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The Efficacy of Cinacalcet in the Treatment of Hyperparathyroidism in Turkish Hemodialysis Patient Population

Türk Hemodiyaliz Hasta Popülasyonunda Hiperparatiroidizm Tedavisinde Sinakalset'in Etkinliği

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ABSTRACT

OBJECTIVE: Cinacalcet reduces parathyroid hormone levels by increasing the sensitivity of the parathyroid gland to calcium. In this study, we firstly aimed to evaluate the efficacy of cinacalcet in Turkish hemodialysis patients.

MATERIAL and METHODS: 4483 hemodialysis patients were screened and 469 patients who had used cinacalcet were included in the study. The patients were divided into 4 groups according to drug usage durations (Group 1: 3 months, Group 2: 6 months, Group 3: 9 months and Group 4: 12 months). The patients' Parathormone, Ca, P and CaxP levels at the 3rd, 6th, 9th and 12th months were compared to the start of treatment and previous months.

RESULTS: The levels of Parathormone, Ca, P and CaxP significantly decreased compared to their initial levels in all groups (from 1412 pg/ml to 1222 pg/mL for Parathormone, p<0,001) in the 3rd month. However, this reduction was not continued in the subsequent months (Parathormone: 1381 pg/ml for the 12th month).

CONCLUSION: Cinacalcet may not provide adequate benefit in control of hyperparathyroidism in Turkish hemodialysis patient population.

KEY WORDS: Cinacalcet, Chronic renal failure, Hemodialysis, Parathormone, Secondary hyperparathyroidism

ÖZ

AMAÇ: Sinakalset paratiroid bezinin kalsiyum'a duyarlılığını artırarak parathormon seviyelerini düşürür. Çalışmada biz ilk olarak Türk hemodiyaliz hastalarında Sinakalset'in etkinliğini değerlendirmeyi amaçladık.

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GEREÇ ve YÖNTEMLER: 4483 hemodiyaliz hastası tarandı ve Sinakalset kullanan 469 hasta çalışmaya alındı. İlaç kullanm sürelerine göre hastalar 4 gruba ayrıldı: (Grup 1: 3 ay, Grup 2: 6 ay, Grup 3: 9 ay ve Grup 4: 12 ay). Hastaların parathormon, Ca,P ve CaxP seviyeleri 3. 6. 9. ve 12. aylarda başlangıç seviyesi ve önceki aylarla karşılaştırıldı.

BULGULAR: Tüm gruplarda 3. ayda parathormon, Ca,P ve Ca x p seviyesi başlangıca göre anlamlı derecede azalmıştı (Parathormon için 1412pg/ml den 1222pg/mL ye, p<0,001). Fakat bu azalma takip eden aylarda devam etmemişti (12. ayda Parathormon:1381pg/ml).

SONUÇ: Sinakalset hiperparatiroidizm tedavisinde Türk hemodiyaliz hasta popülasyonunda beklenen faydayı sağlamıyor olabilir.

ANAHTAR SÖZCÜKLER: Sinakalset, Kronik böbrek yetmezliği, Hemodiyaliz, Parathormon, Sekonder hiperparatiroidizm

INTRODUCTION

Secondary hyperparathyroidism (SHP) is one of the most common metabolic complications of chronic renal failure (CRF). In recent years, it was understood to be associated with vascular calcification, valvular calcification and increased risk of death besides its negative effects on bone and was started to be called chronic kidney disease-mineral bone disorder (CKD-MBD) (1-3). Secondary hyperparathyroidism and mineral metabolism disorders begin in the early stages of kidney failure (below a GFR of approximately 60 mL/min) and while the stage of renal failure progresses, its frequency increases especially in the dialysis patient population. The decreased renal production of vitamin D, phosphorus retention, hypocalcemia, and increased fibroblast growth factor 23 (FGF-23) play a role in the pathogenesis of CKD-MBD (4). Active vitamin D preparations or analogues are usually used in order to control the increase in parathormone (PTH) but treatment goals cannot usually be reached due to side effects such as hypercalcemia and hyperphosphatemia caused by these treatments (5, 6). The levels of PTH were found to be below 300 pg/ml in only 50% of the patients according to 2013 registry data of the Turkish Society of Nephrology (7).

Cinacalcet reduces the synthesis of parathormone by increasing the sensitivity of the calcium sensing receptor to extracellular calcium in parathyroid cells. Cinacalcet not only reduces the synthesis of parathyroid hormone but also provides a decrease in the levels of serum calcium (Ca) and phosphorus (P) (8-12). In many observational and randomized controlled trials, cinacalcet has been shown to be effective in reducing serum PTH, Ca, P and Ca x P levels (8-18). However, there are some studies suggesting that cinacalcet treatment is less effective than it seems for reducing PTH levels and also has a high cost (19). We observed that effectiveness and compliance of cinacalcet was low during the follow-up period in our patients and we recognized that there is no data on this subject in the other centers of our country. Therefore, in this study, we aimed to examine the effect of the usage of cinacalcet on PTH, Ca, P and CaxP levels in the Turkish hemodialysis patient population.

MATERIALS and METHODS

This study is a multicenter, national, retrospective-observational study. The hemodialysis units in provincial and district Ministry of Health hospitals across the country were planned to be included in this study. Hemodialysis centers of Ministry of Health state hospitals were determined in 81 provinces of the Republic of Turkey and a responsible nephrology specialist was interviewed. The patients over 18 years of age who had undergone hemodialysis treatment for at least 3 months and still used cinacalcet or had used cinacalcet for at least 3 months in the past 3 years at the center were included in this study. In our country, cinacalcet treatment can be started when the serum PTH level is above 1000 pg/ml or serum Ca level is above 10.5 mg/dl and the PTH level is above 700 pg/ml according to rules of the budget enforcement organization of the Ministry of Health. Also, the drug is stopped when the serum Ca level is below 8 mg/dl and the serum PTH level is below 400 pg/ml.

The age, sex, reason of chronic renal failure, duration of hemodialysis treatment, accompanying comorbid diseases such as diabetes mellitus or hypertension, and other demographic data were recorded for the patients in this study. The criterion for the presence of a parathyroid adenoma was that the parathyroid adenoma had been detected by parathyroid scintigraphy or ultrasonography.

Calcium-containing phosphorus-lowering drugs and calcium-free phosphorus-lowering drugs and their doses, doses of active vitamin D, vitamin D analogues and their doses and other medical treatments that were still being used by the patients were recorded before initiating therapy with cinacalcet. The start of treatment and 3rd, 6th, 9th and 12th months of the treatment were determined as the evaluation periods for treatment efficacy. The patients were divided into 4 groups according to the drug usage periods. Group 1 was determined as the patients using cinacalcet for 3 months, group 2 as the patients using cinacalcet for 6 months, group 3 as the patients using cinacalcet for 9 months and group 4 as the patients using cinacalcet for 12 months. The levels of Ca, P, CaxP, alkaline phosphatase (ALP), PTH and doses of cinacalcet in treatment evaluation months of every group were compared with both the start of treatment and the previous evaluation months for any changes.

Symptoms that were determined by the following physician based on the observations and that occurred after the start of treatment were recorded in order to determine the observed side effects and their frequency during cinacalcet treatment. The reasons for termination of the drug use were recorded.

The ethics approval for the study was received with decision dated 25.05.2015 and number 06 of the Ethics Committee of Kahramanmaras Sutcu Imam University.

Statistical Analysis

The continuous variables such as age, duration of hemodialysis, and laboratory values were expressed as mean ± SD; discrete variables such as sex and frequency of side effects were expressed as a ratio or number. The paired sample t test was used for the comparison of laboratory values in the treatment evaluation months. SPSS (SPSS, Inc., Chicago, IL, USA) version 15.0 was used for statistical analysis. P <0.05 was considered statistically significant.

RESULTS

Demographical Data

A total of 4483 patients were screened in 77 centers and 469 patients who still used or had used cinacalcet and met the inclusion criteria were included in the study. The average age of the patients was 48.06±14.76 years. Fifty-six percent of the patients were male and 43% were female. Mean duration of hemodialysis treatment was 103.34±61.34 months (minimum 5 months and maximum 348 months). A parathyroid adenoma was detected in 26,5% (118) of the patients. Seventy-two percent of the patients had been treated with vitamin D or its analogues before cinacalcet. Other demographic data have been summarized in Table I. Laboratory data prior to the start of cinacalcet treatment have been summarized in Table II. Before cinacalcet treatment, mean PTH level was 1395±545.52 pg/ml, mean Ca level was 9.13±0.99 mg/dl, mean P level was 6.18±1.45 mg/dl, mean CaxP level was 56.80±15.08 mg^2 /dl^2. The average dose of calcitriol being used was 4.67±2.47 mcg/week and the average dose of paricalcitol being used was 22.47±8.05 mcg/week. 42,9% of the patients had used a calcium-containing phosphorus-lowering agent, 29.6% of the patients had used a calcium-free phosphorus-lowering agent and 20.5% of the patients had used a combination of calcium-containing phosphorus-lowering agent and calcium-free phosphorus-lowering agent.

The Levels of Parathormone, Ca, P and CaxP

The patients were divided into 4 groups according to the drug usage periods and PTH, Ca, P, CaxP, ALP levels and mean doses of cinacalcet were evaluated for changes compared to the baseline and the previous months. In Group 1(n=469), the parameters (PTH, Ca, P, CaxP values) in the 3rd month were significantly reduced compared to the baseline (Table III). In Group 2 (n=317), the parameters in both 3rd and 6th months were found to be significantly lower compared to the baseline. However, although 6th month values were decreased compared to baseline, there was no significant reduction compared to 3rd month despite the significant increase in the cinacalcet dose (Table IV). In Group 3 (n=257), evaluation parameters in 3rd, 6th and 9th months were found to be significantly lower compared

Table I: Demographical data of patient population.

	n= 469
Age, mean±SD (year)	48±15
Sex, % (M/F)	56.9/43.1 (267/202)
Duration of dialysis treatment, mean±SD (month)	103.34±61.34
Diabetes mellitus (DM), %	10.7
Vascular access, %	
Permanent catheter	12
Arteriovenous fistula	85.4
Arteriovenous greft	2.6
Hepatitis Serostatus, %	
HBV	7.1
HCV	7.1
Parathyroid adenoma, % (n)	26.5 (118)
Chronic renal failure etiology, %	
DM	8.6
Hypertension	32.9
Polycystic kidney disease	6.1
Unknown etiology	28.8
Nephrolithiasis	3.6
Chronic pyelonephritis	2.0
Chronic glomerulonephritis	11.3
Amyloidosis	1.1
Miscellaneous etiology	5.4
Usage of vitamin D or analogues before cinacalcet treatment. %	72

Table II: Laboratory parameters of patient population before cinacalcet treatment.

n=469	**Mean±SD**
PTH, pg/ml	1395±545.52
Ca, mg/dl	9.13±0.99
P, mg/dl	6.18±1.45
CaxP, mg^2/dl^2	56.80±15.08
ALP, mg/dl	301.26±313.30
Kt/v	1.54±0.31
Ure reduction rate (URR), %	71.47±7.29
Dose of Calcitriol, mcg/week	4.67±2.47
Dose of Paricalcitol, mcg/week	22.47±8.05
Phosphorus binding agent, %	
Ca containing	42.9
Ca free	29.6
Combined	20.5

to the baseline. The 6th month values were unchanged compared to the 3rd month values. Despite the significant increase in the dose of cinacalcet in the 9th month, a significant increase in PTH and phosphorus P values was observed compared to the 6th month (Table V). In group 4 (n=208), while the 3rd, 6th and 9th month values were significantly lower compared to the baseline, PTH level in the 12th month was not different compared to the baseline. PTH level in the12th month was significantly increased compared to the 6th month. The cinacalcet dose was significantly increased compared to the 6th and 9th months (Table VI). As shown in Figure 1, PTH levels were significantly decreased in the 3rd month in all groups compared to the baseline but this decrease did not continue after 3 months despite the increase in the dose of cinacalcet. When analyzes were repeated by excluding 118 patients with parathyroid adenoma, there was no change in the results. In the analysis performed by excluding patients with parathyroid adenoma, it was observed that the initial PTH value decreased from 1344.40 pg/mL to 1287.63 pg/mL (p> 0.05) in 134 patients receiving cinacalcet for 12 months (data not shown).

Table III: Evaluation of patients' data treated with cinacalcet for 3 months.

n=469	Baseline	3rd month
PTH(pg/ml)	1412.80 ±569.88	1222.03 ±640.51 **
Ca(mg/dl)	9.19±01.02	8.80±0.99 **
P (mg/dl)	6.26±1.45	5.89±1.49 **
CaxP (mg^2/dl^2)	57.78±14.79	52.07±14.5 **
ALP (mg/dl)	301.53±304.83	316.89±300.5
Dose of cinacalcet (mg/day)	56.10±34.76	63.76±35.34 **

* According to baseline p<0.05, ** According to baseline p<0.0001.

The Reasons for Discontinuation and Side Effect Profile of the Drug

The patients' reasons for cessation or discontinuation of drugs are side effects and especially gastrointestinal complaints, inability to meet the reimbursement criteria, and poor compliance. When the reported side effect profile was examined, the most common side effects were gastrointestinal complaints and especially nausea in 42% of the patients. The other reported side effects were hypocalcemia (3.6%), pruritus (2.1%) and musculoskeletal complaints (1.1%).

Table IV: Evaluation of patients' data treated with cinacalcet for 6 months.

n=317	Baseline	3rd month	6th month
PTH(pg/ml)	1408.08 ± 553.44	1206.74 ± 623.38**	1202.83±647.20**
Ca(mg/dl)	9.19±1.03	8.83±1.00**	8.88±0.95 **
P(mg/dl)	6.26±1.48	5.87±1.52 **	5.83±1.29 **
CaxP(mg^2/dl^2)	57.87±15.27	52.05±14.50 **	51.84±12.41 **
ALP(mg/dl)	310.87±328.68	321.24±301.61	326.65±322.86
Dose of cinacalcet (mg/day)	55.67±35.49	62.63±34.86 **	66.34±38.58 **‡

* According to baseline p<0.05, ** According to baseline p<0.0001, ‡ According to 3rd month p<0.05, ‡‡ According to 3rd month p<0.0001.

Table V: Evaluation of patients' data treated with cinacalcet for 9 months.

n=257	Baseline	3rd month	6th month	9th month
PTH (pg/ml)	1445.46±584.92	1235.76±656.13**	1244.76±687.51**	1326.64±683.86* ‡¥
Ca (mg/dl)	9.13±1.03	8.89±1.03 **	8.85±0.98 **	8.93±0.9 *
P (mg/dl)	6.22±1.42	5.94±1.46*	5.79±1.31 **	5.95±1.44 *¥
CaxP (mg^2/dl^2)	57.29±14.74	53.08±14.04**	51.24±12.62 **	53.19±13.81**
ALP (mg/dl)	350.15±386.95	355.57±349.07	354.71±341.56	345.76±345.99
Dose of cinacalcet (mg/day)	55.75±35.52	64.31±35.79 **	66.49±35.56 **	70.48±33.39 ** ‡¥

* According to baseline p<0.05, ** According to baseline p<0.0001, ‡ According to 3rd month p<0.05, ‡‡ According to 3rd month p<0.0001, ¥According to 6th month p<0.05, ¥¥According to 6th month p<0.0001.

Table VI: Evaluation of patients' data treated with cinacalcet for 12 months.

(n=208)	Baseline	3rd month	6th month	9th month	12th month
PTH (pg/ml)	1434.30±586.35	1307.56±675.14 **	1295.75±680.51 **	1328.74±676.74 *	1381.28±780.34 ¥
Ca (mg/dl)	9.11±1.07	8.87±1.05 *	8.84±1.03 *	8.91±0.91*	8.83±1.04 *
P (mg/dl)	6.25±1.42	5.94±1.42 *	5.79±1.23 **	5.91±1.32 *	5.84±1.21 **
CaxP (mg^2/dl^2)	57.57±15.22	52.89±13.93 **	51.36± 12.03 **	52.95±12.97 **	51.84±13.20 **
ALP (mg/dl)	366.61±413.20	374.91±363.55	370.10±358.23	364.84±370.55	388.41±423.17 φ
Dose of cinacalcet (mg/day)	55.25±35.43	64.59±35.39 **	69.32±36.38 **	73.26±35.24 **‡	75.00±42.85 **‡¥

* According to baseline p<0.05, ** According to baseline p<0.0001, ‡ According to 3rd month p<0.05, ‡‡ According to 3rd month <0.0001
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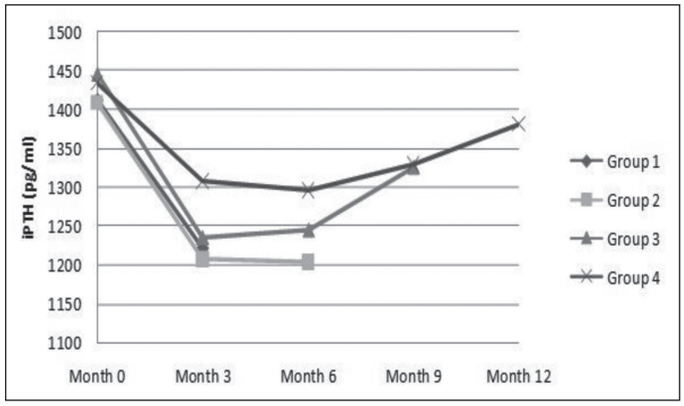

Figure 1: *Effect of cinacalcet usage on iPTH levels in all groups.*

DISCUSSION

In this retrospective observational study, important information regarding the use and results of cinacalcet in Turkey were obtained. The results are important in respect to showing what is actually happening in clinical practice. In this study, although a significant reduction was obtained with cinacalcet in PTH levels in the first 3 months, this reduction was observed not to show continuity.

There are numerous studies and meta-analyses evaluating the efficacy of cinacalcet (8-18). In most of these studies, the percentage of reduction in serum PTH levels, and the average reduction rate in Ca, P, CaxP and PTH levels or the rate of patients reaching NKF-KDOQI goal were evaluated as efficacy parameters. In other studies, the effects of cinacalcet use on mortality and morbidity were evaluated in patients with a bone mineral metabolism disorder and secondary hyperparathyroidism. It was shown in a meta-analysis that was performed in 2012 by Zhang et al. and included 15 studies between 2000-2011 that serum PTH level was mean 294 pg/mL lower, serum Ca level was mean 0,81 mg/dL lower and serum P level was mean 0,29 mg/dL lower in a total of 3387 hemodialysis patients with cinacalcet treatment compared to the control group (15). There was no significant difference in mortality between the group with calcimimetic treatment and the group without calcimimetic treatment. In the study in which Vervloet et al. analyzed Dutch participants of the ECHO study, they found that there was a mean 58% reduction in parathyroid hormone levels compared to the baseline (18). In this population that had relatively higher PTH levels compared to all European cohorts, the initial PTH levels were not useful in predicting response to therapy.

In a double-blind, randomized, placebo-controlled phase 2 study performed by Quarles et al. (10), 71 chronic hemodialysis patients who had received standard therapy of vitamin D were randomized to the cinacalcet and placebo groups. The dose of cinacalcet was titrated up from 25 mg to 100 mg in the 12-week dose-titration phase. At the end of the 18-week study, while PTH levels were decreased by 33% in the group receiving cinacalcet compared to baseline, it was increased by 3% in the placebo group compared to baseline. Ca, P and CaxP values were also significantly decreased in the group receiving cinacalcet. In a randomized controlled study conducted by Block et al.(11), 371 hemodialysis patients were treated with cinacalcet and 370 hemodialysis patients was treated with placebo. After a 12-week dose-titration phase, the primary outcome was defined as a PTH level under 250 pg/mL and the secondary outcome was defined as 30% reduction in the PTH level in the 14-week efficacy assessment phase. The number of patients achieving the primary goal was significantly higher in the cinacalcet group compared to the placebo group (respectively, 43% and 5%). The rate of the patients reaching the secondary outcome was significantly higher in the cinacalcet group compared to the placebo group (respectively, 64% and 11%). Similarly, serum Ca, P and CaxP values were also significantly decreased in the cinacalcet group compared to the placebo group. While the PTH level was decreased by an average of 43% in the cinacalcet group, it was increased by 9% in the placebo group.

The ECHO study (13), which is a large-scale retrospective observational study except some prospective studies above-mentioned is similar to our study in design, has provided important information about the efficacy and side effect profile of cinacalcet. A total of 1865 patients receiving renal replacement therapy in 187 centers from 12 European countries were included in this study. The rate of patients reaching KDOQI goals with the use of cinacalcet for 12 months was increased from 4% to 28%, from 39% to 48%, from 40% to 51% and from 46% to 68% for PTH, P, Ca and CaxP values, respectively. The rate of reaching the goal in combination in all parameters was 18% and the mean rate of PTH reduction was 50%. When patients were grouped according to baseline PTH values, the greatest decrease was observed in the group with severe hyperparathyroidism (PTH>800 pg/ml). In the sub-group analysis of Dutch patients of the ECHO study by Vervloet et al. (18), the initial PTH level was observed not to predict response to treatment. Our study is similar to that study in design. In contrast to the results of that study, we observed a significant reduction in PTH levels in the first 3 months but no greater reduction in the following months. The differences in results can be explained by several factors. Although the patient population in the ECHO study was quite large compared to our study, the initial PTH level was 721 pg/mL. The mean PTH level was about 1422 pg/ml in our study. Two of the studies are retrospective observational studies; the differences between the daily practices of every center in management of hyperparathyroidism may cause the different results. The changes in use depending on the gastrointestinal absorption and possible tolerance differences of drug may cause these results. In our study, although mean dose of cinacalcet at the 12th month was 75±42 mg/day (57±34 mg/day in ECHO study), the reduction in PTH was not enough. Finally, while 12% of peritoneal dialysis patients were also present in ECHO study, there were only hemodialysis patients in our study. In a prospective study performed by Smržová and Urbánek (19), 52 hemodialysis patients who were initiated cinacalcet treatment were evaluated. A significant decrease was observed compared to baseline in serum Ca, P and CaxP values with 12 months of treatment. PTH was decreased with a borderline significance (from 919.0 pg/ml to 372.1 pg/ml for PTH, p=0.055). In this study, the mean dose of cinacalcet was 44 mg/day, and a significant increase in treatment costs was observed.

In all of the studies summarized above, cinacalcet was observed to provide a significant decrease in the Ca, P, CaxP values and PTH levels. However, initial PTH levels in all of these studies were seen to be quite low compared to the PTH levels in our study. Although our study is limited in respect to the number of patients, it is the first and only study in the Turkish patient population. Due to retrospective design of the study, the parathormone and other measurements data come from various laboratories. In contrast to other studies, cinacalcet was observed not to provide a significant decrease in parathyroid hormone levels. We believe that the most important factor that may have contributed to these results is the drug's tolerability problems. The most frequently reported side effects in patients were gastrointestinal complaints, especially nausea. Secondly, our patient population was composed of patients who were followed in our state hospitals. This population is generally less sophisticated than other citizen in terms of socio-cultural nature. Drug compliance tends to be lower in this population. Therefore, patients may be observed to taking the drug, therefore, it might have affected the results of the next three months. The repayment conditions of the social security institution may also prevent the continuation of the drug. As our data belong to the Turkish patient population, we think that there may be ethnic differences in the efficacy and absorption of the drug. Moreover, the results may be affected due to the retrospective feature of study and the application difference between centers.

CONCLUSION

We have determined that cinacalcet was initially effective in the treatment of hyperparathyroidism in our cohort, but the reduction of activity in later times seems to be primarily caused by the reduced compliance of patient. Thus, we concluded that patients should be monitored more closely in terms of drug compliance.

Compliance with Ethical Standards

Funding: This study was not funded by any organization.

Conflict of Interest: The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

This article has not been submitted for publication elsewhere.

For this type of study formal consent is not required

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual participants included in the study

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