Update on Clinical Trials with Cinacalcet in Secondary Hyperparathyroidism due to Chronic Kidney Disease

Atualização sobre os Ensaios Clínicos com Cinacalcete no Hiperparatireoidismo Secundário associado à Doença Renal Crônica

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ABSTRACT

Data from several recent clinical trials reaffirm the efficacy of treatment with cinacalcet for controlling plasma PTH levels among dialysis patients with established secondary HPT. In contrast to results reported previously from studies where cinacalcet was used together with relatively large but constant doses of vitamin D sterols, plasma PTH levels can be reduced effectively during treatment with cinacalcet among patients receiving lower doses of vitamin D sterols. Compared to conventional treatment with vitamin D sterols, serum calcium and phosphorus levels are better controlled with this therapeutic approach, and a larger proportion of patients are able to achieve serum calcium and phosphorus concentrations and values for Ca x P with the ranges recommended in current practice guidelines. Additional prospective clinical trials are needed, however, to determine whether the use of cinacalcet among dialysis patients with secondary HPT affects other important and clinically relevant outcomes such bone morphology, bone mass and/or bone density, skeletal fracture rates, and the need for parathyroidectomy.

Keywords: Calcimimetics. Secondary hyperparathyroidism. Clinical trials.

RESUMO

Dados de vários ensaios clínicos recentes reafirmam a eficácia do tratamento com cinacalcete para controlar o nível plasmático do PTH em pacientes em diálise com hiperparatireoidismo secundário estabelecido. Em contraste com resultados previamente relatados, derivados de estudos onde cinacalcete era usado junto com doses relativamente altas porém constantes de vitamina D ou derivados, os níveis plasmáticos de PTH podem ser efetivamente reduzidos por cinacalcet em pacientes recebendo doses mais baixas de esteróides da vitamina D. Em comparação ao tratamento convencional com esteróides da vitamina D, os níveis séricos de cálcio e fósforo são melhor controlados com esta abordagem terapêutica e uma maior proporção de pacientes pode alcançar concentrações séricas de cálcio e fósforo e valores do produto Ca x P dentro das faixas recomendadas pelas diretrizes atuais. Entretanto, ensaios clínicos prospectivos adicionais são necessários para determinar se o uso de cinacalcete em pacientes em diálise com hiperparatireoidismo secundário afeta outras variáveis importantes e clinicamente relevantes como, por exemplo, a morfologia do osso, a massa e/ou a densidade óssea, a taxa de fraturas, e a necessidade de paratireoidectomia.

Descritores: *Calcimiméticos, Hiperparatireoidismo secundário, Ensaios clínicos.*

BACKGROUND

Secondary hyperparathyroidism (HPT) is common among patients with chronic kidney disease (CKD)[1-3]. The disorder develops early during the course of CKD due primarily to disturbances in vitamin D metabolism that alter calcium homeostasis systemically and lead to adaptive increases in the synthesis and secretion of parathyroid hormone (PTH) by the parathyroid glands[4]. Impairments in the synthesis of calcitriol, or 1,25-dihydroxyvitamin D, by the diseased kidney play an essential role in the pathogenesis of secondary HPT due to their adverse effect on intestinal calcium absorption[4,5].

Calcitriol regulates the expression of several proteins that mediate intestinal calcium transport[6,7]. Among them are the calbindins and two constitutively activated calcium channels that belong to the vanilloid family of transient receptor potential (TRP) proteins, TRPV-5 and TRPV-6[8-10]. The levels of expression of these key molecular determinants of epithelial calcium transport are reduced in intestinal cells when serum calcitriol levels decline due to CKD[8,11]. Accordingly, defects in intestinal calcium absorption are a prominent feature among patients with mild to moderate CKD, and they are largely responsible for the hypocalciuria that characterizes the disorder [12-15]. As in other clinical conditions such as nutritional vitamin D deficiency and dietary calcium restriction where intestinal calcium absorption is suboptimal, secondary HPT represents an appropriate adaptive response that attenuates calcium excretion in the urine and mobilizes calcium from bone, changes that serve to maintain serum calcium concentrations and to preserve calcium homeostasis systemically[4].

Among untreated patients with CKD, plasma PTH levels rise progressively as renal function declines[3,16,17]. Values exceed the upper limit of normal in most patients with a glomerular filtration rate below 30-40 ml/minute[3,16]. Histological changes of hyperparathyroidism are evident when plasma PTH levels are elevated in the majority of patients with stage 3 or stage 4 CKD[18]. As such, the prevention and management of metabolic bone disease represent key therapeutic objectives. Bone loss due to secondary HPT probably contributes to the high skeletal fracture rates among patients with mild to moderate CKD, and it may also explain the reductions in bone mass seen commonly among dialysis patients[19-21].

Once established, secondary HPT is a progressive disorder that increases in severity as a function of the duration of CKD and/or the number years of treatment with dialysis[22-24]. The need for surgical parathyroidectomy also increases with the duration of renal replacement therapy[22,25]. Parathyroid gland hyperplasia probably accounts for these findings, and enlargement of the parathyroid glands is a key determinant not only of disease severity but also of disease progression. The monoclonal proliferation of subpopulations of parathyroid cells can be documented in more than half of parathyroid glands removed surgically from dialysis patients with secondary HPT[26]. Such changes occur both in the diffuse and in nodular forms of parathyroid gland hyperplasia[26]. There is little evidence that the hyperplastic process can be reversed or that the size of enlarged parathyroid glands diminishes either with medical treatment or after successful kidney transplantation.

Traditional approaches to the clinical management of secondary HPT have relied predominantly upon dietary phosphorus restriction and the use of phosphate-binding agents to manage phosphorus retention and hyperphosphatemia[27]. Indeed, current practice guidelines recommend dietary phosphorus restriction and phosphate-binding agents as initial therapeutic interventions to manage secondary HPT among patients with stage 3 or stage 4 CKD[28]. Additional treatment with vitamin D sterols is often required, however, to control plasma PTH levels among patients with CKD[29]. Unfortunately, such measures do not directly address key disturbances in vitamin D and calcium metabolism described previously that account for the development and progression of secondary HPT.

Furthermore, vitamin D sterols have proven to be only partially effective for the clinical management of secondary HPT among patients undergoing dialysis. A minority of patients achieve plasma PTH levels that fall within the therapeutic target range recommended in current practice guidelines, whereas serum calcium and phosphorus levels remain persistently elevated in many patients[30]. These biochemical abnormalities have been associated with adverse clinical outcomes in observational studies[31-33]. Although treatment with vitamin D sterols has been shown to lower plasma PTH levels among dialysis patients with secondary HPT in short-term studies lasting a few months, the efficacy of treatment for more than two years of follow-up has not been assessed. There is a paucity of information from prospective clinical trials about other important outcomes such as skeletal fractures rates, effects on bone mass, and changes in bone histology following treatment with any vitamin D sterol.

Perhaps more importantly, annual parathyroidectomy rates have not changed appreciably despite the widespread use of vitamin D sterols among patients undergoing dialysis regularly[25]. Such findings suggest that traditional approaches to the management of secondary HPT do not effectively retard disease progression or diminish the need for surgical intervention to control the disorder. There is thus considerable interest in new strategies to manage secondary HPT among patients with CKD.

CALCIMIMETIC AGENTS

Calcimimetic agents are small organic molecules that act as allosteric activators of the calcium-sensing receptor (CaR) in the parathyroid glands and selected other tissues[34,35]. The CaR represents the molecular mechanism by which parathyroid cells detect changes in blood ionized calcium concentration and modulate PTH secretion accordingly[36]. By lowering the threshold for activation of the CaR by extracellular calcium ions, calcimimetic agents inhibit PTH secretion and lower plasma PTH levels. Values decrease promptly and consistently within a few hours after the administration of calcimimetic agents both in humans and in experimental animals, and sustained reductions in plasma PTH levels are achieved with ongoing drug administration[37].

Cinacalcet hydrochloride, hereafter called cinacalcet, is the first calcimimetic agent to become available for use clinically to manage secondary HPT among patients undergoing dialysis[35]. It is also used to treat hypercalcemia among patients with parathyroid carcinoma[38]. Because the mechanism of action differs fundamentally from that of the vitamin D sterols, cinacalcet provides another definitive pharmacological intervention for the management of secondary HPT among persons with CKD who require treatment with dialysis[35,39].

Cinacalcet is a relatively hydrophobic compound, and it is not readily soluble in aqueous solutions. A formulation for intravenous administration during hemodialysis procedures is thus not available. Virtually all clinical studies reported to date have used single daily oral doses of cinacalcet to control plasma PTH levels among patients with established secondary HPT.

Despite these considerations, cinacalcet is absorbed rapidly from the gastrointestinal tract after oral administration[40]. Peak levels in plasma are achieved within 60-90 minutes, and they are largely dose-dependent[40-42]. Plasma PTH levels decrease abruptly after single oral doses of cinacalcet and reach a nadir two to four hours later, biochemical changes consistent with prompt activation of the CaR in parathyroid tissue. Plasma PTH levels rise subsequently, however, toward pre-dose levels during the remainder of the day as the serum concentration of cinacalcet declines and as the level of activation of the CaR diminishes[37,40].

The percentage reduction in plasma PTH levels after single oral doses of cinacalcet does not differ substantially among patients with mild, moderate, or severe secondary HPT as judged by baseline, or pre-treatment, plasma PTH values. The therapeutic response to cinacalcet is thus largely unaffected by disease severity. Moreover, the efficacy of cinacalcet for lowering plasma PTH levels is maintained when treatment is continued for as long as three years[43]. As such, the sustained use of cinacalcet thus does not attenuate its effect to inhibit PTH secretion and to lower plasma PTH levels among patients with secondary HPT due to CKD.

RESULTS FROM CLINICAL TRIALS AMONG PATIENTS WITH SECONDARY HPT

The therapeutic efficacy of cinacalcet for lowering plasma PTH levels was documented initially in large prospective, randomized, double-blinded clinical trials among hemodialysis patients with inadequately controlled secondary HPT despite previous management with vitamin D sterols and phosphate-binding agents[44,45]. Two of the studies enrolled more than 700 patients and lasted 26 weeks[44]. Treatment with cinacalcet was started using single daily oral doses of 30 mg, and doses were subsequently titrated upwards to a maximum of 180 mg per day. Forty-three percent of subjects achieved a mean plasma PTH level equal to, or less than, 250 pg/ml, as measured by a conventional first-generation immunometric PTH assay, during a 14-week efficacy-assessment period[44]. Similar responses were observed when PTH measurements were done using a second-generation immunometric PTH assay that detects PTH^{1-84} exclusively[44,46].

In 60% of patients assigned to treatment with cinacalcet, plasma PTH levels decreased by 30% or more[44]. Such changes have been used traditionally to assess the therapeutic efficacy of vitamin D sterols in clinical trials among patients with secondary HPT due to CKD. Interestingly, the proportion of patients who responded in this manner did not differ according to disease severity as judged pre-treatment plasma PTH values. Several reports indicate that the level of expression of the CaR is reduced in hyperplastic parathyroid tissue obtained either from patients or from experimental animals with kidney disease and secondary HPT[47,48]. Moreover, CaR expression is lower in the nodular than in the diffuse form of parathyroid gland hyperplasia[49]. Although such changes might be expected to attenuate the effect of cinacalcet to inhibit PTH secretion and to lower plasma PTH levels, variations in disease severity have not been shown to influence the biochemical response to treatment in controlled clinical trials.

Serum calcium concentrations decline modestly during treatment with cinacalcet, and serum phosphorus levels also decrease[44,45]. Such changes are due not only to reductions in the mobilization of calcium and phosphorus from bone as plasma PTH levels fall but also to the uptake of calcium and phosphorus into a miscible pool within bone[50,51]. As a result, calculated values for the calcium-phosphorus ion product in serum, or Ca x P, decrease during treatment[44]. The use of cinacalcet thus lowers plasma PTH levels and favorably affects several indices of calcium and phosphorus metabolism among patients with secondary HPT receiving constant, but relatively high doses, of vitamin D sterols[44,45].

Some of the patients who participated in the early clinical trials with cinacalcet were managed without concurrent vitamin D therapy[44]. Plasma PTH levels declined substantially in these subjects[44]. Such findings indicate that cinacalcet can be used alone as a primary therapeutic intervention for secondary HPT among patients undergoing dialysis. Indeed, unlike the vitamin D sterols, neither hypercalcemia nor hyperphosphatemia preclude the use of cinacalcet to lower plasma PTH levels among patients who require medical treatment for secondary HPT. Additional studies are required, however, to determine the efficacy of this therapeutic approach.

In *post hoc* analyses, the use of cinacalcet compared to conventional treatment increased the proportion of patients who achieved plasma PTH levels, serum calcium and phosphorus concentrations, and values for Ca x P in serum that fell within the ranges recommended in current practice guidelines[52]. Among cinacalcet-treated

patients, serum calcium concentrations were maintained between 8.4 and 9.5 mg/dL in 49% of subjects, whereas serum phosphorus levels were maintained between 3.5 and 5.5 mg/dL in 46%. Sixty-five percent had Ca x P values equal to, or less than, 55 mg^2/dL^2.

Because vitamin D therapy often raises serum calcium and phosphorus levels among patients with secondary HPT, additional studies have been done to determine whether the use of cinacalcet together with lower doses of vitamin D sterols can attenuate these biochemical abnormalities. This alternative therapeutic approach was assessed initially in a study of patients with adequately controlled plasma PTH levels but persistently elevated values of Ca x P during treatment with vitamin D sterols[53]. Treatment with cinacalcet was shown to maintain plasma PTH levels below 300 pg/mL while doses of vitamin D sterols were reduced to obviate elevations in serum calcium and phosphorus concentrations[53]. As a result, a larger proportion of patients given cinacalcet rather than vitamin D sterols alone achieved serum calcium and phosphorus concentrations that fell within the ranges recommended by current practice guidelines[28,53].

In a subsequent clinical study called TARGET, patients undergoing hemodialysis with inadequately controlled secondary HPT, as judged by plasma PTH levels persistently above 300 pg/mL, were treated with cinacalcet during an eight-week dose-titration phase followed by an eight-week efficacy assessment phase[54]. Initial doses of 30 mg of cinacalcet were titrated as needed to a maximum daily dose of 180 mg to achieve a plasma PTH level less than 160 pg/mL as determined by a second generation immunometric PTH assay, a value equivalent to 300 pg/mL when measured using a first generation immunometric PTH assay[46]. During the second week of study, the doses of vitamin D sterols among patients already receiving these compounds were reduced to an amount equivalent to 2 mcg of paricalcitol with each thrice weekly hemodialysis session, a total weekly dose of 6 mcg. Therapeutic efficacy was assessed by the proportion of patients who achieved a mean plasma PTH level less than, or equal to, 160 pg/mL, a mean Ca x P less than, or equal to, 55 mg^2/dL^2, or a mean value for both biochemical parameters that was below these two pre-determined thresholds during the assessment phase of the study.

Sixty-two percent of subjects in the TARGET trial achieved the therapeutic objective for PTH, 83% reached the therapeutic target for Ca x P, and 54% of study participants reached both biochemical endpoints during the efficacy-assessment phase. During the 16-week study, plasma PTH levels decreased by 35% from baseline values, serum calcium concentrations decreased by 11%, serum phosphorus levels decreased by 7%, and Ca x P values fell by 17%. The average daily dose of cinacalcet was 69 mg. Compared to earlier reports where cinacalcet was used among patients receiving larger doses of vitamin D sterols, the results from the TARGET study suggest that treatment with cinacalcet together with smaller doses of vitamin D sterols is similarly effective for lowering plasma PTH levels but provides better control of serum calcium and phosphorus concentrations in hemodialysis patients with secondary HPT.

In a separate multi-center clinical trial called OPTIMA that was done in Europe, the therapeutic efficacy of cinacalcet was compared to conventional treatment with flexible doses of vitamin D sterols and phosphate-binding agents among patients with inadequately controlled secondary HPT[55]. Patients qualified for study if plasma PTH levels were greater than 300 pg/mL, but less than 800 pg/mL, as measured by a first-generation immunometric PTH assay. Treatments were adjusted during a 16-week dose optimization phase, and efficacy was evaluated using mean values for plasma PTH and serum calcium and phosphorus concentrations during a seven-week efficacy assessment phase. The primary outcome of the study was the proportion of patients in each treatment group who achieved a mean plasma PTH level below 300 pg/mL during the efficacy-assessment phase[55].

For patients assigned to treatment with cinacalcet, the initial dose was 30 mg per day. Doses were raised incrementally to a maximum daily dose of 180 mg to control plasma PTH levels if serum calcium concentrations remained above 8.0 mg/dL. Among cinacalcet-treated patients who were also receiving vitamin D sterols at the start of the trial, the doses of vitamin D were adjusted as needed to maintain serum calcium levels equal to, or less than, 9.5 mg/dL and serum phosphorus levels equal to, or less than, 5.5 mg/dL as recommended by current practice guidelines. For patients assigned to treatment with flexible doses of vitamin D sterols, doses were adjusted to achieve control of plasma PTH levels while maintaining serum calcium levels equal to, or less than, 9.5 mg/dL and serum phosphorus levels equal to, or less than, 5.5 mg/dL.

Overall, 71% of patients treated with cinacalcet but only 22% of those managed with flexible doses of vitamin D sterols achieved a mean plasma PTH level below 300 pg/mL, $p<0.001$, during the efficacy-assessment phase of the study[55]. Seventy-six percent of patients given cinacalcet maintained a serum calcium level equal to, or less than, 9.5 mg/dL and 63% had a serum phosphorus level equal to, or less than, 5.5 mg/dL during the final

seven weeks of study. In contrast, serum calcium and phosphorus levels below these thresholds were achieved in only 33% and 50%, respectively, of patients managed with flexible doses of vitamin D[55].

Not unexpectedly, patients with pre-treatment plasma PTH levels between 300 and 500 pg/mL were more likely to achieve a plasma PTH value within the therapeutic target range compared to those with baseline values between 500 and 800 pg/mL[55]. The average daily dose of cinacalcet for patients in the OPTIMA study was 56 mg, but smaller doses were required among those with pre-treatment PTH levels between 300 and 500 pg/mL. For this subset of patients, the median daily dose of cinacalcet was 30 mg, whereas the median daily dose among patients with baseline plasma PTH levels between 500 and 800 pg/mL was 60 mg[55].

REFERENCES

1. Martin KJ, Olgaard K, Coburn JW, Coen GM, Fukagawa M, Langman C, et al. Diagnosis, assessment, and treatment of bone turnover abnormalities in renal osteodystrophy. Am J Kidney Dis. 2004;43:558-65.
2. Coburn JW, Elangovan L. Prevention of metabolic bone disease in the pre-end-stage-renal disease setting. J Am Soc Nephrol. 1998;9(Suppl):S71-7.
3. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: Results of the study to evaluate early kidney disease. Kidney Int. 2007;71:31-8; Epub 2006 Nov 8.
4. Goodman WG, Quarles LD. Development and progression of secondary hyperparathyroidism in chronic kidney disease: Lessons from molecular genetics. Kidney Int. [Epub ahead of print]
5. Llach F, Massry SG. On the mechanism of secondary hyperparathyroidism in moderate renal insufficiency. J Clin Endocrinol Metab. 1985;61:601-6.
6. Wood RJ, Tchack L, Taparia S. 1,25-Dihydroxyvitamin D3 increases the expression of the CaT1 epithelial calcium channel in the Caco-2 human intestinal cell line. BMC Physiol. 2001;1:11; Epub 2001 Aug 17.
7. Bouhtiauy I, Lajeunesse D, Christakos S, Brunette MG. Two vitamin D_3-dependent calcium binding proteins increase calcium reabsorption by different mechanisms. II. Effect of CaBP 9K. Kidney Int. 1994;45:469-74.
8. van de Graaf SF, Boullart I, Hoenderop JG, Bindels RJ. Regulation of the epithelial Ca2+ channels TRPV5 and TRPV6 by 1alpha,25-dihydroxy Vitamin D3 and dietary Ca2+. J Steroid Biochem Mol Biol. 2004;89-90:303-8.
9. Hoenderop JG, van der Kemp AW, Hartog A, van de Graaf SF, van Os CH, Willems PH, et al. Molecular identification of the apical Ca2+ channel in 1, 25-dihydroxyvitamin D3-responsive epithelia. J Biol Chem. 1999;274:8375-8.
10. Hoenderop JG, Nilius B, Bindels RJ. ECaC: the gatekeeper of transepithelial Ca2+ transport. Biochim Biophys Acta. 2002;1600:6-11.
11. Van Abel M, Hoenderop JG, van der Kemp AW, van Leeuwen JP, Bindels RJ. Regulation of the epithelial Ca2+ channels in small intestine as studied by quantitative mRNA detection. Am J Physiol Gastrointest Liver Physiol. 2003;285:G78-85; Epub 2003 Mar 5.
12. Coburn JW, Koppel MH, Brickman AS, Massry SG. Study of intestinal absorption of calcium in patients with renal failure. Kidney Int. 1973;3:264-72.
13. Charytan C, Coburn JW, Chonchol M, Herman J, Lien YH, Liu W, et al. Cinacalcet hydrochloride is an effective treatment for secondary hyperparathyroidism in patients with CKD not receiving dialysis. Am J Kidney Dis. 2005;46:58-67.
14. Coburn JW, Maung HM, Elangovan L, Germain MJ, Lindberg JS, Sprague SM,et al. Doxercalciferol safely suppresses PTH levels in patients with secondary hyperparathyroidism associated with chronic kidney disease stages 3 and 4. Am J Kidney Dis. 2004;43:877-90.
15. Coyne D, Acharya M, Qiu P, Abboud H, Batlle D, Rosansky S, et al. Paricalcitol capsule for the treatment of secondary hyperparathyroidism in stages 3 and 4 CKD. Am J Kidney Dis. 2006;47:263-76.
16. Martinez I, Saracho R, Montenegro J, Llach F. The importance of dietary calcium and phosphorous in the secondary hyperparathyroidism of patients with early renal failure. Am J Kidney Dis. 1997;29:496-502.
17. De Boer IH, Gorodetskaya I, Young B, Hsu CY, Chertow GM. The severity of secondary hyperparathyroidism in chronic renal insufficiency is GFR-dependent, race-dependent, and associated with cardiovascular disease. J Am Soc Nephrol. 2002;13:2762-9.
18. Hamdy NA, Kanis JA, Beneton MNC, Brown CB, Juttmann JR, Jordans JG, et al. Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure. BMJ. 1995;310:358-63.
19. Bas S, Bas A, Lopez I, Estepa JC, Rodríguez M, Aguilera-Tejero E. Nutritional secondary hyperparathyroidism in rabbits. Domest Anim Endocrinol. 2005;28:380-90.
20. Bas S, guilera-Tejero E, Bas A, Estepa JC, Lopez I, Madueño JA, et al. The influence of the progression of secondary hyperparathyroidism on the set point of the parathyroid hormone-calcium curve. J Endocrinol. 2005;184:241-7.
21. Ureña P, Bernard-Poenaru O, Ostertag A, Baudoin C, Cohen-Solal M, Cantor T, et al. Bone mineral density, biochemical markers and skeletal fractures in haemodialysis patients. Nephrol Dial Transplant. 2003;18:2325-31.
22. Malberti F, Marcelli D, Conte F, Limido A, Spotti D, Locatelli F. Parathyroidectomy in patients on renal replacement therapy: an epidemiologic study. J Am Soc Nephrol. 2001; 12:1242-8.
23. Kestenbaum B, Seliger SL, Gillen DL, Wasse H, Young B, Sherrard DJ, et al. Parathyroidectomy rates among United States dialysis patients: 1990-1999. Kidney Int. 2004;65:282-8.
24. Chertow GM, Plone M, Dillon MA, Burke SK, Slatopolsky E. Hyperparathyroidism and dialysis vintage. Clin Nephrol. 2000;54:295-300.
25. Foley RN, Li S, Liu J, Chen SC, Collins AJ.The fall and rise of parathyroidectomy in U.S. hemodialysis patients, 1992 to 2002. J Am Soc Nephrol 2005;16:210-8; Epub 2004 Nov 24.

26. Arnold A, Brown MF, Ureña P, Gaz RD, Sarfati E, Drüeke TB. Monoclonality of parathyroid tumors in chronic renal failure and in primary parathyroid hyperplasia. J Clin Invest. 1995; 95:2047-53.

27. Slatopolsky E, Delmez JA. Pathogenesis of secondary hyperparathyroidism. Am J Kidney Dis. 1994;23:229-36.

28. Eknoyan G, Levin A, Levin NW. Bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2003; 42(Suppl 3):1-201.

29. Goodman WG. Recent developments in the management of secondary hyperparathyroidism. Kidney Int. 2001; 59:1187-201.

30. Young EW, Akiba T, Albert JM, McCarthy JT, Kerr PG, Mendelssohn DC, et al. Magnitude and impact of abnormal mineral metabolism in hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2004;44(Suppl 2):34-8.

31. Block GA, Hulbert-Shearon TE, Levin NW, Port FK.. Association of serum phosphorus and calcium x phosphorus product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis. 1998;31:607-17.

32. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM.. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004; 15:2208-18.

33. Slinin Y, Foley RN, Collins AJ. Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: The USRDS Waves 1, 3, and 4 Study. J Am Soc Nephrol. 2005;16:1788-93.

34. Nemeth EF, Steffey ME, Hammerland LG, Hung BC, Van Wagenen BC, DelMar EG, et al. Calcimimetics with potent and selective activity on the parathyroid calcium receptor. Proc Natl Acad Sci U S A. 1998;95:4040-5.

35. Goodman WG. Calcimimetics: a remedy for all problems of excess parathyroid hormone activity in chronic kidney disease? Curr Opin Nephrol Hypertens. 2005;14:355-60.

36. Chen RA, Goodman WG. The role of the calcium-sensing receptor in parathyroid gland physiology. Am J Physiol Renal Physiol. 2004;286:F1005-11.

37. Goodman WG, Hladik GA, Turner SA, Blaisdell PW, Goodkin DA, Liu W, et al. The calcimimetic agent AMG 073 lowers plasma parathyroid hormone levels in hemodialysis patients with secondary hyperparathyroidism. J Am Soc Nephrol. 2002;13:1017-24.

38. Collins MT, Skarulis MC, Bilezikian JP, Silverberg SJ, Spiegel AM, Marx SJ. Treatment of hypercalcemia secondary to parathyroid carcinoma with a novel calcimimetic agent. J Clin Endocrinol Metab. 1998;83:1080-3.

39. Goodman WG. Calcimimetic agents and secondary hyperparathyroidism: rationale for use and results from clinical trials. Pediatr Nephrol. 2003;18:1206-10.

40. Harris RZ, Padhi D, Marbury TC, Noveck RJ, Salfi M, Sullivan JT. Pharmacokinetics, pharmacodynamics, and safety of cinacalcet hydrochloride in hemodialysis patients at doses up to 200 mg once daily. Am J Kidney Dis. 2004;44:1070-6.

41. Silverberg SJ, Bone HG 3rd, Marriott TB, Locker FG, Thys-Jacobs S, Dziem G, et al. Short-term inhibition of parathyroid hormone secretion by a calcium-receptor agonist in patients with primary hyperparathyroidism. N Engl J Med. 1997; 337:1506-10.

42. Antonsen JE, Sherrard DJ, Andress DL. A calcimimetic agent acutely suppresses parathyroid hormone levels in patients with chronic renal failure. Rapid communication. Kidney Int. 1998;53:223-7.

43. Moe SM, Cunningham J, Bommer J, Adler S, Rosansky SJ, Urena-Torres P, et al. Long-term treatment of secondary hyperparathyroidism with the calcimimetic cinacalcet HCl. Nephrol Dial Transplant. 2005;20:2186-93; Epub 2005 Jul 19.

44. Block GA, Martin KJ, de Francisco ALM, Turner SA, Avram MM, Suranyi MG, et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med. 2004;350:1516-25.

45. Lindberg JS, Culleton B, Wong G, Borah MF, Clark RV, Shapiro WB, et al. Cinacalcet HCl, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: A randomized, double-blind, multicenter study. J Am Soc Nephrol. 2005;16:800-7; Epub 2005 Feb 2.

46. Martin KJ, Jüppner H, Sherrard DJ, Goodman WG, Kaplan MR, Nassar G, et al. First- and second-generation PTH assays during treatment of hyperparathyroidism with cinacalcet HCl. Kidney Int. 2005;68:1236-43.

47. Kifor O, Moore FD Jr., Wang P, Goldstein M, Vassilev P, Kifor I et al. Reduced immunostaining for the extracellular Ca^{+2}-sensing receptor in primary and uremic secondary hyperparathyroidism. J Clin Endocrinol Metab. 1996;81:1598-1606.

48. Brown AJ, Ritter CS, Finch JL, Slatopolsky EA. Decreased calcium-sensing receptor expression in hyperplastic parathyroid glands of uremic rats: role of dietary phosphate. Kidney Int. 1999;55:1284-92.

49. Martin-Salvago M, Villar-Rodriguez JL, Palma-Alvarez A, Beato-Moreno A, Galera-Davidson H. Decreased expression of calcium receptor in parathyroid tissue in patients with hyperparathyroidism secondary to chronic renal failure. Endocr Pathol. 2003;14:61-70.

50. Goodman WG. Calcium and phosphorus metabolism in patients who have chronic kidney disease. Med Clin North Am. 2005;89:631-47.

51. Parfitt AM. Misconceptions (3): calcium leaves bone only by resorption and enters only by formation. Bone. 2003; 33:259-63.

52. Moe SM, Chertow GM, Coburn JW, Quarles LD, Goodman WG, Block GA, et al. Achieving NKF-K/DOQI™ bone metabolism and disease treatment goals with cinacalcet HCl. Kidney Int. 2005;67:760-71.

53. Chertow GM, Blumenthal S, Turner S, Roppolo M, Stern L, Chi EM, et al. Cinacalcet hydrochloride (Sensipar) in hemodialysis patients on active vitamin D derivatives with controlled PTH and elevated calcium and phosphate. Clin J Am Soc Nephrol. 2006;1:305-12; Epub 2006 Jan 25.

54. Block GA, Zeig S, Sugihara J, Chertow GM, Chi EM, Turner SA, et al. Combined therapy with cinacalcet and low doses of vitamin D sterols in patients with moderate to severe secondary hyperparathyroidism. Nephrol Dial Transplant. [Epub ahead of print]

55. Messa P, Macário F, Yaqoob M, Bouman K, Braun J, von Albertini B, et al. The OPTIMA study: assessing a new cinacalcet (Sensipar/Mimpara) treatment algorithm for secondary hyperparathyroidism. Clin J Am Soc Nephrol. 2008; 3:36-45.