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Review

Calcimimetic agents in the management of secondary hyperparathyroidism among patients with end-stage renal disease; a review article

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Abstract

The current management of secondary hyperparathyroidism (SHPT) among dialysis patients included the administration of oral phosphate binders and vitamin D analogues. However, up to one-half of patients with severe SHPT failed by this management. Calcimimetic agents are now considered as a new therapeutic option among these patients. For this review, we used a variety of sources including PubMed, Scopus, Embase and DOAJ to collect current data about effect of calcimimetic agents in the management of SHPT among dialysis patient. Articles published in English from January 1998 up to October 2014, as full-text articles and as abstract forms were included in our review study. There is increasing evidence that the addition of calcimimetic agents to the current therapeutic management of SHPT significantly increase the percentage of dialysis patients who are able to attain targets recommended by the K/DOQI practice guidelines compared with the use of vitamin D analogues and phosphate binders alone. According to these studies calcimimetic agents may be indicated among dialysis patients with PTH levels greater than 300 pg/ml. The drug should not be started if serum calcium levels are below 8.4 mg/dl and the symptoms of hypocalcemia should be monitored during the treatment courses. There are few studies which have evaluated the effect of cinacalcet on mortality and cardiovascular outcomes of dialysis patients, which their results are conflicting. Calcimimetic agents are effective and well tolerated in the treatment of SHPT among patients with end-stage renal disease (ESRD). However further investigations are needed to determine its effect on mortality and cardiovascular outcomes.

Keywords: Calcimimetics, End-stage renal disease, Hemodialysis

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Introduction

End-stage renal disease (ESRD) is one of the most common life-threatening diseases with significant complication and poor outcomes (1-8). Possibly because of increasing prevalence of obesity, diabetes and hypertension, the number of ESRD patients increases each year and imposes a major social and economic burden on countries (9,10).

Secondary hyperparathyroidism (SHPT) is a well-recognized complication of ESRD which caused as a direct result of decreased renal function (11-13).

The major factors responsible for SHPT among uremic patients are hyperphosphatemia, hypocalcemia and deficiency of 1,25-dihydroxyvitamin D. It is also possible that, the decrease in the activation of the calcium-sensing receptors in the parathyroid gland and also skeletal resistance to the calcemic effect of parathyroid hormone (PTH) may contribute to the development of SHPTH (11,14).

The role of fibroblast growth factor-23 (FGF23) which increases among chronic kidney disease patients possibly as a consequence of hyperphosphatemia is also suggested more recently by Ketteler *et al*. It is proposed that FGF23 suppresses PTH via the activation of FGFR/Klotho complexes (15). However the relationship between FGF23 and PTH is not completely understood and further data are needed.

SHPT is characterized by persistently elevated levels of PTH and induces several forms of renal osteodystrophy, including osteitis fibrosa cystica and mixed osteodystrophy (12). Along with these forms of renal osteodystrophy, SHPT is also complicated by important disturbances in mineral metabolism, principally alterations in serum calcium and serum phosphate levels (12-14).

In the past few decades, the current management of SHPT

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Implication for health policy/practice/research/ medical education

Cinacalcet may be indicated among dialysis patients with parathyroid hormone (PTH) levels greater than 300 pg/ml who have serum calcium levels greater than 8.4 mg/dl. Cinacalcet is initiated at a dose of 30 mg once daily or every other day and the dose of the drug is increased stepwise every four weeks to 60, 90, and 180 mg once daily until maintain intact PTH level between 150-300 pg/ml.

among dialysis patients included the administration of oral phosphate binders (either calcium or non-calcium containing binders) to limit the absorption of dietary phosphate and vitamin D analogues (16).

However, up to one-half of patients with severe SHPT failed to achieve targets recommended by the kidney disease outcomes quality initiative (K/DOQI) of the national kidney foundation for parathyroid hormone, calcium, and phosphorus (17,18).

According to K/DOQI practice guidelines, target plasma levels of calcium, phosphorus, calcium-phosphate product and intact PTH (second generation PTH assay) should be maintained between 3.5 and 5.5 mg/dl (1.13 to 1.78 mmol/l), 8.4 and 9.5 mg/dl (2.10 to 2.37 mmol/l), less than 55 mg^2/dl^2 and 150 to 300 pg/ml respectively for patients with an estimated GFR of less than 15 ml/min per 1.73 m^2 (stage 5 chronic kidney disease) (19,20).

In addition, some reports have delineated that a therapeutic approach relying principally upon calcium-based phosphate binders and high doses of vitamin D analogues may be associated with adverse clinical outcomes (21,22). Moreover, alterations in calcium and phosphorus metabolism, as a result of either these therapeutic measures or SHPT contribute to a high rate of excess vascular calcification (particularly in the form of extensive coronary artery calcification) and an increased risk of adverse cardiovascular outcomes and death (23,24). Therefore, efforts have been made to identify therapeutic alternatives that control SHPT while limiting these side effects and minimizing the risk of paradoxical hypercalcemia and/or hyperphosphatemia.

Calcimimetic agents are now considered as a new therapeutic option for the management of SHPT among patients with ESRD (25-30).

There is increasing evidence that, the addition of calcimimetic agents to current therapeutic management increases the percentage of ESRD patients who are able to attain K/DOQI end-points related to serum PTH, calcium, and phosphate levels compared with the use of vitamin D analogues and phosphate binders alone (31-38).

In addition, numerous prospective randomized studies have also found that the administration of the calcimimetic agents reduce the risk of parathyroidectomy, fracture, and cardiovascular hospitalizations among ESRD patients (36-39). The present article summarizes some of these observations about this issue including mechanism of action, pharmacokinetic or pharmacodynamics of the drug and the studies which are suggested beneficial effect of calcimimetic agents in the management of SHPT.

For this review, we used a variety of sources to collect current data about effect of calcimimetic agents in the management of SHPT among dialysis patient. Search of published articles in PubMed, Scopus, Embase, and DOAJ was performed with key words such as calcimimetics, cinacalcet, sensipar and mimpara.

Cinacalcet is the only available calcimimetic in the US. Sensipar and Mimpara are brand names of cinacalcet which is used in North America, Australia and Europe. Articles published in English from January 1998 up to October 2014, as full-text manuscripts and as abstract forms about calcimimetics, mechanism of action, its effect in the management of SHPT among dialysis patient and its effect on mortality and cardiovascular outcome of ESRD patients were included in our review study.

Mechanism of action

Calcimimetic agents allosterically increase the sensitivity of the calcium-sensing receptor (CaSR) to extracellular levels of calcium ion. This receptor is highly expressed in the chief cells of parathyroid gland and controls calcium homeostasis by regulating the release of PTH (25,26). It is also expressed in other tissues, including the kidneys, bone marrow, osteoclasts and osteoblasts, breast, intestine, some areas of the brain, and others (27). The CaSR senses small changes in the serum ionized calcium concentration and in the parathyroid gland. It permits to sense variations in the serum calcium concentration, leading to the desired changes in PTH secretion. Hypocalcemia is a potent stimulus to the release of PTH and chronic hypocalcemia leads to PTH gene expression and parathyroid cellular proliferation (25-27).

In the kidneys, the CaSR is expressed on the basolateral membrane on the cells of the thick ascending limb of the loop of Henle and is an important regulator of urinary calcium excretion (28,29).

According to the important effect of CaSR in parathyroid gland hyperplasia, in the recent years, this receptor is the major therapeutic target for suppressing parathyroid gland function among patients with chronic kidney disease (CKD) (25-32).

Renal failure induced hypocalcemia which is sensed by the CaSR, is a potent stimulus to the release of parathyroid hormone by parathyroid cells and parathyroid gland hyperplasia. It is also best shown in animal genetic studies that the hypocalcaemia which is sensed by the CaSR is the major regulator of PTH transcription, secretion, and parathyroid gland hyperplasia (31).

Calcimimetics (i.e. it mimics the action of calcium on tissues) after binding to the CaSR inhibit the release of parathyroid hormone by parathyroid gland within a few hours after administration and reduce concomitantly serum parathyroid hormone, serum calcium and serum phosphorus levels (25-32).

Several different compounds of calcimimetic agents have been synthesized, but Cinacalcet is currently the only available calcimimetic in the US, for treatment in human patients. Sensipar and Mimpara are brand names of cinacalcet (Figure 1) which are used in North America, Australia and Europe.

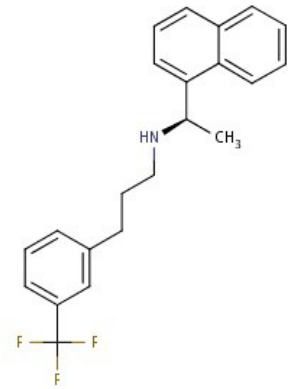

Figure 1. Chemical structure of cinacalcet

The beneficial effect of Calcimimetic agents in the management of SHPT among dialysis patients

Several reliable prospective randomized trials among ESRD patients who receiving maintenance dialysis with mild to severe SHPT have shown that compared with placebo, calcimimetic produces a dose-dependent reduction in the plasma PTH concentration and increases the percentage of ESRD patients who are able to attain K/DOQI end-points related to serum calcium, and phosphate levels (32-48) (Tables 1 and 2).

For example, in one large trial Moe *et al*., investigated the role of cinacalcet HCl (Sensipar trade mark) treatment to improve achievement of target levels of PTH, calcium, phosphorus, and calcium-phosphorus product among 1136 ESRD patients with intact PTH levels of greater than 300 pg/ml (32). In this study (which data have combined from three placebo-controlled, double-blind studies), the patients have randomly assigned to traditional therapy plus cinacalcet HCl or placebo for 26 weeks. To achieve the K/DOQI goals, the dose of oral cinacalcet has titrated from 30 to 180 mg/day. In addition, the dose of cinacalcet was reduced in this study if symptoms attributed to hypocalcemia occurred or if intact PTH levels were less than 100 pg/ml on two or more consecutive visits (32).

The results of this study showed that compared with placebo, cinacalcet-treated subjects are more likely to achieve a mean intact PTH level of less than 300 pg/mL (56% vs.10%), serum calcium levels between 8.4 to 9.5 mg/dl (2.10 to 2.37 mmol/l) (42% vs. 24%), serum phosphorus levels between 3.5 to 5.5 mg/dl (1.13 to 1.78 mmol/l) (46% vs. 33%), and a Ca × P product less than 55 mg^2/dl^2 (4.44 $mmol^2/l^2$) (65% vs. 36%). In addition, according to the results of this study, cinacalcet-treated subjects are also more likely to concurrent achievement of both intact PTH

Table 1. Summary of randomized trials of calcimimetics agents in ESRD patients

Researchers	Country	Date of study	Sample size	Results
Galilei *et al* (16)	(Milan) Italy	1992	83	Mean serum ph increased significantly after 4 months of treatment in patients who showed a decrease of PTH levels and calcium phosphate products exceeded 60.
Antonsen *et al* (42)	(Washington)USA	1998	7	Activation of CARs by a calcimimetic can acutely suppress PTH secretion
Goodman *et al* (21)	(Los Angeles) USA	2000	21	The calcimimetics rapidly and markedly lower plasma PTH levels
Quarles *et al* (45)	(Carolina) USA	2003	71	The calcimimetic provided a safe and effective means to attain significant reductions in PTH and Ca × P levels in ESRD patients
Block *et al* (46)	(Denver) USA	2004	(371 patients) (370 placebo)	Cinacalcet + vitamin D derivatives + phosphate binders, predialysis PTH, calcium, and phosphorus levels decrease
Peacock *et al* (49)	(New York) USA	2005	78	Decrease in serum calcium and an increase in serum phosphorus and only minor changes in serum PTH
Moe *et al* (32)	(Indiana) USA	2005	1136	Cinacalcet has a significant effect in achieving a mean iPTH, Ca, P level to normal range.
Cunningham *et al* (39)	(London) ENG	2005	(697 patients) (487 control)	Cinacalcet, compared with placebo, lowered the risk of parathyroidectomy, fracture, and cardiovascular hospitalization.
Block *et al* (50)	(Denver) USA	2008	444	Cinacalcet combined with low doses of vitamin D sterols improves control of PTH and Ca × P products
Block *et al* (54)	(Denver) USA	2010	5976	Cinacalcet was associated with improved survival among hemodialysis patients
Lucchi *et al* (48)	(Modena) Italy	2011	32	Early treatment with cinacalcet had beneficial effects among HD patients with mild-to-moderate SHPT to achieve target ranges for serum PTH, serum-corrected Ca, and P
Conzo *et al* (51)	(Naples) Italy	2013	50	In SHPT hemodialysis patients affected by severe cardiovascular disease, surgery did not modify cardiovascular morbidity and mortality rates
Chow *et al* (52)	Hong Kong	2014	33	Among patients receiving PD with hyperparathyroidism, significant improvement of parathyroid hormone level was achieved after 52 weeks.

Table 2. Summary of randomized trials of calcimimetics agents in animal studies

Researchers	Country	Date of study	Results
Wada *et al* (53)	Japan	1997	NPS R-568 suppresses PT cell proliferation in rats with renal insufficiency*
Mizobuchi *et al* (54)	Japan	2004	Calcimimetic compound R-568 up-regulates decreased CaR expression, and has an enhancement effect on PTH secretion and parathyroid cell hyperplasia through the improved sensitivity of CaR to Ca^{2+}
Lopez *et al* (55)	Spain	2006	In uremic rats, R-568** reduces elevated PTH levels without inducing vascular calcification.
Lopez *et al* (56)	Spain	2008	AMG 641*** + paricalcitol, provided excellent control of SHPT and prevented mortality associated with the use of vitamin D derivatives without causing tissue calcification.
Mendoza *et al* (57)	Spain	2009	Acute increase in CaSR mRNA and VDR mRNA in the parathyroid glands of uremic rats treated with AMG 641. Supporting a direct effect of calcimimetics on CaSR and VDR expression by hyperplastic parathyroid cells.

*(NPS R-568) is a phenylalkylamine compound that acts as an agonist (calcimimetic) at the cell surface calcium receptor (CaR). **Calcimimetic R-568. ***Calcimimetic AMG 641

level of less than 300 pg/ml and the Ca × P product of less than 55 m^2/dl^2 (4.44 $mmol^2/l^2$) (41% vs. 6%) (32).

The beneficial effect of cinacalcet in the management of SHPT has also been observed in Lucchi *et al.* study (48). In a three-year clinical experience, they investigated if early treatment with cinacalcet had beneficial effects among HD patients with mild-to-moderate SHPT to achieve K/DOQI targets for bone mineral parameters including serum PTH, serum-corrected calcium (Ca), and phosphorus (P) while minimizing the risk of paradoxical hypercalcemia and/or hyperphosphatemia.

Similar to the Moe *et al.* study, the dose of cinacalcet was also started at a dose of 30 mg/day or every other day in this study and titrated thereafter to achieve intact PTH level less than 300 pg/ml. The results of Lucchi *et al.* study showed that early treatment with cinacalcet in HD patients with SHPT significantly decreases in intact PTH, calcium, and calcium-phosphorus product and increases the proportion of patients achieving and maintaining K/DOQI targets (48).

There are many other prospective randomized studies which have also shown the beneficial effect of cinacalcet to achievement the K/DOQI targets for bone mineral parameters among patients on maintenance dialysis with elevated PTH levels who were unable to take adequate doses of vitamin D because of hypercalcemia and/or hyperphosphatemia (33-48,58,59).

In contrast to ESRD patients on maintenance dialysis, there are few studies about safety and efficacy of cinacalcet among patients with CKD not yet on dialysis (60-62). The results of Charytan *et al* study showed that among patients with CKD (glomerular filtration rates between 15 to 50 ml/min) and SHPT, the addition of cinacalcet significantly reduced intact PTH levels (32% decrease versus 5% increase with placebo), but was associated with hyperphosphatemia, which was likely due to the reduction in PTH levels. In addition, four patients withdrew in the study because of hypocalcemia at the lowest dose of cinacalcet (30 mg/day) (61).

In another long-term, randomized, double-blind, placebo-controlled study, Chonchol *et al.*, have also evaluated the efficacy and safety of cinacalcet among 404 patients with stages 3 and 4 of CKD. In this study cinacalcet lowered the mean PTH level by 43% after 32 weeks of treatment. However it also led to a 9% decrease in serum calcium level and a 21% increase in serum phosphorus level (62).

The results of two above studies provide evidence that cinacalcet is efficacious for the treatment of SHPT in subjects with CKD not receiving dialysis, however because of the risk of hypocalcemia and hyperphosphatemia, close monitoring of serum calcium and phosphorus are needed to allow dose titration of the drug and to maintain mean serum calcium and phosphate levels within the normal ranges.

Clinical approach for use of calcimimetic agents

According to the results of above studies and according to the K/DOQI and KDIGO clinical practice guidelines, cinacalcet may be indicated among dialysis patients with PTH levels greater than 300 pg/ml who have serum calcium levels greater than 8.4 mg/dl (19,20,33-48,58,59). Hyperphosphatemia is not a contraindication for use of cinacalcet among these patients. Cinacalcet is initiated at a dose of 30 mg once daily or every other day. The dose of cinacalcet is increased stepwise every four weeks to 60, 90, and 180 mg once daily until maintain intact PTH level between 150-300 pg/ml. Gastrointestinal side effects including nausea (31% to 66%), vomiting (27% to 52%), diarrhea (≤21%), anorexia (6% to 21%) and constipation (10% to 18%) are the most frequently reported side effects of cinacalcet but these symptoms usually resolve with continued use (19,20,33-48,58,59).

We have to mention that cinacalcet should not be started if serum calcium levels are below 8.4 mg/dl. The serum calcium and symptoms of hypocalcemia (e.g., cramps, myalgia, paresthesia, seizure, and tetany) should be monitored during the treatment courses. If hypocalcemia occurs, it is managed by adjustments in calcium-based phosphate binders and vitamin D sterols to raise serum calcium levels (19,20). If hypocalcemia symptoms persist and the doses of vitamin D and calcium-based phosphate binders cannot be increased, the dose of cinacalcet is reduced and or is discontinued until rise of serum calcium levels above 8 mg/dl and/or symptoms of hypocalcemia resolve and then the drug is reinitiated at the next lowest dose (19,20).

Caution should be used especially among patients with seizure disorders, since hypocalcemia may lead to seizures

and QT prolongation (60).
Caution should also be used among patients with impaired cardiovascular function since cases of idiosyncratic hypotension, worsening of heart failure, and/or arrhythmia have been reported. It is suggested that these cardiovascular effects may be correlated with decreased serum calcium levels (60).
Adynamic bone disease is another complication of calcimimetic agents which is developed if intact PTH levels are suppressed to below100 pg/ml and therefore the dose of cinacalcet is reduced and or is discontinued if intact PTH levels decrease below 150-300 pg/ml (19,20).
The use of cinacalcet among predialysis patients with CKD and SHPT is controversial. Although cinacalcet is a potential option among these patients especially among patients who are refractory to therapy with vitamin D analogues and phosphate binders, however, according to the absence of significant data about efficacy and safety of cinacalcet in predialysis patients with CKD, it seems that more data are needed before suggesting that calcimimetics could be used among these patients (60-62).

The effect of cinacalcet on mortality and cardiovascular outcome of ESRD patients

Several observational studies have shown that disorders of bone and mineral metabolism including hyperphosphatemia, hypercalcemia, and SHPT may be associated with increased risks of death and cardiovascular events among ESRD patients. Disorders of mineral metabolism are thought to contribute to atherosclerosis and vascular calcification contributing to myocardial ischemia and heart failure (21-24).
According to these studies, it is proposed that the treatment of SHPT by use of calcimimetic agents can reduce rates of death, cardiovascular events, or other major complications of this disorder.
There is increasing evidence that the addition of calcimimetics to current therapeutic management increases the percentage of ESRD patients who are able to attain K/DOQI end-points related to serum PTH, calcium, and phosphate levels and there is also numerous experimental studies which have shown that calcimimetics are able to inhibit the mineralization of vascular smooth muscle cells and reduce the progression of atherosclerosis and vascular calcification (29-34). However the beneficial effect of cinacalcet on mortality and cardiovascular outcomes of ESRD patients is not clear and there is few studies which have evaluated this issue among these patients and their results are conflicting (63,64).
Some of prospective observational studies have shown that the use of cinacalcet is associated with improved survival among dialysis patients. For example Block *et al.*, prospectively evaluated whether prescription of the cinacalcet to ESRD patients who were undergoing HD improved their survival and cardiovascular outcomes. In this study, from 19,186 ESRD patients, 5,976 received cinacalcet and followed from November 2004, a time coincident with the commercial availability of cinacalcet in the US for up to 26 months. The results of the study showed that all-cause and cardiovascular mortality rates were significantly lower among ESRD patients who treated with cinacalcet than for other patients who did not receive (63).
In contrast to the results of Block *et al.* study, cinacalcet did not decrease the risk of death or major cardiovascular events in the multicenter, prospective, randomized, placebo-controlled trial of Chertow *et al.* In this trial, 3,883 adults ESRD patients undergoing dialysis were randomly assigned to receive cinacalcet or placebo in addition to conventional therapy including phosphate binders, vitamin D sterols, and calcium supplements. Although there was a seven percent reduction in the risk of the primary composite end point with cinacalcet in the intention-to-treat analysis, however it was not significant. In addition there was no significant difference between cinacalcet and placebo groups in the first nonfatal cardiovascular event including myocardial infarction, heart failure, hospitalization for unstable angina and peripheral vascular events (64).

Conclusion

SHPT is a well-recognized complication of ESRD and there is increasing evidence that it may be associated with increased risks of death and cardiovascular events among these patients. In the past few decades, the current management of SHPT included the administration of oral phosphate binders and vitamin D analogues. However, up to one-half of patients with severe SHPT failed by this management. In addition, a number of reports have delineated that this therapeutic approach may be associated with significant side effects including paradoxical hypercalcemia and/or hyperphosphatemia which are contributed to the high rate of vascular and coronary artery calcification among these patients.
Calcimimetic agents which increase the sensitivity of the CaSR are now considered as a new therapeutic option that control SHPT while minimizing the risk of these side effects. Calcimimetics after binding to the CaSR inhibit the release of parathyroid hormone and reduce concomitantly serum calcium and serum phosphorus levels. Several reliable prospective randomized trials have shown that compared with placebo, calcimimetics produces a dose-dependent reduction in the plasma PTH concentration and significantly increases the percentage of ESRD patients who are able to attain targets recommended by the K/DOQI practice guidelines. According to these studies cinacalcet may be indicated among dialysis patients with PTH levels greater than 300 pg/ml who have serum calcium levels greater than 8.4 mg/dl. Cinacalcet is initiated at a dose of 30 mg once daily or every other day and the dose of the drug is increased stepwise every four weeks to 60, 90, and 180 mg once daily until maintain intact PTH level between 150-300 pg/ml. Gastrointestinal side effects including nausea and vomiting are the most frequently reported side effects but usually resolve with continued use. Cinacalcet should not be started if serum

calcium levels are below 8.4 mg/dl and the serum calcium and symptoms of hypocalcemia should be monitored during the treatment courses.

Although cinacalcet is a potential option among patients with CKD not yet on dialysis, however it seems that more data are needed before suggesting that calcimimetics could be used among these patients.

The beneficial effect of cinacalcet on mortality and cardiovascular outcomes of ESRD patients is not clear and there is few studies which have evaluated this issue among these patients and their results are conflicting.

Authors' contributions

SSBM and MF wrote the paper equally.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

Conflict of Interests

There were no points of conflicts.

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