistically significant for iPTH (p<0.001), Ca (p<0.001), and CaxP (p=0.0184). No statistically significant differences were observed between P levels (p=0.320). Evolution of iPTH median values is presented in Figure 1.

Neither gender, age nor time on dialysis, had a significant influence on treatment response.

The group of patients that did not achieve K/DOQI iPTH targets had a statistically higher mean baseline iPTH value (749.6±410 *vs.* 557.8±223.1; p=0.018).

The mean cinacalcet dose at 6 months was significantly higher for patients who did not achieve K/DOQI iPTH targets at 12 months (61.4±25.1 *vs.* 48.4±23.6 mg/day; p=0.014).

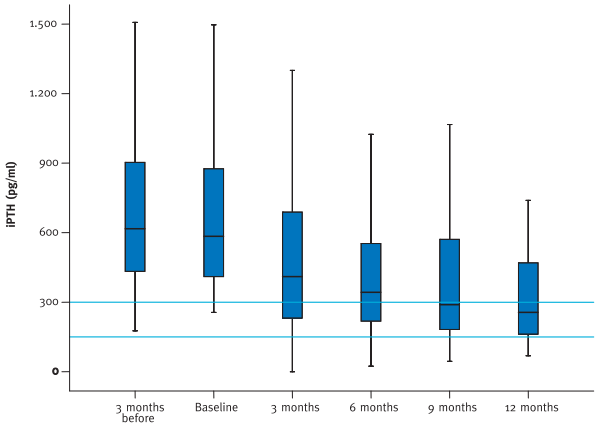

Figure 1

Evolution of the plasma iPTH median levels during the study. Median value (quartiles). The blue lines represent the recommended KDOQI range for iPTH.

At 6 and 12 months the percentage of patients with iPTH value inferior to 150 pg/mL was 13.9% and 16.7%, respectively.

The mean daily doses of cinacalcet were 30 mg/day at baseline and 57.1±29.7 and 62.6±26.5 mg/day at 6 and 12 months of treatment, respectively. Mean variations in daily doses between periods were statistically significant (baseline *vs.* 6 months and baseline *vs.* 12 months; p<0.001).

Concomitant medication

At baseline, mean intravenous and oral calcitriol doses were 3.6±1.6 and 2.0±1.4 µg/week, respectively., Mean baseline doses of calcium-containing phosphate binders and sevelamer were 2.6±1.6 g/day and 4932.0±2169.3 mg/day, respectively. At the 12th month, mean intravenous (IV) and oral calcitriol doses were 3.0±1.4 and 1.3±0.8 µg/week, respectively. The mean doses at the 12th month of calcium-containing phosphate binders and sevelamer were 3.7±2.2 g/day and 4211.6±2148.6 mg/day respectively.

Neither the vitamin D sterols nor sevelamer average doses significantly changed throughout the 12

month treatment period. Mean dose of calcium-containing phosphate binder significantly increased during the study (baseline *vs*. 6 months, p=0.01; baseline *vs*. 12 months, p=0.03).

Safety analysis

Vomiting (15 patients), epigastralgia (10 patients), and respiratory infection (9 patients) were the most common side effects.

Twenty hospitalisations were registered during the study (mean hospitalisation period of 12.5±16.7 days), none of those considered drug-related.

DISCUSSION

The results of this study suggest that in regular clinical practice cinacalcet consistently reduces iPTH levels in patients with SHPT on dialysis. This result is observed without increasing Ca, P or CaxP, allowing the percentage of patients achieving the K/DOQI recommended targets to increase. Other studies have reported similar results in consistently achieving the K/DOQI recommendations for iPTH, namely through comparisons with vitamin D therapy, Ca, P and CaxP product[6-9].

According to the literature, iPTH above the maximum K/DOQI recommended level is associated with increased mortality risk[11]. At baseline, all enrolled patients had elevated iPTH levels despite the use of vitamin D sterols and phosphate binders, representing a group of patients that poorly responded to conventional therapy. With cinacalcet, the number of patients in that situation was rapidly and significantly reduced, and this response was sustained along the study. In fact, a large percentage of patients had iPTH levels ‹300 pg/ml, after 6 and 12 months of cinacalcet administration. This iPTH level has been associated with relatively normal bone turnover[3,5,19,20] and is consistent with the K/DOQI guidelines[5].

The use of vitamin D analogues, particularly in combination with calcium-containing phosphate binders, may suppress iPTH concentrations, but can often cause hypercalcaemia and hyperphosphataemia by increasing intestinal absorption of calcium and phosphorus. These limitations frequently lead to undertreatment of the disease, discontinuation of therapy, and further progression of SHPT[17,18,21].

In our study, the cinacalcet-induced reduction in iPTH was accompanied by decreases in serum Ca, P, and CaxP levels. After six months of treatment with cinacalcet, 69%, 63.6% and 61.8% of the patients experienced reduction in Ca, P, and CaxP product levels, respectively, demonstrating cinacalcet's ability to control iPTH without increasing serum calcium and phosphorus concentrations. These results hold particular interest since increases in serum phosphorus and CaxP concentrations in patients with CKD have been associated with adverse cardiovascular outcomes and high mortality rates[10-12,22].

Aiming at determining the influence of baseline characteristics on treatment outcomes, patients who achieved iPTH targets and those who did not were compared. Baseline iPTH was significantly higher in patients who did not achieve target recommendations, which leads to the conclusion that disease severity is a relevant factor in achieving iPTH target levels, highlighting the need to start the treatment early. This observation conforms with previous reports of larger populations treated with cinacalcet during the initial phase III trials[8,23]. No other differences were observed in demographics or in clinical variables.

The correct control of iPTH levels assumes a major importance to avoid two extreme situations; on the one hand the risk of undertreatment, and on the other the oversuppression of PTH with the consequent development of adynamic bone disease.

Cinacalcet generally had a good safety profile and, as reported by other studies, minor gastrointestinal symptoms were the most frequent adverse events[8,9,13,24].

CONCLUSIONS

Cinacalcet is an effective option for reducing iPTH levels with the beneficial effect of decreasing calcium, phosphorus and calcium x phosphorus product. The incidence of hypercalcaemia or hyperphosphataemia,

which currently complicate secondary hyperparathyroidism and its conventional management, is decreased. Cinacalcet used either with phosphate binders alone or in combination with vitamin D sterols and phosphate binders increases the possibility of SHPT patients on dialysis achieving and maintaining the K/DOQI treatment targets.

Conflict of interest statement. João M. Frazão receives consultancy fees from Amgen and Genzyme and participates in advisory board activities for Amgen and Genzyme.

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