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Journal of Parathyroid Disease

Journal of Parathyroid Disease 2018,6(2),80–86
DOI: 10.15171/jpd.2018.26

Original

Cinacalcet therapy for achievement of the NKF/K-DOQI™ clinical practice guidelines for bone and mineral metabolism in individuals under regular hemodialysis

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Abstract

Introduction: Cinacalcet (CNL) suppresses the secretion of parathyroid hormone (PTH).

Objective: To consider the effect of CNL administration on achievement of K/DOQI™ (Kidney Disease Outcomes Quality Initiative) targets in a group of hemodialysis (HD) patients with secondary hyperparathyroidism (SHPT).

Patients and Methods: Patients undergoing HD who had initiated CNL enrolled in the study. Data were collected at the baseline and after 12 months. This data consisted of serum calcium (Ca), phosphorus (P), intact PTH (iPTH), proportion of calcium in dialysate, administered doses of CNL and proportion of administered phosphate binders and proportion of patients attaining K/DOQI™ targets were gathered.

Results: Twenty HD patients enrolled in the study. The proportions of individuals attaining K/DOQI™ targets at month 12 were 35% for iPTH, 65% for P, 60% for Ca and 80% for Ca×P product, compared with 0%, 45%, 55% and 50% at the baseline respectively. Around 35% of individuals had attained the combined K/DOQI™ targets for Ca, P and iPTH compared with 0% at the starting point.

Conclusion: CNL ameliorates attainment of K/DOQI™ targets in individuals with SHPT. This result is consistent with findings from other studies.

Keywords: Calcimimetic, Parathyroid hormone, Bone metabolism, Secondary hyperparathyroidism, Parathormone, hypercalcemia, hyperphosphatemia

Please cite this paper as: Aatif T, El Esper N, Moriniere PH, Choukroun G, Fournier A. Cinacalcet therapy for achievement of the NKF/K-DOQI TM clinical practice guidelines for bone and mineral metabolism in individuals under regular hemodialysis. J Parathyr Dis. 2018;6(2):80-86. doi: 10.15171/jpd.2018.26.

Introduction

Secondary hyperparathyroidism (SHPT) is a common complication of end-stage renal disease (ESRD). Uremic individuals with SHPT exhibit persistently raised parathyroid hormone (PTH) levels, which can deleteriously influence the functionality of multiple organs (1). Heart and vessels complications may also happen (2). These implications are accompanied by an increase in mortality and morbidity (3,4). To ameliorate care of dialysis individuals, the National Kidney Foundation's Kidney Diseases Outcomes Quality Initiative (NKF-K/DOQI™) advocates targets for serum intact PTH (iPTH) (150–300 ρg/mL), total corrected serum calcium (Ca) (8.4-9.5 mg/dL), serum phosphorus (P) (3.5-5.5 mg/dL), and the calcium phosphorus product (Ca×P product) (<55 mg^2/dL^2) (5). The reaching of the suggested targets is powerfully predictive of survival (6). However, only a small proportion of dialysis individuals with SHPT receiving regular treatments (Ca salts, vitamin D sterols and phosphate binders) reach and maintain control of these targets (7). Additionally, Ca salts and vitamin D sterol treatment can increase Ca and/or P levels, causing hypercalcemia and/or hyperphosphatemia, respectively. Ca salts and vitamin D sterol treatment may also increase the risk of cardiovascular and soft tissue calcifications. The calcifications of soft tissues necessitate interruption of these drugs which, potentially allowing disease progression too (8,9).

The Ca-sensing receptor regulates the secretion of PTH. Calcimimetic agents increase the sensitivity of the Ca receptors of parathyroid cells to extracellular Ca ions, to inhibit the release of PTH, and to decrease PTH levels within a few hours after administration (10,11). This mechanism of action differs fundamentally from that of vitamin D, which decreases the transcription of the PTH gene and hormone synthesis over a period of many hours

Received: 8 August 2017, Accepted: 2 November 2017, ePublished: 23 November 2017

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Implication for health policy/practice/research/medical education

Treatment with cinacalcet offers marked amendments in biochemical parameters, helping renal failure patients to achieve K/DOQI™ (kidney disease outcomes quality initiative) targets for serum levels of iPTH, Ca, Ca×P product and P.

or several days (12). Results of previous studies indicate that cinacalcet (CNL) ameliorates patients' likelihood of attaining the recommended K/DOQI™ targets for bone and mineral disorders (BMD). Therapy with CNL has also detected to provide more constant control of iPTH and Ca×P product at an appropriate value (7,13).

Objective

The aim was to test the effect of CNL administration on to reach of K/DOQI™ targets, in hemodialysis (HD) patients with SHPT.

Patients and Methods

Study design

This was a retrospective observational single centre study. Patients were included between November 2006 and October 2009. History of previous disease, comorbidities, concurrent drug therapies and laboratory parameters were gathered. The variables collected were, primary etiology of ESRD, age at enrolment, gender, medical history and HD opening time, dialysis method and proportion of HD per week at admission, probable history of renal transplantation and parathyroidectomy. Additionally we considered serum iPTH, P, Ca and Ca × P product and albumin plasma levels. Accordingly, P-binder and vitamin D administration and also dialysate Ca concentration was envisaged.

The criteria for administration of CNL are SHPT (iPTH >300 ρg/mL) with difficulty to use vitamin D either because of hypercalcemia and/or hyperphosphatemia. The exclusion criterion is serum Ca below 8.4 mg/dL. All HD individuals with these criteria were included to the investigation. The study period was 12 months after initiation of CNL. The quantity of individuals reaching K/DOQI™ targets for iPTH, P, Ca and Ca × P product calculated at beginning, at six months and at the end of 12 months interval after introduction of CNL.

Patients

HD patients in medically stable condition who had been prescribed CNL for SHPT were included. All patients had 18 years of age at least and had been treated with regular thrice-weekly HD for at least 6 months, using 1.4-2.1 m^2 synthetic dialyzers. All patients were under a stable HD schedule and alike regimen of dialysis in all study period.

Objectives, quality standards and K/DOQI™ recommendations

From 2003, the objectives of K/DOQI™ recommendations were to keep iPTH (Guideline 1.4) levels between 150 and 300 ρg/mL. Serum Ca levels to be between 8.4 and 9.5 mg/dL (Guideline 6.2) and they recommended serum P levels (Guideline 3.2), to be between 3.5 and 5.5 mg/dL and Ca×P product (Guideline 6.5) below than 55 mg^2/dL^2. Accordingly guidelines seven and eight recommend that vitamin D metabolites must be decreased or withdrawn when serum Ca levels are more than 10.2 mg/dL, or serum P levels are more than 5.5 mg/dL, and when Ca×P product is more than 55 mg^2/dl^2, or also when iPTH levels are decreased below than 150 ρg/mL. Additionally, guideline five recommends that total administered dose of elemental Ca offered by Ca-based phosphate binders should not more than 1500 mg/d and thus non-Ca-containing phosphate binders are selected in HD individuals with soft-tissue or vascular calcifications. Finally, guideline nine advises the administration of dialysate solution with a Ca content 2.5 mEq/L.

Treatments

In included HD individuals, we commenced by increasing 30 mg of CNL orally once daily to their earlier native vitamin D therapy (calcifediol) that was administered orally immediately after HD sessions. The dialysate Ca content should increase to prevent the hypocalcemia accompanied by CNL introduction. A combination of Ca-based phosphate-binding drugs (Ca carbonate), and non-Ca, non-aluminum, non-magnesium-containing phosphate-binding substances (sevelamer; lanthanum carbonate) administered to attain the serum P target. This program primarily kept without alterations when CNL was initiated. Doses were regulated consistent with subject's response. Principles for vitamin D native and/or CNL dose modification were based on the K/DOQI™ guidelines recommended for levels of Ca, P and/or iPTH. Since iPTH levels were more than 300 ρg/mL, also when serum Ca was below 8.4 mg/dL and there was no hyperphosphatemia (P more than 5.5 mg/dL), then, the dose of native vitamin D added. If serum Ca was more than 9.5 mg/dL or serum P below 5.5 mg/dL, the dose of CNL was added accordingly. In the condition of iPTH more than 150 ρg/mL, the dose of native vitamin D was lowered to reach to a serum Ca and/or P levels as previously mentioned. The aim was to keep a mixture of the smallest probable dosages of both substances, to achieve the K/DOQI™ suggested items with lowest side effects.

Monitoring

The iPTH was regularly assessed each 3 months, while serum Ca and P levels, measured each month. In individuals in whom drug dosage alterations were conducted or CNL was initiated, iPTH, Ca and P were assessed more repeatedly (iPTH monthly; Ca and P weekly or biweekly). The subsequent parameters were noted; serum Ca, P and iPTH, and Ca × P levels in each individual; Ca in dialysate (mEq/L). The proportion of administered native vitamin D; dosages of CNL, and the proportion of P binders used

(Ca-based, sevelamer hydrochloride and lanthanum carbonate) were mentioned accordingly.
The proportion of individuals reaching K/DOQI™ targets for iPTH, Ca, P and Ca × P product recorded at the beginning and at the end of the 12th month.

Laboratory tests

We evaluated Ca and P by UV-Vis spectrophotometry (normal ranges respectively; 8.6-10.4 mg/dL; 2.7-4.5 mg/dL) and iPTH by immunometric assay (normal ranges, 10-65 pg/mL). There were no changes in laboratory techniques in periods of study.

Ethical Issues

1) The research followed the tenets of the Declaration of Helsinki. 2) Informed consent obtained. 3) This study was approved by the Ethics Committee of University Hospital Center of Amiens, France. The goals of the study described to all HD patients and all of them accepted to participate in this investigation.

Statistical analysis

Quantitative variables were expressed as mean and standard deviation or median with interquartile ranges. The paired student's *t* test was applied to compare means. Categorical variables were expressed as numbers and proportions. Statistical analysis was conducted using SPSS 10.0 software, and a *P* value lower than 5% was considered statistically significant.

Results

Demographic characteristics

There are 20 HD patients, mean age at the baseline was 68 ± 16.6 years. The median duration of HD was 28.5 months. Around nine patients (45%) were male and 11 patients (55%) were female. At CNL administration, nearly all individuals were obtaining conventional SHPT therapy consisting of calcifediol (70%) and phosphate-binding agents (95% of patients). Mean baseline values of iPTH, Ca, P and Ca×P product were exceeded the K/DOQI™ recommended targets. Table 1 shows the patients' demographic and baseline laboratory data at beginning of CNL therapy.

Achievement of K/DOQI™ recommended goals

The recommended goals amended for all four indices from baseline to 12 months after introduction of CNL (Figure 1 and Table 2). The proportions of patients attaining K/DOQI™ targets at month 12 were 35% for serum iPTH, 65% for serum P, 60% for serum Ca and 80% for Ca×P product, compared with 0%, 45%, 55% and 50% at the baseline respectively. At month 12, 35% of patients had achieved total targets for simultaneous Ca, P and iPTH compared with 0% at the baseline.

Table 1. Patients' demographics and baseline laboratory values at initiation of cinacalcet therapy

Variable	Total (n = 20)
Demographic	
Mean (SD) age, years	68 (16.6)
Gender, n (%)	
Male	9 (45)
Female	11 (55)
Median [Q1, Q3] duration of hemodialysis, months	28.5 [9, 6]
History of diabetes, n (%)	6 (30)
Previous renal transplantation, n (%)	1 (5)
Previous parathyroidectomy, n (%)	0 (0)
Conventional drug use	
Calcifediol use, n (%)	14 (70)
Phosphate binder use, n (%)	15 (75)
Calcium based	12 (60)
Sevelamer	9 (45)
Lanthanum carbonate	4 (20)
Calcium based and sevelamer	6 (30)
Laboratory parameters, mean (SD)	
Serum iPTH (pg/mL)	537.9 (204)
Serum calcium (mg/dL)	8.9 (0.8)
Serum phosphorus (mg/dL)	5.7 (1.8)
Serum Ca×P product (mg^2/dL^2)	51 (16.5)

Abbreviations: SD, standard deviation; Q, quartile; iPTH, intact parathyroid hormone; Ca × P, calcium phosphorus.

Comparison of pre- and post-cinacalcet phases

After the initiation of CNL, a significant decrease in mean serum iPTH (537.9 ± 204 vs 393.7 ± 262.2 pg/mL; $P = 0.014$) was detected. Additionally, mean pre-dialysis decrease of serum Ca levels (8.9 ± 0.8 vs 8.1 ± 0.9 mg/dL; $P = 0.011$) and Ca × P product (51 ± 16.5 vs 39 ± 10.8 mg^2/dL^2; $P = 0.004$) was seen too. There was no significant decrease in mean serum P levels (5.7 ± 1.8 vs 4.8 ± 1.3 mg/dL; $P = 0.057$) (Table 3).

Table 2. Percentages of achievement of the K/DOQI™ recommended goals before (0 months) and after (12 months) cinacalcet treatment (n = 20 patients)

	Before cinacalcet (0 months)	After cinacalcet (12 months)
Patients with iPTH between 150 and 300 pg/mL (%)	0	35
Patients with calcium <9.5 mg/dL (%)	55	60
Patients with phosphorus <5.5 mg/dL (%)	45	65
Patients with Ca × P products <55 mg^2/dL^2 (%)	50	80
Patients with simultaneous calcium, phosphorus and iPTH goal achievement (%)	0	35

Abbreviations: iPTH, intact parathyroid hormone; Ca × P, calcium phosphorus.

Table 3. Changes in mean serum levels of iPTH, calcium and phosphorus after the introduction of cinacalcet

	Baseline	6 Months	12 Months	*P**
Serum iPTH (pg/mL)	537.9±204	457.6±413.8	393.7±262.2	**0.014**
Serum calcium (mg/dL)	8.9±0.8	8.6±0.9	8.1±0.9	**0.011**
Serum phosphorus (mg/dL)	5.7±1.8	5.2±1.9	4.8±1.3	0.057
Ca × P product (mg^2/dL^2)	51±16.5	44.7±15.4	39±10.8	**0.004**

**P* value refers to the comparison between the start (0 months) and the end (12 months) of cinacalcet treatment.
Abbreviations: iPTH, intact parathyroid hormone; Ca × P, calcium phosphorus.

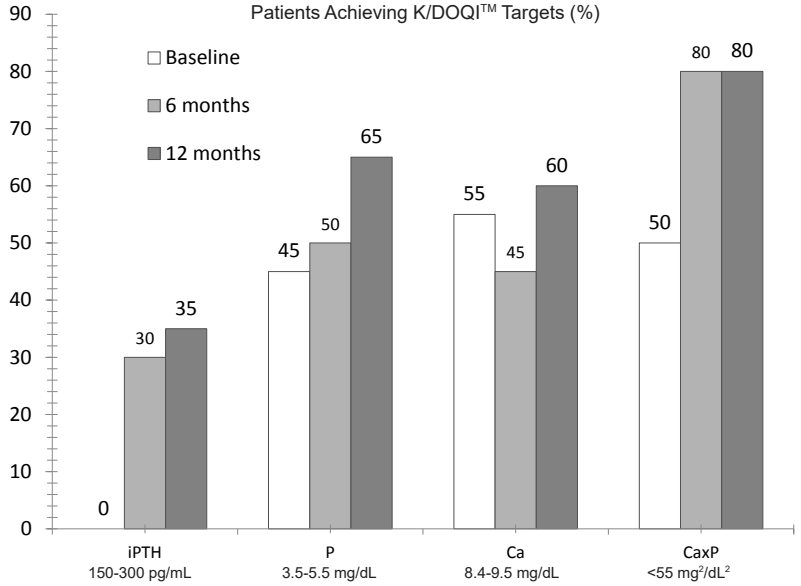

Figure 1. Proportion of patients achieving Kidney Disease Outcomes Quality Initiative (K/DOQI™) recommended targets at the baseline, 6 months and 12 months. iPTH, intact parathyroid hormone; P, phosphorus; Ca, calcium; Ca×P, calcium phosphorus product.

Alterations in the different components of bone metabolism treatment

The proportion of patients taking calcifediol was increased over the research period (70% at the baseline, 85% at month six and 85% at month twelve). There was no patient receiving active vitamin D sterols over the study. Of the 95% of individuals prescribed phosphate binders at baseline, utmost obtained Ca based agents (60%) and/or sevelamer (45%). Around, 30% individuals received a mixture of both sevelamer and Ca based substances. Lanthanum carbonate was used in only 20% patients. Some changes in phosphate binder administration were observed during CNL treatment. From the baseline to month 12, sevelamer administration decreased by 5%, while the administration of Ca-based phosphate binders enhanced by 10%.

The mean quantity of CNL was increased over the study: 30 mg/d at the baseline to 58.5 mg/d at 12 months. Two individuals complained of gastrointestinal discomfort (nausea/vomiting and diarrhea) that improve after nightly use of CNL. No clinical signs or symptoms of hypocalcemia (confusion, abdominal pain or muscle spasms,) were stated. No subject was withdrawn from the investigation due to hypocalcaemia.

At the end of the study, 90% patients were using phosphate binders, 70% Ca based agents, 40% sevelamer and 25% lanthanum carbonate. Thirty-five percent of individuals taken a combination of both sevelamer and Ca based substances.

In the post-CNL period, mean dialysate Ca content increased at 6 months (1.6 ± 0.17 vs 1.71 ± 0.09 mmol/L; $P = 0.009$) and at 12 months (1.6 ± 0.17 vs 1.72 ± 0.07 mmol/L; $P = 0.004$). At the introduction of CNL treatment, 10% patients received a dialysat Ca content of 2.50 mEql/L, 40% received 3 mEq/L and 50% received 3.5 mEq/L. At the end of investigation, 90 % of individuals were changed to a dialysat with 3.5 mEq/L and 10% to 3 mEq/L (Table 4).

Discussion

The guidelines for the management of hyperparathyroidism in ESRD compiled by K/DOQI™ was formulated based on work published up until 2001, before calcimimetics was available. Calcimimetics are substances that enhance the sensitivity of Ca-sensing receptors in the cells of parathyroid glands. This condition

Table 4. Changes in the different components of bone metabolism treatment and cinacalcet dose during the study

	Baseline	6 Months	12 Months
Calcifediol use (%)	70	85	85
Phosphate binder administration (%)	95	80	90
Calcium based	60	65	70
Sevelamer	45	45	40
Lanthanum carbonate	20	25	25
Calcium based and sevelamer	30	35	35
Calcium in dialysate (mmol/L), Mean (SD)	1.6 (0.17)	1.71 (0.09)	1.72 (0.07)
Cinacalcet dose (mg/d), Mean (SD)	30 (0)	52.5 (23.5)	58.5 (32.9)

Abbreviation: SD, standard deviation.

allows for a simultaneous diminution of both PTH and extracellular Ca concentrations. Hence, they are different from currently accessible vitamin D treatments (14-16). Diminution of the Ca×P product is a desirable aspect of calcimimetic treatment and would accelerate attainments to reach to the targets for correction of SHPT (13).

This investigation indicates that CNL therapy ameliorates attainment of K/DOQI™ targets for serum iPTH, P, Ca and Ca×P product in ESRD patients under dialysis with SHPT in the real world setting. CNL efficacy in practice is compatible with reports in similar individuals in randomized, controlled trials and in a recent observational retrospective research (13,17-19).

At the baseline, iPTH levels were uncontrolled in all subjects (mean baseline serum iPTH level, 537.9 ρg/mL). Similarly, serum P, Ca and Ca×P product were also inadequately controlled, with mean baseline levels surpassing K/DOQI™ targets for P and Ca×P product. This data highlighted the presence of a group of ESRD on dialysis with various stages of SHPT requiring additional modalities to enable patients to achieve K/DOQI™ for BMD targets.

After presentation of CNL, its favorable impacts detected for all bone metabolism indices in subjects with uncontrolled illness. CNL therapy has augmented the quantity of individuals reaching K/DOQI™ targets after the end of the study, especially for iPTH (35% vs 0%), for Ca×P product (80% versus 50%), for P (65% vs 45%) and for Ca (60% vs 55%). In fact, 35% of the patients have reached Ca, P, Ca×P product and iPTH objectives simultaneously. These findings agree with past interventional and observational studies of the effect of CNL treatment in comparable patients (13,17,18,20). A meta-analysis by Strippoli et al (21) examined most of these studies. The authors of the meta-analysis concluded that the addition of CNL to standard-of-care significantly improve control of Ca × P product, iPTH, Ca and P levels, and resulted in a greater percentage of patients reaching the K/DOQI™ for BMD targets compared with the standard-of-care. When stratified by gender, race, age, diabetic status, duration of dialysis, and mineral metabolism parameters, CNL and standard therapy have consistently been shown to be superior to standard therapy alone in reach PTH reduction. Improvement in K/DOQI™ targets achievement is an essential finding, given the correlation between constant monitoring of biomarkers of bone and mineral metabolism and survival in dialysis individuals (6).

The calcimimetic CNL sensitizes the parathyroid cells to the extracellular Ca signal, suppressing PTH release and synthesis and preventing parathyroid cell proliferation. This primary PTH suppression decreases the release of Ca and P from bone without increasing their intestinal absorption. Therefore, CNL increases the risk of hypocalcemia. This could justify its combined use with high doses of Ca-containing oral phosphate binders and a dialysate Ca concentration of up to 3.5 mEq/L, in order to prevent hypocalcemia. Nevertheless, the K/DOQI™ has mentioned limitations of supplemental elemental Ca to 1.5 g/d (Guideline 5) and guideline nine recommends the administration of dialysate with a Ca content of 2.5 mEq/L. In our study, the proportion of patients treated with Ca-containing oral phosphate binders was increased (60% in the beginning vs 70% at the end) following CNL treatment, and the mean dose of Ca-containing oral phosphate binders could be stabilized and was well below the 1500 mg/d suggested in K/DOQI™ guidelines.

The suggestion of dialysate Ca concentration up to 2.5 mEq/L (Guideline nine) is controversial (22) while concentrations within this range might simulate parathyroid glands and aggravate radiological findings of renal osteodystrophy (osteitis fibrosa cystica). Indeed, some investigations have detected an inverse correlation between PTH values and Ca concentration in dialysate, and also a deteriorating of SHPT in HD individuals with low Ca content in the dialysate (23,24), perhaps as a result of the provocative impact of low Ca content in the dialysate on parathyroid glands due to negative Ca balance during the HD session. Taking of calcimimetics, which diminish serum Ca levels, allows the administration of a higher dialysate Ca concentration. Following the initiation of CNL therapy, the mean Ca in dialysate was increased (3.2 mEq/L in the beginning vs 3.44 mEq/L at the end).

The proportion of patients administered calcifediol was increased over the study (70% in the beginning vs 85% at the end). The combined administration of CNL and native vitamin D treatment permitted for the administration of lower dosages of CNL, while mean doses at month 12

were 58.5 mg/d. These reasonably low doses, possibly related to the infrequent number of undesirable effects due to CNL. No patient had to discontinue CNL due to undesirable effects. Moreover, recent findings have recommended that vitamin D can have various other physiological roles, containing protection against some autoimmune diseases, like diabetes mellitus, and various malignant diseases comprising breast and prostate cancer (25), which could be another motivation to explain the combined administration of the two drugs.

Conclusion

In summary, in spite of its limitations, this investigation reports important information on current SHPT management. The analysis of current clinical practice among this study showed that CNL provides marked improvements in biochemical parameters of bone and mineral metabolism, helping patients to achieve K/DOQI™ targets.

Limitations of the study

This investigation conducted on a limited proportion of HD patients. Thus, larger studies on this feature of HD are necessary.

Authors' contribution

TA, NEE, PM; study design. TA; study design, data collection and statistical analysis. TA; primary draft preparing. GC, AF; final draft preparing. All authors read and signed the final paper.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

This study extracted from HD unit for Nephrology Department, University Hospital Center of Amiens, France.

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