

Cinacalcet Hydrochloride in Chronic Kidney Disease—Mineral Bone Disorder

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Secondary hyperparathyroidism (SHPT) has been recognized as an important therapeutic target because it triggers vascular and visceral calcification, thereby contributing to the substantially increased risk for cardiovascular death in patients with ESRD during dialysis. Calcium-sensing receptor (CaSR) is a G protein-coupled receptor identified as an essential molecule for the regulation of parathyroid hormone (PTH) secretion by extracellular calcium (Ca). Binding of extracellular Ca inhibits PTH secretion. Calcimimetic drugs such as cinacalcet suppress PTH secretion by sensitizing CaSR to extracellular Ca. In the United States, cinacalcet became commercially available in May 2004.

Previous randomized, controlled trials among patients with persistent SHPT despite combined use of intravenous vitamin D and phosphate binder demonstrated that the addition of cinacalcet considerably reduced serum calcium, phosphorus, and PTH values (1–3). These results appreciably add to existing data on the efficacy and safety of cinacalcet, including data from several double-blind, randomized, placebo-controlled studies that followed dialysis patients for 26 to 52 wk (1,2,4), as well as a small study on long-term efficacy that followed 59 patients for up to 2 yr and 16 patients for up to 3 yr (5). Clinical trial studies have been performed (1–4,6–13) (Table 1). All of these studies have consistently shown that cinacalcet effectively reduces PTH, Ca, P, and calcium-phosphorus product (Ca × P) levels in patients who have stage 5 chronic kidney disease and receive dialysis.

In this issue, Sprague *et al.* (14) demonstrate that this efficacy can be maintained for up to 180 wk (3.5 yr) without any attenuation of effect and without requiring cinacalcet dosing escalation over time to sustain the effect. In this study, the longest and most robust analysis of therapeutic options for SHPT, administration of cinacalcet in patients who were receiving dialysis demonstrated effective, well-tolerated management of SHPT through simultaneous control of PTH, Ca, P, and Ca × P levels in accordance with recommended guidelines for up to 3.5 yr. Overall, these results suggest the potential for long-term

cinacalcet therapy to stabilize or slow disease progression, thereby decreasing risk for bone and mineral metabolism disorder and cardiovascular morbidity and mortality.

The clinical use of cinacalcet should bring benefits to the treatment of chronic kidney disease–mineral bone disease, but, at the same time, cinacalcet might increase the medical cost. From the cost standpoint, we should consider whether cinacalcet can restore the secretion and morphology of the altered parathyroid glands. Martin *et al.* (15) reported that cinacalcet does not change PTH (1-84)/N-terminally truncated PTH ratio. Meola *et al.* (16) reported that cinacalcet reduced the size of enlarged parathyroid glands when their volume was <500 mm³. They also noted that some glands had their size reduced even when the volume was ≥500 mm³.

If cinacalcet can normalize the parathyroid gland cells, then for how long does it have to be administered? Jean *et al.* (17) administered cinacalcet to six patients with SHPT in an observational study. Average PTH level changed from 1039 pg/ml before treatment to <100 pg/ml at the end of treatment 1 yr later. In addition, they reported the continued effect of cinacalcet with an average PTH level of 143 pg/ml 6 mo after cinacalcet cessation. This is presumably caused by the qualitative alteration of the parathyroid glands from cinacalcet treatment.

The expression of vitamin D receptor and that of CaSR are reduced in the nodular lesions of SHPT. In addition, the nodular lesions are resistant to active vitamin D treatment and serum Ca increase. Does cinacalcet bring a qualitative alteration to these lesions? Mizobuchi *et al.* (18) administered R-568, the first-generation calcimimetics, in rats with renal failure and examined its impact on CaSR expression. R-568 rats demonstrated similar CaSR expression to the control that received sham surgery. These data may suggest that the change in PTH secretion, the reduction in parathyroid gland size, and the qualitative alteration of the parathyroid glands may indicate the possibility of complete weaning of cinacalcet.

We now discuss another issue, the concomitant use of cinacalcet and vitamin D. Rodriguez *et al.* (19) reported that the concomitant administration of R-568 and vitamin D in rats with renal failure additionally expressed vitamin D receptor. St. Peter *et al.* (20) examined the change in frequency of cinacalcet treatment in 45,487 patients who were undergoing hemodialysis and reported that frequency of cinacalcet treatment in-

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Table 1. Clinical studies for cinacalcet hydrochloride

Study	No. of Patients	Reduction Rate (%)			Promotion of K/DOQI Treatment Goals (%)	Study Design
		Ca	P	iPTH		
Block <i>et al.</i> (1), 2004	371	6.8	8.4	43.00	—	Double-blind, placebo-controlled study
Lindberg <i>et al.</i> (2), 2005	294	6.5	7.2	40.50	—	Double-blind, placebo-controlled study
Moe <i>et al.</i> (3), 2005	665	—	—	—	41.0	Open-label study
Chertow <i>et al.</i> (6), 2006	72	9.7	11.1	1.80	47.0	Open-label study
Arenas <i>et al.</i> (7), 2007	28	13.1	10.4	70.00	64.7	Open-label study
Sterrett <i>et al.</i> (4), 2007	99	6.5	3.6	47.80	42.0	Double-blind, placebo-controlled study
Lazar <i>et al.</i> (8), 2007	35	8.1	10.1	29.60	43.0	Double-blind, placebo-controlled study
Block <i>et al.</i> (9), 2008	444	—	—	—	54.0	Open-label study
Fishbane <i>et al.</i> (10), 2008	87	7.1	1.2	47.30	33.0	Open-label study
Messa <i>et al.</i> (11), 2008	368	7.0	5.0	46.00	59.0	Open-label study
Fukagawa <i>et al.</i> (12), 2008	72	8.1	10.2	54.36	26.4	Double-blind, placebo-controlled study
Shigematsu <i>et al.</i> (13), 2009	199	—	—	52.38	—	Open-label study

iPTH, intact PTH; K/DOQI, Kidney Disease Outcomes Quality Initiative.

creased only slightly and most of the patients received the concomitant therapy.

From now on, it is believed that fractures, cardiovascular diseases, and life prognosis will attract much attention. Cunningham *et al.* (21) conducted a double-blind, placebo-controlled, randomized, controlled trial of 1184 untreated patients with SHPT (PTH \geq 300 pg/ml) and ESRD. The result demonstrated the significant reduction of hospitalization risk as a result of cardiovascular diseases, fracture, or parathyroidectomy in the cinacalcet group. Wada *et al.* (22) administered R-568 to rats with renal failure and found that osteitis fibrosa was halted or reversed as a result of its PTH-lowering effect. Malluche *et al.* (23) also demonstrated the similar reduction of osteitis fibrosa in their study, although their study had only 19 patients in the cinacalcet group and 13 in the placebo group.

On suppression of vascular calcification, Kawata *et al.* (24) used 5/6 nephrectomized rats to investigate the effect of cinacalcet on the suppression of calcification. Alizarin red staining demonstrated the suppressed calcification of arterial smooth muscle cells in the cinacalcet group. The level of expression of calcification-related factors also indicated that cinacalcet suppresses vascular calcifications against calcification and phosphate load caused by vitamin D administration.

Then, can cinacalcet reduce calcifications that have already been developed? Can it occur in humans? Aladren *et al.* (25) reported that cinacalcet reduced vascular calcifications in their case study in which cinacalcet was given to treat ectopic calcifications in the lung.

Moreover, cinacalcet is expected to demonstrate effects in addition to its activity for the reduction of PTH. The Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE Study) is currently under way in North America, Europe, and Australia (scheduled to be completed in 2010) to determine the therapeutic algorithm for reducing the risk for cardiovascular complications, which are a severe problem for dialysis patients (patients with SHPT). This study is a double-blind, randomized, comparative trial that has enrolled 3800 patients who are from 22 countries and are allocated to either a cinacalcet group or a placebo group. A total of 1900 patients each in the cinacalcet group and placebo group are being prospectively followed up for 4 yr. The time until the occurrence of death or a complex of nonfatal cardiovascular events (myocardial infarction, unstable angina, heart failure, and peripheral vascular disease) is the primary efficacy end point, and the time until the occurrence of death, cardiovascular death, onset of arteriosclerosis, hospitalization as a result of the onset of unstable angina, heart failure, peripheral disease, and cerebral infarction are also assessed after classifying the events as fatal and nonfatal. Interim analysis is being performed at present because 2.5 of the 4 yr have passed (26). The EVOLVE Study will elucidate the effect of cinacalcet on cardiovascular disease.

Cinacalcet not only reduces PTH but also the Ca, P, and Ca \times P levels. Drugs that increase Ca, such as active vitamin D or P binders that contain Ca are used as conventional therapy for SHPT, but the use of P adsorbents that do not increase the Ca level, such as sevelamer hydrochloride and lanthanum carbon-

ate, necessitates the selection of a drug in consideration of the Ca balance. SHPT was considered to be a problem solved when the clinical use of active vitamin D became possible in the 1980s; however, it is questionable whether SHPT can be controlled solely by suppression of Ca receptors. In fact, the effect of cinacalcet is considered to vary among individuals. The gene polymorphism of Ca receptors is considered to be involved in the response of PTH to extracellular Ca (27). The Ca channel is also involved in the mechanism of Ca sensitivity. Involvement of new molecules such as Klotho and fibroblast growth factor 23 has been suggested in the onset of SHPT, and the effect of cinacalcet on the kinetics of these molecules should be elucidated.

Disclosures

None.

References

- Block GA, Martin KJ, de Francisco AL, Turner SA, Avram MM, Suranyi MG, Hercz G, Cunningham J, Abu-Alfa AK, Messa P, Coyne DW, Locatelli F, Cohen RM, Evenepoel P, Moe SM, Fournier A, Braun J, McCary LC, Zani VJ, Olson KA, Drueke TB, Goodman WG: Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med* 350: 1516–1525, 2004
- Lindberg JS, Culleton B, Wong G, Borah MF, Clark RV, Shapiro W, Roger SD, Husserl FE, Klassen PS, Guo MD, Albizem MB, Coburn JW: 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* 16: 800–807, 2005
- Moe SM, Cunningham J, Bommer J, Adler S, Rosansky SJ, Urena-Torres P, Albizem MB, Guo MD, Zani VJ, Goodman WG, Sprague SM: Long-term treatment of secondary hyperparathyroidism with the calcimimetic cinacalcet HCl. *Nephrol Dial Transplant* 20: 2186–2193, 2005
- Sterrett JR, Strom J, Stummvoll H-K, Bahner U, Disney A, Soroka SD, Corpier C, Arruda JA, Schwanauer LE, Klassen PS, Olson KA, Block GA: Cinacalcet HCl (Sensipar/Mimpara) is an effective chronic therapy for hemodialysis patients with secondary hyperparathyroidism. *Clin Nephrol* 68: 10–17, 2007
- Moe SM, Chertow GM, Coburn JW, Quarles LD, Goodman WG, Block GA, Drueke TB, Cunningham J, Sherrard DJ, McCary LC, Olson KA, Turner SA, Martin KJ: Achieving NKF-K/DOQI bone metabolism and disease treatment goals with cinacalcet HCl. *Kidney Int* 67: 760–771, 2005
- Chertow GM, Blumenthal S, Turner S, Roppolo M, Stern L, Chi EM, Reed J: CONTROL Investigators: Cinacalcet hydrochloride (Sensipar) in hemodialysis patients on active vitamin D derivatives with controlled PTH and elevated calcium x phosphate. *Clin J Am Soc Nephrol* 2: 305–312, 2006
- Arenas MD, Alvarez-Ude F, Gil MT, Moledous A, Malek T, Nuñez C, Devesa R, Carretón MA, Soriano A: Implementation of 'K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease' after the introduction of cinacalcet in a population of patients on chronic haemodialysis. *Nephrol Dial Transplant* 6: 1639–1644, 2007
- Lazar E, Hebert K, Poma T, Stankus N: Long-term outcomes of cinacalcet and paricalcitol titration protocol for treatment of secondary hyperparathyroidism. *Am J Nephrol* 27: 274–278, 2007
- Block GA, Zeig S, Sugihara J, Chertow GM, Chi EM, Turner SA, Bushinsky DA, TARGET Investigators: Combined therapy with cinacalcet and low doses of vitamin D sterols in patients with moderate to severe secondary hyperparathyroidism. *Nephrol Dial Transplant* 23: 2311–2318, 2008
- Fishbane S, Shapiro WB, Corry DB, Vicks SL, Roppolo M, Rappaport K, Ling X, Goodman WG, Turner S, Charytan C: Cinacalcet HCl and concurrent low-dose vitamin D improves treatment of secondary hyperparathyroidism in dialysis patients compared with vitamin D alone: The ACHIEVE study results. *Clin J Am Soc Nephrol* 3: 1718–1725, 2008
- Messa P, Macário F, Yaqoob M, Bouman K, Braun J, von Albertini B, Brink H, Maduell F, Graf H, Frazão JM, Bos WJ, Torregrosa V, Saha H, Reichel H, Wilkie M, Zani VJ, Molemans B, Carter D, Locatelli F: The OPTIMA study: Assessing a new cinacalcet (Sensipar/Mimpara) treatment algorithm for secondary hyperparathyroidism. *Clin J Am Soc Nephrol* 3: 36–45, 2008
- Fukagawa M, Yumita S, Akizawa T, Uchida E, Tsukamoto Y, Iwasaki M, Koshikawa S: KRN1493 Study Group: Cinacalcet (KRN1493) effectively decreases the serum intact PTH level with favorable control of the serum phosphorus and calcium levels in Japanese dialysis patients. *Nephrol Dial Transplant* 23: 328–335, 2008
- Shigematsu T, Akizawa T, Uchida E, Tsukamoto Y, Iwasaki M, Koshikawa S: KRN1493 Study Group: Long-term cinacalcet HCl treatment improved bone metabolism in Japanese hemodialysis patients with secondary hyperparathyroidism. *Am J Nephrol* 29: 230–236, 2009
- Sprague SM, Evenepoel P, Curzi MP, González MT, Husserl FE, Kopyt N, Sterling LR, Mix C, Wong G: Simultaneous control of PTH and Ca x P is sustained over three years of treatment with cinacalcet HCl. *Clin J Am Soc Nephrol* 4: 1465–1476
- Martin KJ, Jüppner H, Sherrard DJ, Goodman WG, Kaplan MR, Nassar G, Campbell P, Curzi M, Charytan C, McCary LC, Guo MD, Turner SA, Bushinsky DA: First- and second-generation immunometric PTH assays during treatment of hyperparathyroidism with cinacalcet HCl. *Kidney Int* 68: 1236–1243, 2005
- Meola M, Petrucci I, Giuliano B: Long-term treatment with cinacalcet and conventional therapy reduces parathyroid hyperplasia in severe secondary hyperparathyroidism. *Nephrol Dial Transplant* 24: 982–989, 2009
- Jean G, Chazot C, Charra B: Six cases of successful cinacalcet cessation in haemodialysis patients treated for secondary hyperparathyroidism. *Nephrol Dial Transplant* 22: 2102–2103, 2007
- Mizobuchi M, Hatamura I, Ogata H, Saji F, Uda S, Shiizaki K, Sakaguchi T, Negi S, Kinugasa E, Koshikawa S, Akizawa T: Calcimimetic compound upregulates decreased calcium-sensing receptor expression level in para-

- thyroid glands of rats with chronic renal insufficiency. *J Am Soc Nephrol* 15: 2579–2587, 2004
19. Rodriguez ME, Almaden Y, Canadillas A, Canalejo A, Siendones E, Lopez I, Aguilera-Tejero E, Martin D, Rodriguez M: The calcimimetic R-568 increases vitamin D receptor expression in rat parathyroid glands. *Am J Physiol Renal Physiol* 292: F1390–F1395, 2007
 20. St Peter WL, Li Q, Liu J, Persky M, Nieman K, Arko C, Block GA: Cinacalcet use patterns and effect on laboratory values and other medications in a large dialysis organization, 2004 through 2006. *Clin J Am Soc Nephrol* 4: 354–360, 2009
 21. Cunningham J, Danese M, Olson K, Klassen P, Chertow GM: Effects of the calcimimetic cinacalcet HCL on cardiovascular disease, fracture, and health related quality of life in secondary hyperparathyroidism. *Kidney Int* 68: 1793–1800, 2005
 22. Wada M, Ishii H, Furuya Y, Fox J, Nemeth EF, Nagano N: NPS R-568 halts or reverses osteitis fibrosa in uremic rats. *Kidney Int* 53: 448–453, 1998
 23. Malluche HH, Monier-Faugere MC, Wang G, Frazā O JM, Charytan C, Coburn JW, Coyne DW, Kaplan MR, Baker N, McCary LC, Turner SA, Goodman WG: An assessment of cinacalcet HCl effects on bone histology in dialysis patients with secondary hyperparathyroidism. *Clin Nephrol* 69: 269–278, 2008
 24. Kawata T, Nagano N, Obi M, Miyata S, Koyama C, Kobayashi N, Wakita S, Wada M: Cinacalcet suppresses calcification of the aorta and heart in uremic rats. *Kidney Int* 74: 1270–1277, 2008
 25. Aladren Regidor MJ: Cinacalcet reduces vascular and soft tissue calcification in secondary hyperparathyroidism (SHPT) in hemodialysis patients. *Clin Nephrol* 71: 207–213, 2009
 26. Chertow GM, Blumenthal S, Turner S, Roppolo M, Stern L, Chi EM, Reed J: CONTROL Investigators: Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE): Rationale and design overview. *Clin J Am Nephrol* 2: 898–905, 2007
 27. Yokoyama K, Shigematsu T, Tsukada T, Hara S, Yamada A, Kawaguchi Y, Hosoya T: Calcium-sensing receptor gene polymorphism affects the parathyroid response to moderate hypercalcemic suppression in patients with end-stage renal disease. *Clin Nephrol* 57: 131–135, 2002

See related article, “Simultaneous Control of PTH and Ca \times P Is Sustained over Three Years of Treatment with Cinacalcet HCl,” on pages 1465–1476.