Cinacalcet – Clinical and Laboratory Effectiveness, Concomitant Treatment Patterns and Treatment Cost: Could We Do Better and How?

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Key Words

Cinacalcet • Itching • Phosphate binders • Hyperparathyroidism, secondary • Vitamin D • Dialysis, cost of • Chronic kidney failure

Abstract

Background: The cost and effectiveness patterns in the treatment of secondary hyperparathyroidism (SHPT) in dialysis patients in the Czech Republic are unknown. **Methods:** 52 dialysis patients from 17 centers were followed up in a multi-center prospective study of laboratory and clinical (hospitalization rate, clinical complaints questionnaire) responses to 12-month cinacalcet treatment. Treatment patterns and cost (including phosphate binders, vitamin D, and cinacalcet) were evaluated. **Results:** The mean s-Ca dropped significantly from 2.36 ± 0.24 to 2.21 ± 0.20 mmol/l, s-P from 2.45 ± 0.54 to 2.01 ± 0.53 mmol/l, Ca $\times$ P from 5.79 ± 1.25 to 4.42 ± 1.13 mmol²/l², and iPTH dropped from 919.0 ± 465.6 to 372.1 ± 294.6 pg/ml. The mean cinacalcet dose reached 44.1 ± 23.0 mg/day after 12 months. Itching intensity decreased significantly. No change in hospitalization rate was observed. The direct cost of daily SHPT treatment rose significantly from EUR 8.77 ± 9.59 to 20.62 ± 9.22 . **Conclusions:** Cinacalcet decreased elevated s-Ca, s-P, Ca $\times$ P, and iPTH, alleviated itching, and significantly raised the SHPT treatment cost. A minority of patients reached K/DOQI targets, especially due to poor phosphate control caused by insufficient phosphate binder treatment, cinacalcet underdosing, and advanced SHPT.

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Introduction

Chronic kidney disease patients often develop secondary hyperparathyroidism (SHPT) due to altered calcium, phosphate, and vitamin D metabolism [1, 2]. The calcium-sensing receptor (CaR) on parathyroid gland cells plays a key role in the PTH production and secretion regulation as it induces PTH production and secretion in hypocalcemia. On the other hand, the production and secretion of PTH are lowered by active vitamin D, which acts on the nucleic vitamin D receptor. If PTH production is stimulated for a long time, parathyroid cell proliferation occurs, leading to diffuse or (later) to nodular hyperplasia. In such a situation, the expression of CaR and vitamin D on parathyroid cells diminishes, thus making the PTH production control by calcemia or vitamin D less effective.

The treatment of SHPT must be complex. The cornerstone of treatment is good hyperphosphatemia control using (1) a sufficient dose and frequency of dialysis, (2) low-phosphorus diet, and (3) phosphate binders in sufficient doses, administered the right way.

Two types of drugs are able to act directly against SHPT – the group of active vitamin D and its analogs or precursors acting via the vitamin D receptor, and calcimimetics that exert their action via CaR. Vitamin D sterols often lead to hypercalcemia and/or hyperphosphatemia and induce soft tissue calcifications, which limit their use [3–6]. Cinacalcet, the only clinically available

calcimimetic, is an allosteric modulator of CaR that sensitizes the receptor to extracellular calcium and thus suppresses PTH secretion [7]. The drop in iPTH is accompanied by a drop in calcemia (s-Ca), phosphatemia (s-P), and the calcium-phosphorus product ($\text{Ca} \times \text{P}$) [8]. As for the Kidney Disease Outcomes Quality Initiative (K/DOQI) targets for s-Ca, s-P, $\text{Ca} \times \text{P}$, and iPTH [9], cinacalcet raises the proportion of patients meeting them [10, 11]. The prevention or regression of hypertrophy of the parathyroid glands with the use of cinacalcet have also been described [12, 13].

Cinacalcet became available on the Czech market in 2005. Due to prescription limitations enforced by medical care insurance companies as well as its high price, in most dialysis centers of the Czech Republic only a small proportion of patients is treated. Therefore, the clinical experience in using the drug is still rather limited. To address this issue, we conducted the Mimpara Management in Moravia (MMM) study presented below (Moravia is part of the Czech Republic where the study was carried out).

Subjects and Methods

Study Design

The MMM was a prospective multicenter 1-year follow-up of dialysis patients who started treatment with cinacalcet for SHPT.

The aims of the study were as follows: (1) to describe the profile of patients who started treatment with cinacalcet in the Czech Republic; (2) to assess treatment with cinacalcet in terms of dose, side effects, and concomitant treatment of SHPT; (3) to evaluate the effectiveness of treatment in terms of clinical and laboratory data; (4) to assess the percentage of patients meeting the K/DOQI criteria for calcium-phosphorus metabolism during and before treatment with cinacalcet; (5) to compare the hospitalization rate during and before treatment with cinacalcet, and (6) to compare the direct cost of medical SHPT therapy during and before treatment with cinacalcet.

Population

The inclusion criteria included moderate to severe SHPT (with iPTH of >476 pg/ml, e.g. 50 pmol/l), dialysis treatment, age over 18 years, and consent to cinacalcet treatment and participation in the study. Noncompliance with treatment occurring during the follow-up did not represent an exclusion criterion.

Data Collection

Patients were enrolled from 17 of 27 centers in the region (the participation in the study being voluntary) between November 2006 and April 2007, and the data were collected during the 12-month follow-up. The data from a 6-month period preceding cinacalcet treatment were collected retrospectively. No treatment or examination protocols were provided and no clinic visits were required other than those regularly scheduled. Therefore, the

study observed the current clinical practice. The following variables were collected by the patients' nephrologists at baseline: age, gender, etiology of chronic kidney disease, medical history including kidney transplantation and parathyroidectomy, comorbidities, dialysis start date, dialysis modality, dialysis frequency and duration, concurrent medication. Laboratory findings, drugs prescribed, adverse drug reactions, and need for hospitalization were registered throughout the study.

Biochemical and hematological tests (calcemia, phosphatemia, iPTH level, albuminemia, magnesemia, CRP, hemoglobin concentration, vitamin D, calcidiol and calcitriol blood level, blood pH, pCO_2 , HCO_3^- , alkaline phosphatase) were carried out in local laboratories. Blood samples were taken before the start of the dialysis session. Kt/V was calculated by the Daugirdas equation of the 2nd generation, one-compartment model. Complementary examinations (skeleton X-ray, sonography, CT, and scintigraphy of parathyroid glands) were done in local facilities and were recommended by the patients' nephrologist. Only examinations made during the study or within 6 months prior to the start of the study were considered for evaluation.

The intensity of clinical complaints was evaluated on an analog scale from 0 (no complaint) to 10 (maximum intensity) with a simple questionnaire at the start of the cinacalcet treatment (month 0) as well as 6 and 12 months later. The questionnaire assessed the intensity of itching, fatigue, digestive problems, bone pain, and muscle weakness.

To assess the effectiveness of cinacalcet treatment, we used the K/DOQI criteria from 2003 (s-Ca 2.10–2.38 mmol/l, s-P 1.13–1.78 mmol/l, $\text{Ca} \times \text{P} < 4.44$ mmol²/l² and iPTH 150–300 pg/ml) [9] as the study was designed in 2006 when the K/DOQI targets were used most widely in the Czech Republic.

As for the assessment of treatment cost, only direct expenses were included in the calculation (the cost of cinacalcet, vitamin D or its analogs, phosphate binders). The indirect costs of the SHPT treatment (e.g. costs of examinations and laboratory tests, hospitalization, parathyroidectomy, other treatments including the treatment of complications) were not included in the calculation. The prices of drugs valid in July 2007 were considered for the calculation.

Statistical Analysis

Statistical analysis was performed with the statistical software SPSS 15.0 (SPSS for Windows, Rel. 15.0.5. (2006); SPSS Inc., Chicago, Ill., USA). Summary statistics are expressed as frequencies for categorical variables, mean values with SD for normally distributed variables. The repeated ANOVA measures, paired Student's *t* test or an unpaired *t* test where appropriate were used for comparisons of data relating to the time before and during the treatment. The comparisons of treatment effect between subgroups were done using paired Student's *t* test or unpaired *t* test, Wilcoxon sign test, Kruskal-Wallis test, and χ^2 test. For all comparisons, $p < 0.05$ was considered statistically significant.

Missing laboratory data were calculated by linear interpolation for the use of ANOVA. This way, 3.27% of s-Ca values, 3.62% of s-P and $\text{Ca} \times \text{P}$ values, and 8.98% of iPTH values were calculated.

Results

Profile of Patients Who Started the Cinacalcet Treatment

52 patients from 17 centers entered the study. Their baseline demographic and laboratory data are listed in table 1.

Cinacalcet Dose, Side Effects of Treatment, and Concomitant Treatment of SHPT

The cinacalcet dose was raised linearly until month 4 and was not changed afterwards. The dose in month 12 was 44.1 ± 23.0 mg/day. The most frequently used doses were 30 and 60 mg/day.

Four patients (7.7%) discontinued treatment, the reasons being: (1) hypocalcemia and elevation of transaminases (month 1); (2) nausea, vomiting, abdominal pain and tiredness (month 4); (3) heart failure (month 5), and (4) dyspepsia (month 8). In 2 patients (3.8%), the drug was discontinued transiently, in 1 for severe hypocalcemia and drop in iPTH (month 3), in the other patient for health status deterioration stemming from inadequate peritoneal dialysis (month 3). The following events were noted during the treatment: hypocalcemia without cramps (1 patient); hypocalcemia and cramps (1 patient); dyspepsia (1 patient); newly reported extra-osseal calcifications (1 patient), and collapses and worsening hypertension (1 patient). One patient with chronic sepsis died during the study because of bronchopneumonia.

Use of vitamin D sterols was lowered immediately after the start of cinacalcet treatment (from 67.3 to 44.8% of patients). Nevertheless, most of the patients resumed taking the drug and thus 63.2% of patients were on vitamin D sterols at the end of study. Otherwise, while the changes in mean doses were not significant, the shift from pulse towards continuous vitamin D administration was (table 2).

87.8% of patients were prescribed phosphate binders at baseline; most received sevelamer (61.1%) and/or calcium carbonate (49.1%). Other available binders were lanthanum carbonate and aluminium-based binders. The doses of phosphate binders did not change significantly. However, a wider use of combination therapy (2 different phosphate binders) was noted (18.4 vs. 29.3%). Lanthanum carbonate was used more often, but only a few patients received it (table 3).

Calcium concentrations in the dialysate were 1.46 ± 0.21 and 1.51 ± 0.21 mmol/l, respectively, but the difference was not significant (Wilks' $\lambda = 0.639$, $F = 1,638$, d.f. = 10, $p = 0.145$).

Table 1. Patient demographics and baseline laboratory values before the start of cinacalcet treatment

Variable	Total (n = 52)
<i>Demographics</i>	
Mean age $\pm$ SD, years	55.5 ± 12.1
Male gender, %	53.8
Previous kidney transplant, %	13.5
Dialysis vintage $\pm$ SD, months	59.3 ± 55.6
<i>Type of dialysis</i>	
Peritoneal dialysis, %	3.8
Hemodialysis, %	96.2
Low-flux HD, %	38.5
High-flux HD, %	25.0
Hemodiafiltration, %	23.1
Low-flux HD + hemodiafiltration, %	5.8
High-flux HD + hemodiafiltration, %	3.8
Number of dialysis sessions/week (range)	2.98 (2–4)
Dialysis session duration, h (range)	4.2 (3–5)
Weekly dialysis duration, h (range)	12.5 (8–15)
Kt/V, mean $\pm$ SD	1.42 ± 0.31
URR (%), mean $\pm$ SD	69.6 ± 6.6
<i>Calcifications</i>	
Vascular calcifications, %	42.3
Non-vascular calcifications, %	26.9
Valvular, %	19.2
Periarticular, %	19.2
Pulmonary, %	1.9
Corneal, %	1.9
Other soft tissue, %	5.8
<i>Comorbidities</i>	
Diabetes mellitus, %	21.1
Arterial hypertension, %	80.8
Left ventricle hypertrophy, %	42.3
Peripheral artery disease, %	23.1
Chronic heart failure, %	21.1
Myocardial infarction, %	15.3
Cerebrovascular disease, %	15.3
Arrhythmias, %	13.5
Other cardiovascular comorbidities, %	9.6
<i>Parathyroid gland examination</i>	
Ultrasonography, %	61.5
Scintigraphy, %	26.9
Computed tomography, %	9.6
No examination performed, %	38.5
Enlarged parathyroid glands, %	42.3
Normal finding on parathyroid glands, %	19.2
Previous surgical parathyroidectomy, %	5.8
Previous chemical parathyroidectomy, %	3.8

Fig. 1. Calcemia and phosphatemia during the cinacalcet treatment. The administration of cinacalcet started in month 0. The increase in borderline significance of s-P ($\lambda = 0.885$, $F = 2.861$, d.f. = 2, $p = 0.068$) and no changes in s-Ca ($\lambda = 0.955$, $F = 1.060$, d.f. = 2, $p = 0.355$) before the start of the cinacalcet treatment are shown; as are the significant quadratic and cubic decreasing trend for s-Ca ($\lambda = 0.314$, $F = 4.205$, d.f. = 14, $p = 0.001$) and significant linear and cubic decreasing trend for s-P ($\lambda = 0.253$, $F = 7.700$, d.f. = 14, $p = 0.000$) during treatment.

Clinical and Laboratory Impact of the Treatment

As shown in figures 1 and 2, we observed a significant drop in s-Ca, s-P, $\text{Ca} \times \text{P}$, and iPTH levels during the cinacalcet treatment. Mean s-Ca dropped from 2.36 ± 0.24 to 2.21 ± 0.20 mmol/l, s-P from 2.45 ± 0.54 to 2.01 ± 0.53 mmol/l, $\text{Ca} \times \text{P}$ from 5.79 ± 1.25 to 4.42 ± 1.13 mmol²/l², and iPTH from 919.0 ± 465.6 to 372.1 ± 294.6 pg/ml between months 0 and 12. The changes were significant except for iPTH where the decrease was of borderline significance ($p = 0.055$). In addition, the multivariate test demonstrated a significant raising trend in s-P and $\text{Ca} \times \text{P}$ during the 6 months preceding the start of the cinacalcet treatment, whereas the changes in s-Ca and iPTH were not significant during this period.

As for the clinical complaints, cinacalcet manifested a more pronounced beneficial effect over the first 6 months than it did over the following 6 months. Over the first 6 months, the intensity of itching, fatigue, bone pain, and muscle weakness, but not that of digestive disorders, dropped significantly. It returned to previous values for fatigue, bone pain, and muscle weakness in month 12. Only the alleviation of itching remained stable over the 12 months. The total score of clinical complaints dropped from 13.74 ± 10.86 to 10.09 ± 8.53 from months 0 to 6 ($p = 0.000$) and reached the value of 11.05 ± 8.53 (n.s.) in month 12. The results are listed in table 4.

Fig. 2. iPTH levels during the cinacalcet treatment; the administration of cinacalcet started in month 0. Significant variations in iPTH levels ($\lambda = 0.855$, $F = 3.607$, d.f. = 2, $p = 0.030$) before the start of the cinacalcet treatment ending up in a quadratic type of curve; linear and quadratic decreasing trend of borderline significance ($\lambda = 0.102$, $F = 3.784$, d.f. = 14, $p = 0.055$) during the treatment.

Percentage of Patients Meeting the K/DOQI Criteria for Calcium-Phosphorus Metabolism

The percentage of patients meeting the targets at baseline and in month 12 increased significantly for s-Ca (40.8 and 65.9%; $p = 0.002$), $\text{Ca} \times \text{P}$ (14.3 and 51.2%; $p = 0.000$), and for iPTH (6.4 and 39%; $p = 0.000$). The increase for s-P was not significant (6.1 and 17.1%; $p = 0.160$). The data are presented in detail in figure 3. The percentage of patients meeting a combination of 2, 3 or 4 K/DOQI targets increased during treatment (fig. 4), but only 7.3% met all 4 K/DOQI targets in month 12, whereas no patient did so at baseline.

Comparison of Hospitalization Rates during and before Cinacalcet Treatment

There was no difference in the hospitalization rate before treatment and during the first 6 months of treatment (0.51 hospitalizations/patient/6 months, e.g. 85.0 hospitalizations/1,000 patient months vs. 0.40 hospitalizations/patient/6 months, e.g. 66.7 hospitalizations/1,000 patient months; $p = 0.553$). The same applies to the rates before and during the following 6 months of treatment (0.52 hospitalizations/patient/6 months, e.g. 87.3 hospitalizations/1,000 patient months; $p = 0.864$).

Comparison of Direct Cost of Medical SHPT Therapy during and before Cinacalcet Treatment

The total direct cost of mineral and bone disorder treatment during chronic kidney disease including the

Table 2. Use of vitamin D sterols

Drug	Treated patients at baseline, %	Mean dose at baseline $\mu\text{g}/\text{week}$	Treated patients after 12 months on cinacalcet %	Mean dose after 12 months on cinacalcet, $\mu\text{g}/\text{week}$	Significance p
Vitamin D sterols	67.3		63.2		
Calcitriol	34.7	2.04 ± 1.42	34.7	2.13 ± 1.44	n.s.
Paricalcitol	34.7	19.59 ± 12.22	26.5	13.00 ± 9.97	n.s.
Alfacalcidol	2.0	7.0	2.0	1.75	n.s.
Pulse administration	46.9		29.3		<0.05
Continuous administration	20.4		41.3		<0.05

Table 3. Use of phosphate binders

Drug	Treated patients at baseline, %	Mean dose at baseline mg/day	Treated patients after 12 months on cinacalcet, %	Mean dose after 12 months on cinacalcet, mg/day	Significance p
Phosphate binders	87.8		87.8		
Calcium carbonate, tbl. 500 mg	44.9	$2,450 \pm 1,050$	43.9	$2,600 \pm 1,450$	n.s.
Sevelamer HCl, tbl. 800 mg	61.2	$4,240 \pm 1,520$	61.0	$4,320 \pm 1,840$	n.s.
Lanthanum carbonate, tbl. 500 mg	2.0	1,500	12.2	$2,100 \pm 630$	n.s.
Aluminium based	0	–	0	–	n.s.
Combination of 2 binders	18.4		29.3		<0.05

Table 4. Clinical complaints evaluated at the start of the study and after 6 and 12 months of cinacalcet treatment in 46 patients

	At the start (month 0)	After 6 months (month 6)	After 12 months (month 12)	Month 0 vs. month 6	Month 6 vs. month 12	Month 0 vs. month 12
Itching	3.39 ± 3.08	1.91 ± 2.07	1.76 ± 1.92	0.000	1.000	0.006
Fatigue	3.24 ± 2.53	2.59 ± 2.15	3.18 ± 2.14	0.000	0.010	0.250
Digestive problems	0.74 ± 1.69	0.80 ± 1.53	1.13 ± 1.67	0.773	0.224	0.332
Bone pain	3.35 ± 3.31	2.43 ± 2.55	2.20 ± 2.49	0.001	0.576	0.260
Muscle weakness	3.40 ± 3.22	2.77 ± 2.77	3.05 ± 2.55	0.004	0.324	0.814
Total	13.74 ± 10.86	10.09 ± 8.53	11.05 ± 8.53	0.000	0.159	0.326

Muscle weakness was not evaluated in 3 locomotively challenged patients.

price of all administered drugs (cinacalcet, phosphate binders, and vitamin D and its analogs) was 228.10 ± 249.45 CZK/day (approximately 8.77 ± 9.59 EUR, using the conversion rate 1 EUR = 26.0 CZK valid in August 2009) before the start of the cinacalcet treatment and rose significantly ($p = 0.000$) to 536.11 ± 239.59 CZK/day (20.62 ± 9.22 EUR) in month 12. The cost of the treatment rose from months 0 to 4 and remained stable afterwards.

Discussion

Profile of Patients Who Started Cinacalcet Treatment

The average age of patients and the prevalence of diabetes in our study were lower than the average in the Czech Republic [14] (the lower incidence of SHPT in diabetic and elderly patients is well known [15]).

The intensity of hemodialysis treatment corresponded to the current practice in the country. A short dialysis and

Fig. 3. Percentage of patients meeting the Kidney Disease Outcomes Quality Initiative (K/DOQI) recommended targets for serum calcium (a), phosphorus (b), calcium-phosphorus product (c), and iPTH (d). Month 0 = Start of the cinacalcet treatment.

Fig. 4. Percentage of patients meeting a combination of Kidney Disease Outcomes Quality Initiative (K/DOQI) recommended targets at the start of the study and after 12 months of cinacalcet treatment.

a low number of dialysis sessions per week usually result in a positive phosphate balance, especially in patients with adequate protein intake. In 7.7% of patients the dialysis sessions were shorter than 4 h and 5.8% of patients had only 2 dialysis sessions a week. A more intense dialysis treatment might thus improve the rather poor phosphate control in our group of patients. Nevertheless, the dialysis adequacy, assessed by Kt/V and urea reduction ratio, was satisfactory.

The percentage of patients with calcifications was strikingly low compared to other studies where the prevalence of calcifications in non-selected dialysis populations was usually as high as 60–80% [6]. The reason for this phenomenon might be the relatively low mean age of our group as well as the poor diagnostics of extra-osseal calcifications. Most of the nephrologists did not perform any calcification screening. Due to the observational character of the study, the nephrologists were not obliged to conduct any extra examinations, they did not screen the patients for extra-osseal calcifications and thus the calcifications may have remained undiagnosed.

As for the examination of the parathyroid glands, a surprisingly large number of patients (38.5%) did not undergo any parathyroid gland examination during the 18-month period (starting 6 months before the commencement of the study until its end). Even in those with large parathyroid glands, parathyroidectomy was not considered.

Cinacalcet Dose, Side Effects of the Treatment, and Concomitant Treatment of SHPT

The mean dose of 44.1 mg/d in month 12 was lower than in other published studies, e.g. 52.0 and 62.3 mg in the 4th and 9th months, respectively, in a Spanish study [16], 55 mg [17], 57 mg in the treated population in the

ECHO study [18], and 55 mg in a large study on a DaVita dialysis population [17]. It was much higher in studies with a strict dosing protocol, where it reached 107 mg [19]. Insufficient up-titrating has already been described elsewhere [17, 18]. Given the fact that the control of calcium-phosphate disturbances was not optimal, the reason for drug underdosing might be either its side effects, patients' refusal to take a higher dose, or the price of the drug that limits its prescribed amount (in the Czech Republic, medical insurance companies set a financial limit for prescription drugs and penalize healthcare providers for exceeding it).

Surprisingly, asymptomatic hypocalcemia was not reported as a side effect except for 1 case, and it was the cause of discontinuation in other 2 cases. Nonetheless, 32.6% of patient had s-Ca of <2.1 mmol/l in month 6.

More than 2/3 of the patients were taking active vitamin D or its analogs even though only 6.1 and 17.1% of the patients did not have hyperphosphatemia in months 0 and 12, respectively. If the active vitamin D prescription recommendations had been strictly adhered to, only the patient without hyperphosphatemia (and hypercalcemia) would have been allowed to take it. This shows that nephrologists often do not adhere to the prescription recommendations in order to reduce the elevated iPTH levels. The use of vitamin D together with cinacalcet was much more common in the DaVita population where less than 8% of patients on cinacalcet were not treated with vitamin D [17].

As expected, we noticed a shift from the pulse to continuous vitamin D administration during the study.

The usage of phosphate binders was insufficient throughout the study. Phosphate binders have been employed in rather low doses compared to other studies [16, 17], and the use of a combination of 2 binders was rather rare – 18.4 and 29.3% of patients in months 0 and 12, respectively. Non-calcium-based phosphate binders were never combined together and were used in 73.2% of patients, whereas in the DaVita population, as much as 82% of the patients were receiving them and the dosage was higher by 31% for lanthanum carbonate and by 112% for sevelamer [17]. By contrast, calcium carbonate was used slightly more often in our group of patients and its mean dose was higher by 43% [17], probably for its low cost. 12.2% of the patients did not take any phosphate binder both in months 0 and 12. The differences between the numbers of patients and the doses of phosphate binders used before and at the end of the study were not significant except for lanthanum carbonate, the usage of which increased probably because of its introduction to the

Czech market at the start of the study. To our surprise, there was no rise in the use of calcium carbonate, which could have helped to treat the hypocalcemia observed in 1/3 of the patients in month 6.

Clinical and Laboratory Impact of Treatment

As expected, we observed a statistically significant drop in s-Ca, s-P, $\text{Ca} \times \text{P}$, and iPTH. The decreasing trend seems to be yet more important in the light of the fact that there was an increasing trend in s-P and $\text{Ca} \times \text{P}$ during the 6 months before the treatment (data not shown). When comparing our results with other studies, we have to point out that the initial mean iPTH of 919.0 ± 465.6 pg/ml (which dropped to 372.1 ± 294.6 pg/ml) in our group of patients was far higher than it was in other studies. For instance, Moe et al. [20] in their study indicate an iPTH of 590 ± 39 pg/ml with a drop to 451 ± 65 pg/ml after 100 weeks of treatment with no change in s-Ca (2.42 mmol/l) and a drop in s-P from 1.87 to 1.84 mmol/l. In another study, the start iPTH of 426 ± 274 dropped to 300 ± 228 pg/ml, s-Ca reached the values of 2.37 and 2.20 mmol/l, respectively, and s-P 2.00 and 1.78 mmol/l, respectively [21]. In the recently published ECHO study, the mean iPTH was 721 pg/ml [18], and in the DaVita population, it reached 576.9 ± 505.8 pmol/l [17]. This shows that our patients had more severe SHPT than the other treated groups of patients. This might be partly due to the reimbursement policy valid throughout the study where cinacalcet was only reimbursed in the patients with an iPTH of >476 pg/ml. The drop in s-Ca in our patients is comparable to or even higher than that in the other studies. The drop in s-P is comparable, but the levels of s-P are consistently higher. The reason for this might be either the insufficient usage of phosphate binders, or uncontrolled SHPT with 56.1% of patients with undesirably high iPTH levels after 12 months of treatment.

With regard to the clinical complaints, we observed just temporary alleviation of fatigue, bone pain, and muscle weakness in month 6, as their intensity returned to the original values in month 12. We have not found any comparable data elsewhere. Cinacalcet diminished the intensity of itching and this effect lasted until month 12. The intensity of digestive disorders, which is a commonly described side effect of cinacalcet, was generally low.

Percentage of Patients Meeting the K/DOQI Criteria for Calcium-Phosphorus Metabolism

We decided to use the K/DOQI criteria to assess the effect of cinacalcet treatment as the study was designed

in 2006 when the K/DOQI targets were most widely used in the Czech Republic. The percentage of patients meeting the K/DOQI criteria for calcium-phosphorus metabolism remained low even in month 12. The main problem was the poor phosphatemia control with 75.6% of patients being still hyperphosphatemic in month 12. According to the treatment analysis (see above), this might have been caused by the insufficient dosing of phosphate binders as well as a relatively low use of phosphate binder combinations rather than inadequate dialysis. 22% of patients were hypocalcemic in month 12, which probably contributed to the high percentage of patients with persistent hyperparathyroidism. The cinacalcet underdosing and advanced SHPT with hypertrophic parathyroid glands (in at least 36.5% of patients) might have been another cause of insufficient hyperparathyroidism control as the initial as well as final levels of iPTH in the patients with hypertrophic parathyroid glands were significantly higher than the ones in the patients without a proven hypertrophic parathyroid gland (data not shown).

Only 7.3% of patients met all the four K/DOQI criteria in month 12, whereas in a 9-month Spain study, this number was as high as 64.7% [16]. Here the s-P was in the target range in 71% of patients at the start and in 88% of patients at the end of the study. s-Ca was in the target range in 18 and 94% of the patients, respectively. Calcium-containing phosphate binders were used in 50% of patients, aluminium-based phosphate binders in 29%, and sevelamer hydrochloride in 86%. The last one was administered at doses of 11.4 tablets/day at the start and 7.2 tablets/day at the end of the study. Similarly, in the OPTIMA study, where conventional therapy with cinacalcet (in 368 patients) was compared with conventional therapy without cinacalcet, 77% of the patients on cinacalcet met the targets for iPTH and only 22% did so on conventional therapy without cinacalcet. The targets for $\text{Ca} \times \text{P}$ were met in 77 and 58% of patients, for s-Ca in 76 and 33%, and for s-P in 63 and 50% of patients, respectively [22]. Our results turned out to be closer to those of an older 6-month study where the targets were met in 49% of the patients for s-Ca, in 46% for s-P, in 65% for $\text{Ca} \times \text{P}$, and in 41% of the patients for iPTH [19]; but here again, the phosphatemia control was superior to that in our study. In the recently published ECHO study reflecting real practice, the percentage of patients meeting the targets for iPTH and $\text{Ca} \times \text{P}$ was 18% [18], and in the large DaVita population, all the K/DOQI targets were met in 6.2% of the patients [17].

The increase in the proportion of patients achieving the K/DOQI targets proves pivotal when it comes to the association of the control of calcium-phosphate metabolism parameters and survival in dialysis patients [23].

Comparison of Hospitalization Rates during and before Cinacalcet Treatment

The hospitalization rate before and during cinacalcet treatment did not change significantly. The hospitalization rates were surprisingly low, 2–5 times lower than in other large studies [24, 25]. The reason for this might be that cinacalcet as an expensive drug was prescribed to a group of patients with fewer comorbidities. The low hospitalization rates and the low number of patients in our study might account for why we did not observe a drop in the cardiovascular hospitalization rate described elsewhere [25].

Comparison of Direct Cost of Medical SHPT Therapy during and before Cinacalcet Treatment

The total direct costs of medical SHPT therapy were significantly higher with cinacalcet. The same finding was reported by Arenas et al. [16], with a rise in direct monthly costs from 569.3 to 739.9 EUR (the calculated daily cost thus rose from 19 to 24.7 EUR), even with a reduction in daily vitamin D and phosphate binder doses. Our calculated daily costs are a bit lower, in all probability due to the lower cinacalcet and phosphate binders dosages. In the USA, the direct drug cost for treating SHPT in hemodialysis patients was USD 80.20/week for generic i.v. calcitriol and USD 278/week for cinacalcet [26].

Considering the high price of cinacalcet, Narayan et al. [27] recommend that cinacalcet be used in patients with short expected survival or those awaiting kidney transplant as it proves cost-effective only in patients who are to be dialyzed for less than 7.25 ± 0.25 months. In all other patients, parathyroidectomy is the most cost-effective treatment [27]. The cost-effectiveness of long-term cinacalcet treatment was questioned by Garside et al. [28] as well, who, nevertheless, used a high mean daily dose of 94 mg/day for their analysis.

For pharmaco-economical assessment, it is vital to know the impact of cinacalcet on patients' morbidity and, more importantly, mortality. This is the goal of ongoing studies like EVOLVE – Evaluation of Cinacalcet HCl Therapy to Lower CV Events [29] or the ADVANCE study aiming to test coronary calcification progression in hemodialysis patients treated with cinacalcet and low doses of vitamin D. Retrospective analyses of the 3rd phase

clinical studies show that cinacalcet added to standard SHPT treatment with phosphate binders and vitamin D lowers the need for parathyroidectomy by 93%, the risk of fracture by 54%, and the cardiovascular hospitalization risk by 39% [30].

Conclusion

Cinacalcet is a potent drug for the treatment of SHPT in dialysis patients, even in patients with advanced SHPT. Not only does it improve the patients' laboratory profile and raises the probability of meeting the K/DOQI recommended targets, it also relieves itching, and transiently alleviates fatigue, bone pain, and muscle weakness.

Phosphate binders administered in sufficient dosage and vitamin D sterols are still the cornerstones of the SHPT therapy even when cinacalcet is administered. Hyperphosphatemia and hypocalcemia during cinacalcet treatment still represent a challenge. Constant monitoring of the laboratory results achieved helps to tailor therapy. The high cost of cinacalcet should be considered chiefly when it is to be prescribed in the long run.

Our results indicate that, in the Czech Republic, the following issues should be attended to: (1) diagnostics of parathyroid adenoma; (2) diagnostics of extra-osseal calcifications; (3) low usage of higher doses of phosphate

binders, usage of combination of binders, usage of aluminium-based binders; (4) underdosing of cinacalcet; (5) monitoring and treating hypocalcemia occurring during cinacalcet treatment; (6) parathyroidectomy in advanced SHPT, and (7) a change in reimbursement policy enabling the treatment of patients with less advanced SHPT.

In our group of patients, we identified the need to raise the doses of phosphate binders, monitoring and treating hypocalcemia, and the need for adequate doses of cinacalcet. In some patients with advanced SHPT, parathyroidectomy instead of cinacalcet treatment should be considered.

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