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# Effective use of cinacalcet for the treatment of secondary hyperparathyroidism in Austrian dialysis patients – Results of the Austrian cohort of the ECHO study

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## Erfolgreicher Einsatz von Cinacalcet in der Therapie des sekundären Hyperparathyreoidismus bei österreichischen Dialysepatienten – Ergebnisse der österreichischen Kohorte der ECHO-Studie

**Zusammenfassung.** *Hintergrund:* Trotz extensiven Einsatzes der vorhandenen Standardtherapeutika befindet sich der Großteil der österreichischen Dialysepatienten mit sekundärem Hyperparathyreoidismus (sHPT) außerhalb der empfohlenen Therapieziele. In einer pan-europäischen Beobachtungsstudie (ECHO) wurde die Effizienz des Kalzimimetikums Cinacalcet in der Therapie des sHPT in der realen klinischen Praxis untersucht. In dieser Arbeit wird die Subanalyse der österreichischen Studienkohorte präsentiert.

*Methodik:* In die Studie wurden erwachsene Dialysepatienten, bei denen eine Therapie mit Cinacalcet begonnen worden war, eingeschlossen. Biochemische Parameter des Knochen- und Mineralstoffwechsels (intaktes Parathormon [iPTH], Kalzium [Ca] und Phosphat [P]) sowie die Begleitmedikation wurden 6 Monate vor Beginn der Cinacalcettherapie, zum Zeitpunkt des Beginns (Baseline) und schließlich bis zu 12 Monate nach Beginn der Cinacalcettherapie erfasst.

*Ergebnisse:* Insgesamt wurden 320 Patienten (mittleres Alter (±SD): 56 (±14) Jahre) in 34 österreichischen Dialysezentren eingeschlossen. Zur Baseline präsentierten sich die Patienten mit erhöhtem iPTH (Median 605 pg/ml) und Hyperphosphatämie (Median 2.1 mmol/l). Nach 12-monatiger Cinacalcettherapie fand sich eine Reduktion der Serumspiegel von iPTH (mediane prozentuelle Abnahme –48 %), Kalzium (–2 %) und Phosphat (–6 %). Die deutlichste iPTH-Abnahme (–66 %) ließ sich bei Patienten mit am stärksten ausgeprägtem sHPT (iPTH >800 pg/ml bei Cinacalcettherapiebeginn) beobachten. Der Anteil der die empfohlenen NKF/K-DOQI™ Therapieziele erreichenden Patienten erhöhte sich während der Therapiephase bis zum Monat 12 für iPTH (von 3 % auf 36 %) und Phosphat (von 24 % auf 39 %) und blieb für Kalzium konstant (von 51 % auf 50 %). Zu Studienbeginn fand sich kein Patient mit allen 3 Parametern gleichzeitig innerhalb der NKF/K-DOQI™ Therapieziele, nach 12 Monaten erreichten 7 % dieses Therapieziel. Während der Beobachtungszeit änderte sich der anteilsmäßige Einsatz des Phosphatbinders Sevelamer nicht, während der Einsatz kalziumhältiger Phosphatbinder anstieg und jener aluminiumbasierter abnahm. Hinsichtlich des Einsatzes von Vitamin D Analoga ergab sich keine wesentliche Änderung im Studienverlauf.

*Schlussfolgerung:* Der zusätzliche Einsatz von Cinacalcet verbesserte die Kontrolle der Knochen- und Mineralstoffwechselparameter und ermöglichte einem größeren Anteil an österreichischen Dialysepatienten, die empfohlenen KDOQI™ Therapieziele für Serum iPTH, Kalzium und Phosphat zu erreichen.

**Summary.** *Background:* Despite extensive use of standard therapy for secondary hyperparathyroidism (sHPT) in dialysis patients, still most patients do not achieve the

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recommended treatment targets. In a pan-European observational study (ECHO), the effectiveness of the calcimimetic cinacalcet for the treatment of sHPT was evaluated in real-world clinical practice. A sub-analysis of the entire Austrian study cohort is presented.

*Methods:* Adult dialysis patients who had initiated cinacalcet therapy were included. Data on biochemical parameters of bone and mineral metabolism (intact parathyroid hormone [iPTH], calcium [Ca] and phosphorus [P]) and concurrent medication were collected 6 months prior to the initiation of cinacalcet, at initiation (baseline) and after up to 12 months of active treatment.

*Results:* A total of 320 patients (mean age (±SD): 56 (±14) years) from 34 Austrian dialysis centres were enrolled. At baseline, patients presented with elevated serum iPTH (median 605 pg/ml) and hyperphosphataemia (median 2.1 mmol/l). After 12 months of cinacalcet treatment, serum iPTH (median percentage change –48%), calcium (–2%) and phosphorus (–6%) decreased. The greatest iPTH reduction (–66%) was found in patients with most severe sHPT (>800 pg/ml at baseline). The proportion of patients achieving the recommended NKF/K-DOQI™ treatment targets increased from baseline to month 12 for iPTH (3–36%) and phosphorus (24 to 39%) and remained stable for calcium (51 to 50%), respectively. No patient had all 3 parameters simultaneously within NKF/K-DOQI™ treatment targets at baseline, while 7% of patients achieved this treatment goal after 12 months. During the study the use of the phosphate binder sevelamer remained fairly stable, while the relative percentage use of calcium-based phosphate binders increased and the usage of aluminium-containing binders decreased; vitamin D analogue use remained stable.

*Conclusion:* Additional use of cinacalcet improved biochemical parameters of bone and mineral metabolism and enabled more patients to achieve and maintain the KDOQI™ treatment targets for serum iPTH, calcium and phosphorus.

**Key words:** Cinacalcet, secondary hyperparathyroidism, calcimimetic, dialysis, hyperphosphataemia.

## Introduction

Declining renal function in chronic kidney disease (CKD) leads to a number of profound disturbances in mineral metabolism that consequently cause secondary hyperparathyroidism (sHPT). SHPT represents the adaptive response of the organism to control the disturbed homeostasis of calcium (Ca), phosphorus (P) and vitamin D metabolism caused by CKD [1]. Evidence is available that these disturbances in mineral metabolism lead to vascular [2, 3] and valvular [4] calcifications and are directly linked to an increased risk of cardiovascular morbidity and mortality as well as excess all-cause mortality [5–7]. Apart from extra-skeletal side effects, sHPT also leads to profound alterations in bone metabolism which become obvious in the different forms of renal osteodystrophy [8]. This clinical syndrome encompassing mineral, bone and cardiovascular abnormalities has recently been termed CKD-related Mineral and Bone Disorder (CKD-MBD) [9]. In an attempt to improve clinical care, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI™ [KDOQI™]) has recommended target ranges for serum intact PTH (iPTH), serum P and total corrected serum Ca [10]. More recently, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for diagnosis, evaluation, prevention and treatment of CKD-MBD have been published [11]. To date, only a small proportion of dialysis patients with sHPT receiving conventional medical therapy including calcium-containing and non-calcium-containing phosphate binders and vitamin D analogues achieve and sustain control of KDOQI™ treatment targets [12]. Recently, Danese and co-workers found that failure to achieve these target ranges for iPTH, Ca and P increases the risk for death by 51% compared to patients simultaneously achieving targets for all three biochemical markers [13].

In Austria, the prevalence of end-stage renal disease for 2008 was found to be as high as 485.5 haemodialysis (HD) and peritoneal dialysis (PD) patients per million inhabitants, a number that has progressively increased over the past ten years [14]. Despite the treatment efforts to reach the recommended KDOQI™ targets, the majority of these patients were outside the recommended target ranges [14].

The complex interplay of the three biochemical key measures of bone and mineral metabolism is hard to control with the medical treatment regimens currently available. Calcium-containing phosphate binders and vitamin D analogues, although effective in lowering iPTH, can elevate Ca and/or P levels, causing hypercalcaemia and/or hyperphosphataemia, respectively, adding to the already high disease-related risk of cardiovascular and soft-tissue calcification [15–17].

The calcimimetic cinacalcet was approved for the treatment of sHPT in dialysis patients in 2004 in Europe. With its targeted mode of action, cinacalcet acts directly upon the parathyroid cell calcium-sensing receptor (CaSR). Upon binding, it allosterically increases its sensitivity to extracellular calcium thus suppressing PTH secretion and production without increasing Ca or P levels [18]. Phase III studies have shown that cinacalcet enables more patients to reach the recommended KDOQI™ targets [19, 20].

These prospective, randomized, clinical trials provide limited information about the efficacy in an unselected patient population, and thus real-life clinical practice. Additionally, cinacalcet registration trials have been conducted prior to publication of the KDOQI™ guidelines and followed different target values for the biochemical key measures of mineral metabolism. ECHO (Evaluation of the Clinical Use of Mimpara® in Haemodialysis and Peritoneal Dialysis Patients, an Observational Study) is the first pan-European observational study to investigate the use and effectiveness of cinacalcet in unselected dialysis patients with various stages of sHPT and was conducted soon after market initiation of cinacalcet. The study population was therefore representative of a population treated with tradi-

  

tional therapy. Overall European results have recently been published [21]. In the present paper, the detailed Austrian subset of data with additional novel sub-analyses is being reported.

## Methods

### Patients

Detailed methodological information and the study design have been published recently [21]. Briefly, data were collected from adult patients on dialysis that had been prescribed cinacalcet (Mimpara®); patients treated with cinacalcet in any interventional clinical trial were excluded. Patients provided written informed consent if required by local regulations; the study was approved by an independent ethics committee/institutional review board.

### Study design

ECHO was a multicentre, multinational, part-retrospective/part-prospective, observational study. Patients were enrolled between July 2005 and October 2006. Data collection followed usual patient care, with data being taken retrospectively from patients' records to provide a total of 6 months data from patients receiving vitamin D analogues and/or phosphate-binding agents alone before the initiation of cinacalcet. Consecutively, data were collected retrospectively or prospectively after initiation of cinacalcet for up to 12 months. The decision to initiate cinacalcet was made by the treating physician, no study-specific treatment algorithm was prescribed, nor were any additional clinical visits or laboratory tests performed for the purpose of the study solely. Relevant medical histories, comorbidities, concurrent medication and laboratory data were collected in case report forms.

### Key parameters

The key parameters of this analysis were the proportion of patients attaining KDOQI™ treatment targets for serum iPTH, P, Ca and the combination of iPTH + Ca + P simultaneously during cinacalcet therapy. Additionally, absolute values of these biochemical markers over time and percentage changes in serum iPTH, P and Ca were determined. Practice patterns in sHPT management were assessed by analyzing the usage of cinacalcet, vitamin D analogues and phosphate binders (PBs) alone or in combination. In an attempt to determine the influence of cinacalcet and changes in concomitant vitamin D or PB therapy on P reduction, all patients with a lower serum P at month 12 compared to baseline were divided into three groups: 1) vitamin D reduced or stopped, 2) vitamin D unchanged and 3) vitamin D increased or started. The latter two groups were then further analysed depending on changes in PB therapy and categorized either in: 1) patients with no change or a decrease in PB or in 2) patients with an increase in PB. The detailed algorithm used for the classification of PB-groups depending on these three criteria is shown in Table 1.

### Statistical analyses

A sample size was selected based on the need to have sufficient data to enable the analyses to be run separately for individual countries (or country clusters). The number of participants from each country or country cluster was aimed to reflect the proportion of dialysis patients in that country or country cluster as compared with the whole European dialysis population. The number of participants was intended to range from approximately 100 patients to 600 patients within each country/country cluster. As the study was not designed to conduct formal statistical comparisons, analyses of the Austrian data were descriptive only. Analyses used observed data from all patients treated by cinacalcet; percentages were calculated according to the total number of patients in the full analysis set with no missing data. Patients not reporting data on a parameter at a particular time point were excluded from the analysis at that time point. The investigation of the P lowering effect is based on patients who completed 12 months of cinacalcet therapy.

## Results

In Austria 34 centres enrolled a total of 320 patients, representing 17% of the total European study population. Pa-

**Table 1.** Algorithm for the classification of phosphate binder therapy in patients with reduced phosphorus levels at month 12 and unchanged, newly started or increased vitamin D therapy

| Criterion 1 | Criterion 2 | Criterion 3 | Classification |
|---|---|---|---|
| Same set of phosphate binders at baseline and month 12 | No dose change for all phosphate binders | | No change |
| | Increase or no dose change for all phosphate binder doses | At least one dose increase | Increase |
| | Decrease or no dose change for all phosphate binder doses | At least one dose decrease | Decrease |
| Different set of phosphate binders at baseline and month 12, or unknown types of phosphate binders, both at baseline and at month 12 | Number of phosphate binders with a dose increase* > number of phosphate binders with a dose decrease** | Increase in overall dose***<br>Decrease in overall dose<br>Overall dose not changed | Increase<br>No change<br>Increase |
| | Number of phosphate binders with a dose increase < number of phosphate binders with a dose decrease | Increase in overall dose<br>Decrease in overall dose<br>Overall dose not changed | No change<br>Decrease<br>Decrease |
| | Number of phosphate binders with a dose increase = number of phosphate binders with a dose decrease | Increase in overall dose<br>Decrease in overall dose<br>Overall dose not changed | Increase<br>Decrease<br>No change |

*Includes starting a new phosphate binder.
**Includes stopping an existing phosphate binder.
***Overall dose is the sum of all phosphate binder doses, derived at baseline and month 12.

tients had a mean age (±SD) of 56 (±14) years, 62% of the Austrian study group were men, and the mean haemodialysis and peritoneal dialysis vintage was 62 and 41 months, respectively. Only 20% of all dialysis patients were incident (<1 year dialysis) patients, with the majority of patients having a dialysis vintage between 1 and 5 years (51%). At baseline 71 patients (22%) had previously undergone kidney transplantation, while 126 patients (39%) were on the kidney transplant waiting list at that time (Table 2).

Concomitant use of PB was high at baseline with a prevalence of 92%. Most patients received either sevelamer (53%), calcium-based (43%) or aluminium-containing (32%) binders, with 7–17% of patients having various combinations of these three drugs. During the study, the use of sevelamer remained fairly stable (50% at month 12), while the relative percentage use of calcium-based PBs increased (49% at month 12) and the usage of aluminium-containing binders sharply decreased (22% at month 12). The mean overall dose of all PB types was quite comparable between baseline and study end. At baseline 57% of all patients were treated with active vitamin D (29% alfacalcidol and 28% calcitriol). During the study, vitamin D use remained stable with only a small decrease in mean intravenous alfacalcidol dose (4.9 after 12 months *vs.* 6.7 µg/week at baseline).

At the initiation of cinacalcet, patients presented with elevated iPTH (median 605 pg/ml) and serum P (median 2.1 mmol/l) levels exceeding the KDOQI™ treatment targets (Table 2). During active treatment iPTH sharply decreased with a median percentage change of –48% from baseline to month 12, resulting in a median iPTH level of 305 pg/ml at study end (Fig. 1). Stratifying patients in 3 groups of sHPT severity dependent on baseline iPTH (*mild*: iPTH 300–499 pg/ml; *moderate*: 500–800 pg/ml; *severe*: >800 pg/ml), the greatest iPTH reduction after 12 months was found in patients with severe sHPT with –66% median change, compared to –48% in moderate and –36% in mild sHPT. The proportion of patients achieving the recommended KDOQI™ target after 12 months was higher in patients with mild (48%) compared to moderate (33%) and severe (23%) sHPT. In total 36% of the Austrian study patients achieved the KDOQI™ treatment target for iPTH (150–300 pg/ml) at month 12 compared to 3% at baseline (Fig. 2). This proportion was higher compared to the entire European study population (28% at month 12).

Serum Ca concentrations modestly decreased with a median percentage change of –2% after 12 months (2.20 after 12 months *vs.* 2.30 mmol/l at baseline), with the highest median reduction of –8% after 6 months (Fig. 1). The percentage of patients achieving KDOQI™ targets for Ca did not substantially change over 12 months (50% after 12 months *vs.* 51% at baseline), whereas the proportion of patients with a serum calcium concentration <2.1 mmol/l nearly doubled (31% at month 12 *vs.* 16% at baseline).

Baseline median serum P levels were higher in the Austrian patients compared to the overall European group (2.10 *vs.* 1.89 mmol/l) and decreased to a lesser extent with a median percentage change of –6% from baseline (–9% in overall ECHO group), as shown in Fig. 1. Thirty-nine percent of the Austrian patients achieved the recommended KDOQI™ target after 12 months compared to 24% at baseline (Fig. 2). Despite this reduction, median serum P concentration (1.90 mmol/l) of the whole Austrian study group still remained above the KDOQI™ treatment target.

None of our patients had all three parameters (iPTH, Ca and P) controlled simultaneously within recommended KDOQI™ target ranges at baseline. During cinacalcet therapy 18 patients at 6 months (6%) and 18

**Table 2.** Baseline characteristics and demographics

| | | |
|---|---|---|
| Number of patients | 320 (17% of total study group) | |
| Number of study centres | 34 (18% of all study centres) | |
| Mean age (SD), years | 56 (14) | |
| Male/female, n (%) | 199 (62)/121 (38) | |
| Dialysis modality, n (%) | | |
| Haemodialysis/haemodiafiltration | 292 (91) | |
| Peritoneal dialysis | 27 (8) | |
| Mean dialysis vintage (SD), months | | |
| Haemodialysis | 62 (71) | |
| Peritoneal dialysis | 41 (68) | |
| Dialysis vintage, n (%) | Haemodialysis | Peritoneal dialysis |
| <1 year | 56 (19) | 7 (26) |
| 1–5 years | 147 (50) | 17 (63) |
| >5 years | 88 (30) | 3 (11) |
| Cause of ESRD, n (%) | | |
| Hypertension | 34 (11) | |
| Glomerulonephritis | 67 (21) | |
| Diabetes mellitus | 51 (16) | |
| Interstitial/Obstructive nephropathy | 28 (9) | |
| Polycystic kidney disease/Hereditary disease | 47 (15) | |
| Tumor | 3 (1) | |
| Others/Unknown/Not recorded | 90 (28) | |
| Previous renal transplantation, *n* (%) | 71 (22) | |
| Awaiting renal transplantation, *n* (%) | 126 (39) | |
| Previous parathyroidectomy, *n* (%) | 21 (7) | |
| Vitamin D analogue use, *n* (%) | 196 (61) | |
| Phosphate binder use, *n* (%) | 294 (92) | |
| calcium-based | 139 (43) | |
| sevelamer | 168 (53) | |
| aluminium-based | 103 (32) | |
| lanthanum carbonate | 3 (1) | |
| calcium-based + sevelamer | 46 (14) | |
| calcium-based + aluminium-based | 23 (7) | |
| sevelamer + aluminum-based | 55 (17) | |
| Median serum iPTH (Q1, Q3), pg/ml | 605 (438, 831) | |
| Median serum phosphorus (Q1, Q3), mmol/l | 2.1 (1.7, 2.4) | |
| Median serum calcium (Q1, Q3), mmol/l | 2.3 (2.1, 2.5) | |
| Median serum Ca × P (Q1, Q3), $mmol^2/l^2$ | 4.7 (3.8, 5.6) | |

*SD*, standard deviation; *ESRD*, end-stage renal disease; *iPTH*, intact parathyroid hormone; *Q*, quartile; *Ca × P*, calcium-phosphorus product.

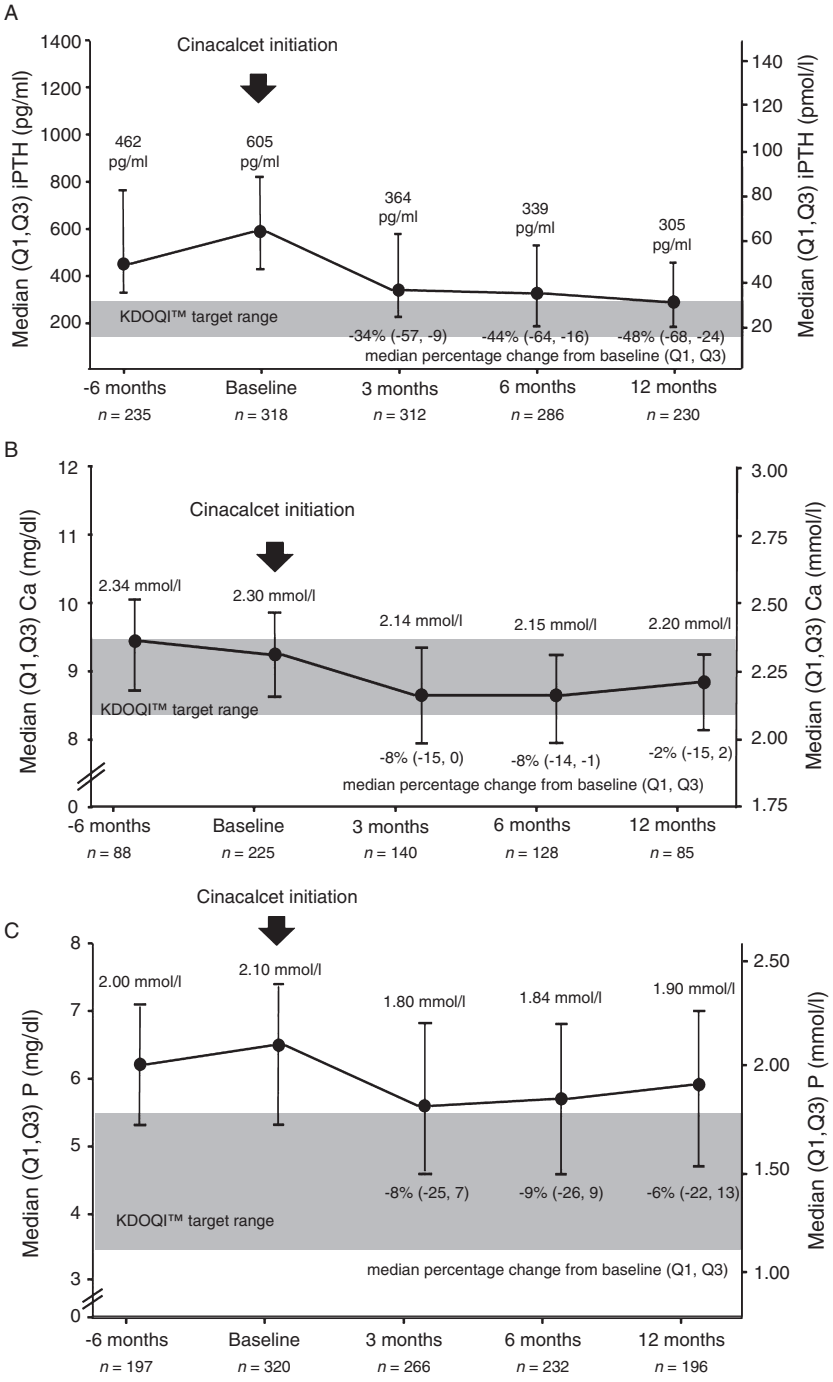


**Fig. 1.** Changes in serum levels of biochemical parameters over time during treatment period: (A) iPTH, (B) calcium, (C) phosphorus. *iPTH* intact parathyroid hormone; *Ca* calcium; *P* phosphorus; *Q* quartile

patients at 12 months (7%) achieved the recommended treatment targets for all three biochemical parameters simultaneously.

In order to further investigate the P lowering effect of cinacalcet, we did an additional analysis in those patients with a lower P after 12 months compared to baseline on a per-patient basis including changes in concomitant medication (vitamin D and PB; $n = 100$). In 22 of these patients (22%), vitamin D analogues were stopped or decreased in dose, in 45 patients (45%) vitamin D analogue dose remained completely stable over the whole study period or no vitamin D analogue was given neither at baseline nor during the study. In 28 of the latter 45 patients, PB dose either remained unchanged or was reduced, whereas in 13 patients PB dose was increased over the study period. In the remaining 24 patients (24%) with P-reduction during treatment period, vitamin D analogue therapy was initiated after the addition of cinacalcet or vitamin D analogue

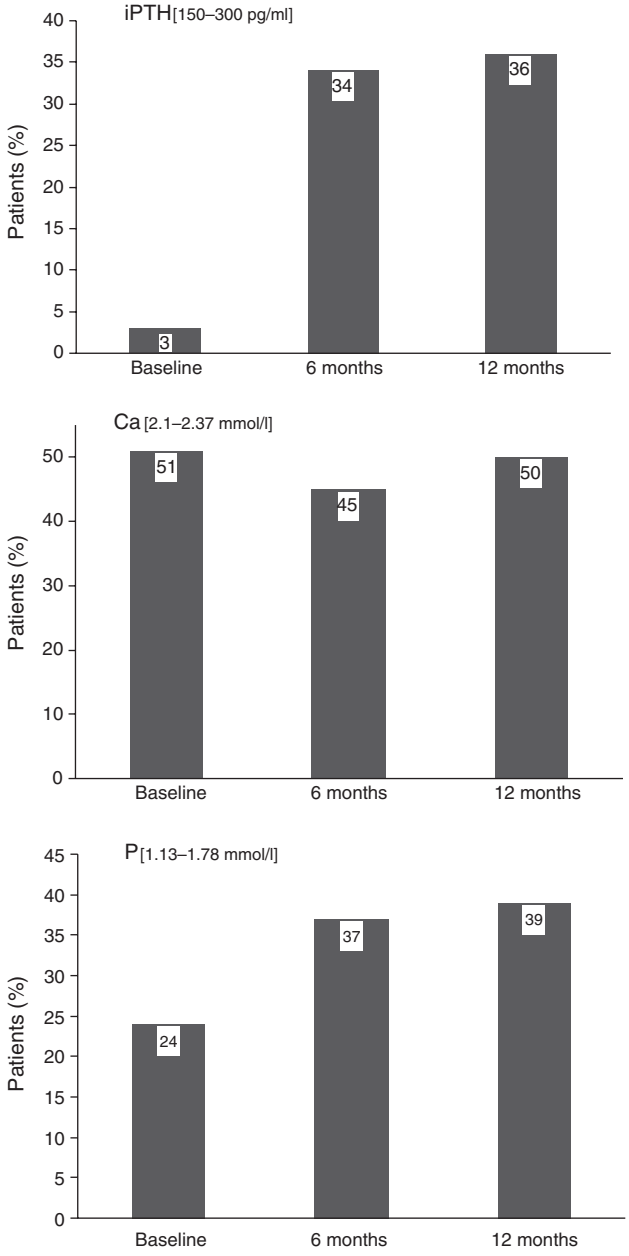


**Fig. 2.** Proportion of patients achieving KDOQI™ recommended treatment targets for iPTH (150–300 pg/ml; 16.5–330 pmol/l), Ca (2.1–2.37 mmol/l; 8.4–9.5 mg/dl) and P (1.13–1.78 mmol/l; 3.5–5.5 mg/dl) at baseline and after 6 and 12 months. *iPTH* intact parathyroid hormone; *Ca* calcium; *P* phosphorus

dose was increased from baseline to month 12. In 15 of these patients PB dose either remained stable or was reduced. By contrast, in 9 patients PB dose was increased. From this analysis the observed decrease in serum P could be attributed to changes in vitamin D therapy in 22% (decrease in dose or vitamin D therapy stopped), to cinacalcet in 43% (unchanged vitamin D therapy and concomitantly unchanged or decreased PB dose [28%] or increased vitamin D dose and concomitantly unchanged or reduced PB dose [15%]) and to the combination of cinacalcet and changes in PB therapy in 22% (unchanged vitamin D therapy and concomitantly increased PB dose [13%] or increased vitamin D dose and concomitantly increased PB dose [9%]) of the patients. Changes in vitamin dosage were unknown in 9 patients, PB dose in 4 patients.

Mean (±SD) daily dose of cinacalcet at month 12 ($n = 271$) was 54 (±43) mg [median (Q1, Q3): 60 (30, 60) mg]. From all patients who recorded a cinacalcet dose at month 12 ($n = 274$), most of them received either 30 mg/day (26%) or 60 mg/day (27%). Other observed dosing regimens were: 90 mg/day (12%), 120 mg/day (6%), 150 mg/day (1%), 180 mg/day (4%), other (14%) and no dose (11%). Stratifying the patients dependent on achievement of KDOQI™ treatment targets for iPTH (150–300 pg/ml), in patients reaching the target the mean cinacalcet dose (±SD) used was 44 (±31) mg/day, whereas in patients below the target 31 (±23) mg/day and in patients above the target 71 (±49) mg/day, respectively.

## Discussion

The results of this large-scale observational study indicate that cinacalcet treatment on top of standard therapy for sHPT in Austrian dialysis patients enables a higher probability of achieving the recommended KDOQI™ treatment targets for iPTH, Ca and P. These data corroborate the pan-European results [21] and previous randomized trials [19, 20].

With a median iPTH of 605 pg/ml and only 3% of patients within KDOQI™ targets for iPTH at baseline despite the prior use of standard sHPT therapy, patients included in this study presented with moderate sHPT. Initiation of cinacalcet at this stage enabled a considerable improvement in metabolic control of bone and mineral metabolism parameters (iPTH, Ca and P) with a considerable increase in the proportion of patients achieving and maintaining KDOQI™ treatment targets during the treatment period. As shown by Danese et al. achievement of these target ranges translates into improved survival [13]. Pooled analysis of safety data from 4 randomised, double-blind, placebo-controlled clinical trials found a cinacalcet-based therapy to be associated with a lower risk of parathyroidectomy, fracture, cardiovascular hospitalisation and an improved health-related quality of life [22]. Whether cinacalcet improves clinical outcome besides biochemical surrogate parameters and achievement of treatment targets is under investigation in the ongoing prospective randomized, double-blind and placebo-controlled EVOLVE study, which evaluates the effects of cinacalcet on mortality and cardiovascular events in haemodialysis patients with sHPT [23].

Our data clearly indicate that cinacalcet is effective throughout all stages of sHPT severity. The highest median iPTH reduction was observed in patients with the most severe sHPT (iPTH > 800 pg/ml) at baseline. In patients with progressive and long-standing sHPT, the risk of monoclonal nodular hyperplasia increases with time [24, 25]. Uremic patients with sHPT have reduced vitamin D receptor (VDR), CaSR, Klotho and FGFR1 expression in hyperplastic parathyroid tissue, even more pronounced in nodular parts [26–29]. This complicates the control of PTH secretion due to diminished responsiveness of parathyroid tissue to medical treatment [30]. Besides an improved

  

biochemical response, calcimimetics have also been shown experimentally to upregulate VDR and CaSR expression in parathyroid glands [31, 32]. These effects may explain the good response in severe forms of sHPT and allow a better achievement of recommended targets and improved management of sHPT.

Nevertheless, the highest therapeutic success rate was found in patients with mild sHPT (iPTH 300–499 pg/ml at baseline), as 46% of the Austrian patients in this group achieved the then recommended KDOQI™ treatment targets. This suggests that a combination therapy including PB, vitamin D analogue and cinacalcet early during development of sHPT could be beneficial.

We applied the KDOQI™ target ranges as they might be more appropriate in order to predict all-cause mortality, as recently shown by Floege et al. [33], even though application of the recently published novel KDIGO (Kidney Disease: Improving Global Outcomes) guidelines, suggesting to maintain an iPTH level in the range of 2–9 times the upper limit of normal levels [11] would lead to a higher success rate of cinacalcet therapy.

In our Austrian study cohort a disproportionately high use of aluminium-based PBs was found at baseline as compared to the overall study population. Despite their high efficacy in P lowering, KDOQI™ and KDIGO guidelines highly recommend their restrictive use, because of concerns about skeletal, haematological and neurological toxicity of aluminium hydroxide [34, 35]. After the introduction of cinacalcet, the proportion of patients receiving aluminium-containing PB considerably decreased (from 32% at baseline to 22% at month 12), therefore allowing the implementation of these practical guidelines in many more patients. This may partly be attributed to the reduction of serum P levels with the use of cinacalcet, partly to the increased use of calcium-based PB.

Using the Austrian data set, we additionally tried to determine the potential effect of a cinacalcet-based sHPT therapy to reduce serum P levels. Cinacalcet on top of vitamin D analogues and PB has shown in various prospective randomized trials and observational studies to significantly reduce serum P [19, 21, 36–38]. Until now, there have been no studies addressing the question, whether this effect is solely caused directly by cinacalcet-induced PTH-lowering and associated reduced P mobilization out of the bone, or caused by changes in concomitant medication after the initiation of cinacalcet, i.e. decrease of vitamin D analogues or increase in PB, resulting in lower P levels. In a cautious attempt to give a preliminary answer to this question, we investigated all patients receiving cinacalcet for 12 months that had a decrease in serum P at month 12 compared to baseline. These patients were categorized in three groups depending on changes in vitamin D therapy and then further subdivided dependent on changes in PB therapy. From this analysis it can be hypothesized, that the observed P lowering effect during the 1 year study period was probably due to a decrease in vitamin D analogue dose in 22% of the patients, while cinacalcet seemed to be responsible for the reduction in serum phosphorus in 43% (accompanying stable or increased vitamin D analogue dose, stable or decreased PB dose) and partially in 22% of patients in whom PBs were increased at the same time. Of course, these preliminary findings can only be the starting point for further studies evaluating the effect of cinacalcet on serum P reduction.

## Conclusion

Despite the inherent limitations of an observational study, this analysis provides an important insight into current real-world practical management of sHPT in Austria. With the use of standard sHPT therapy, many patients still remain outside the recommended target ranges. Patients receiving cinacalcet showed improvement in biochemical parameters of bone and mineral metabolism, and more patients achieved and maintained KDOQI™ treatment targets for serum iPTH, calcium and phosphorus.

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**Conflict of interest**

EZ has received honoraria for lectures from Amgen and Genzyme; AR has received honoraria for lectures from Abbott, Amgen and Genzyme, and grant support from Amgen; F.P. has contributed on behalf of Amgen Europe GmbH; BW has received honoraria for lectures and as advisory board member from Amgen and Abbott; all other authors have nothing to declare.

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