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Calcimimetic Agents for the Treatment of Secondary Hyperparathyroidism

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Calcimimetic agents function as allosteric activators of the calcium-sensing receptor (CaSR). In parathyroid tissue, they decrease the threshold for CaSR activation by extracellular calcium ions and diminish parathyroid hormone (PTH) secretion directly. Results from small clinical studies in hemodialysis patients with secondary hyperparathyroidism have shown that single oral doses of calcimimetic compounds abruptly decrease plasma PTH levels within 1 to 2 hours in a dose-dependent manner. Sustained decreases in plasma PTH levels can be achieved when daily oral doses are given for as long as 18 weeks. Decreases in plasma PTH levels often are associated with modest decreases in serum calcium and phosphorus levels, but symptomatic hypocalcemia is uncommon. Data gathered during larger more recent clinical trials lasting 12 to 24 months again indicate that plasma PTH levels can be decreased effectively with persistent and favorable decreases in serum phosphorus levels and in values for the calcium-phosphorus ion product in serum. Calcimimetic agents thus offer a novel treatment for secondary hyperparathyroidism in patients with chronic kidney disease stage 5, who are managed with dialysis. Unlike the vitamin D sterols, calcimimetic compounds effectively decrease plasma PTH levels without aggravating disturbances in mineral metabolism that have been associated with adverse clinical outcomes.

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Calcimimetic agents are small organic molecules that act as allosteric activators of the calcium-sensing receptor (CaSR). In the parathyroid glands, they decrease the threshold for CaSR activation by extracellular calcium ions and diminish parathyroid hormone (PTH) secretion. This mechanism of action differs fundamentally from that of the vitamin D sterols, which diminish pre-pro-PTH gene transcription over many hours or several days, making less hormone available for release into the circulation. Calcimimetic compounds thus provide a new intervention for managing clinical conditions that are characterized by excess PTH secretion and persistently increased plasma PTH levels. Among these disorders is secondary hyperparathyroidism caused by chronic kidney disease (CKD).

During the past several years, a number of small clinical trials have been performed to assess the safety and efficacy of several calcimimetic compounds for treating secondary hyperparathyroidism in patients undergoing long-term hemodialysis. The current review summarizes these results and provides an overview of the potential therapeutic use of calcimimetic agents for this clinical disorder.

Clinical Studies With a First-Generation Calcimimetic Agent: R-568

Antonsen et al¹ reported the initial experience with a first-generation calcimimetic compound, R-568, in hemodialysis patients with secondary hyperparathyroidism. This and subsequent preliminary studies characterized the acute biochemical responses to the administration of calcimimetic agents among adult patients with established secondary hyperparathyroidism.

Calcimimetic agents are phenylalkylamines.² They are highly lipophilic and are absorbed rapidly from the gastroin-

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testinal tract after oral administration. Accordingly, single oral doses of R-568 were shown to decrease plasma PTH levels within only 1 to 2 hours in patients with secondary hyperparathyroidism caused by CKD.^{1,2} After a rapid initial decrease, plasma PTH levels increased subsequently toward pretreatment values but remained below baseline levels for the remainder of the day in those given relatively larger doses.^{1,2} Both the magnitude of the decrease in plasma PTH levels and the duration of the decrease in PTH concentrations were largely dose dependent. Such findings thus confirmed results from preclinical studies in animal experiments.^{3,4} Decreases in plasma PTH levels were observed in all patients evaluated, and the magnitude of the response, as judged by the percentage decrease in plasma PTH levels, did not differ by disease severity as defined by baseline plasma PTH values.

In addition to acutely decreasing plasma PTH levels, the administration of R-568 to hemodialysis patients with secondary hyperparathyroidism produced transient decreases in blood ionized calcium concentration in those given small doses. Blood ionized calcium levels decreased progressively, however, over 48 hours in patients given larger doses for 2 consecutive days.² The decrease in blood ionized calcium concentration followed the initial decrease in plasma PTH levels. The mechanism that accounts for this change remains uncertain, but it may reflect substantive decreases in calcium efflux from bone as plasma PTH levels decrease abruptly. Similar biochemical changes occur immediately after surgical parathyroidectomy, in which PTH-mediated decreases in calcium efflux from bone together with continued high rates of skeletal calcium uptake often lead to hypocalcemia. It is possible, however, that activation of the CaSR in bone or other tissues also could contribute.^{5,6}

The experience with R-568 during early phase II clinical trials documented that blood ionized calcium and serum total calcium concentrations could be decreased substantially in some patients who received relatively large initial doses and in others who were given fixed daily doses repeatedly with downward dosage adjustments.² To circumvent this potentially dose-limiting side effect, a dose-titration scheme was used in subsequent phase II and phase III clinical studies to diminish the calcium-decreasing effect of calcimimetic therapy and to decrease the risk for overt hypocalcemia during ongoing treatment. Indeed, substantial decreases in serum calcium levels largely can be avoided by using small initial doses and by increasing doses incrementally as serum calcium levels are monitored. Modifying the doses of oral calcium supplements and vitamin D sterols in patients receiving these agents provides another method for maintaining serum calcium levels during treatment with calcimimetic compounds.

The clinical development of R-568 was terminated because the bioavailability of this compound after oral administration was rather low. Its pharmacokinetic characteristics also were somewhat variable, and it had the potential to interfere with the metabolism of a variety of drugs via the hepatic cytochrome P-450 pathway. A second-generation calcimimetic agent, AMG 073 or cinacalcet hydrochloride, thus was introduced for further evaluation. The bioavailabil-

ity of cinacalcet HCl is substantially greater than that of R-568, and its pharmacokinetics and pharmacodynamics are much more consistent.

Clinical Studies With a Second-Generation Calcimimetic Agent: AMG 073 Or Cinacalcet HCl

Short-term studies using single oral doses of AMG 073 or cinacalcet confirmed earlier findings using R-568 in patients with secondary hyperparathyroidism caused by CKD. Amounts ranging from 25 to 100 mg substantially decreased plasma PTH levels in a dose-dependent manner.⁷ The nadir of plasma PTH levels was reached within 2 to 4 hours, but the percentage decreases in plasma PTH levels after single oral doses again was unrelated to baseline PTH values. Patients with mild, moderate, or severe disease thus responded similarly, and all patients given cinacalcet experienced a decrease in plasma PTH levels. Although mean serum total calcium concentrations decreased by approximately 1.0 mg/dL from baseline values 8 to 12 hours after 75- or 100-mg doses, none of the patients experienced symptoms of hypocalcemia.⁷

The response to repeated, single, daily, oral doses of cinacalcet ranging from 10 to 50 mg was assessed in a placebo-controlled trial of 30 adult hemodialysis patients receiving standard care with phosphate-binding agents and vitamin D sterols.⁷ Plasma PTH levels decreased by 25% to 40% after 8 days of treatment in patients receiving 25- or 50-mg doses, but values did not change in those given 10 mg or placebo. Serum calcium levels decreased by 5% to 10% in subjects given daily doses of 25 or 50 mg, whereas serum phosphorus levels decreased unexpectedly by 20% to 25% after 8 days of treatment. Calculated values for the calcium-phosphorus ion product in serum also decreased.⁷

Treatment with cinacalcet thus effectively decreased plasma PTH levels when added to conventional therapy in patients with established secondary hyperparathyroidism. Moreover, serum phosphorus levels and values for the calcium-phosphorus ion product in serum decreased substantially. Cinacalcet therapy thus favorably affected 2 important biochemical disturbances that have been associated with adverse clinical outcomes in patients undergoing long-term dialysis. Whether similar benefits can be documented in long-term clinical trials has yet to be determined. Although decreases in serum calcium concentration represent a potentially dose-limiting side effect of calcimimetic therapy, the dose-titration schemes used in subsequent phase II and phase III clinical trials attenuate the calcium-decreasing effects of cinacalcet and limit substantially the frequency of episodes of hypocalcemia.

Two separate, double-blind, prospective, placebo-controlled phase II clinical trials of 18 weeks duration were performed to assess the safety and efficacy of sustained treatment with cinacalcet in adult patients with secondary hyperparathyroidism. In both studies, pretreatment

plasma PTH levels exceeded 300 pg/mL whether or not patients also were receiving vitamin D sterols. In one study, the initial daily dose of cinacalcet was 20 mg, and doses were increased by increments of 10 mg at 3-week intervals if plasma PTH levels remained greater than a therapeutic target level of 250 pg/mL and if serum calcium levels were greater than 8.4 mg/dL. The maximum allowable daily dose of cinacalcet was 50 mg.⁸ In the other 18-week study, the initial dose of cinacalcet was 25 mg and doses were increased in 25-mg increments to a maximum daily dose of 100 mg using the same safety criteria.⁹ The average plasma PTH level achieved during the final 6 weeks of study was used to assess efficacy.

In the first of these trials, mean plasma PTH levels were 26% lower than pretreatment values during the 6-week efficacy assessment phase.⁸ Values were more than 30% below baseline during the maintenance phase of study in 40% of cinacalcet-treated patients compared with only 8% of placebo-treated patients. Serum phosphorus levels decreased by approximately 10%, whereas values for the calcium-phosphorus ion product in serum decreased by 17%.⁸

In the other 18-week trial, which used a larger maximum daily dose of cinacalcet, plasma PTH levels decreased by an average of 33% from baseline during the 6-week maintenance phase of the study, and 53% of cinacalcet-treated patients experienced a 30% or greater decrease in mean plasma PTH levels.⁹ Values for the calcium-phosphorus ion product in serum also decreased substantially compared with placebo. For patients given cinacalcet, serum calcium concentrations during the maintenance phase of study averaged 9.1 ± 1.0 mg/dL compared with a pretreatment mean of 9.6 ± 0.1 mg/dL.⁹ Thus, cinacalcet effectively decreased plasma PTH levels with only modest decreases in serum calcium concentration.

Results from another 12-week study conducted in Europe confirm these findings.¹⁰ Overall, treatment with cinacalcet has been tolerated quite well, and the frequency of adverse events generally has been no different from that reported among patients given placebo. Nausea and vomiting occur, however, in some patients.

To date, all studies of cinacalcet in patients with secondary hyperparathyroidism have used single daily oral doses. More frequent dosing strategies have not been evaluated in such patients. A twice-daily oral dosing strategy has been used in patients with primary hyperparathyroidism,¹¹ but the safety and efficacy of this approach has yet to be assessed in patients with CKD.

It is important to recognize that the biochemical response to treatment with cinacalcet in patients with secondary hyperparathyroidism has been based on PTH determinations obtained in blood samples collected 24 hours after the preceding dose.⁷⁻⁹ Because plasma PTH levels decrease rapidly within the first few hours after drug administration but increase subsequently toward predose values after 24 hours, measurements obtained 24 hours after daily doses of cinacalcet reflect the minimum degree to which plasma PTH levels have been decreased during the day.⁷ Time-averaged plasma PTH levels are substan-

tially lower. Recognizing that PTH levels vary substantially throughout the day in patients receiving cinacalcet, information about the time of day at which blood samples were obtained and the relationship to previous doses of cinacalcet will be required to interpret plasma PTH levels properly during ongoing treatment.

Summary

Treatment with cinacalcet effectively decreases plasma PTH levels and improves several biochemical abnormalities that complicate secondary hyperparathyroidism and its clinical management in patients undergoing hemodialysis. Plasma PTH levels decrease whether or not patients also are treated with vitamin D. Although serum calcium concentrations decrease modestly, the frequency of episodes of hypocalcemia is no greater in those given cinacalcet alone than in patients given cinacalcet together with vitamin D sterols. Moreover, the calcium-decreasing effect of cinacalcet is attenuated by using small initial doses followed-up by modest increases in dose to achieve a decrease in plasma PTH levels. Serum phosphorus levels often decrease during treatment, and this biochemical change distinguishes the response to cinacalcet from that seen during vitamin D therapy.

Available data suggest that cinacalcet can be used safely as a primary therapeutic intervention for decreasing plasma PTH levels in patients with secondary hyperparathyroidism. It should be useful for treating patients who cannot be given vitamin D sterols safely because increased serum calcium and/or phosphorus levels preclude their use. Because of different mechanisms of action, the combined use of cinacalcet and vitamin D may provide a particularly effective therapeutic intervention for patients with more advanced disease. By selectively targeting the CaSR, calcimimetic compounds such as cinacalcet offer a novel approach to managing secondary hyperparathyroidism that favorably influences several disturbances in mineral metabolism that have been associated with adverse long-term outcomes in patients undergoing regular hemodialysis.

References

1. Antonsen JE, Sherrard DJ, Andress DL: A calcimimetic agent acutely suppresses parathyroid hormone levels in patients with chronic renal failure. Rapid communication. *Kidney Int* 53:223-227, 1998
2. Goodman WG, Frazao JM, Goodkin DA, et al: A calcimimetic agent lowers plasma parathyroid hormone levels in patients with secondary hyperparathyroidism. *Kidney Int* 58:436-445, 2000
3. Fox J, Lowe SH, Petty BA, et al: NPS R-568: A type II calcimimetic compound that acts on parathyroid cell calcium receptor of rats to reduce plasma levels of parathyroid hormone and calcium. *J Pharmacol Exp Ther* 290:473-479, 1999
4. Fox J, Lowe SH, Conklin RL, et al: The calcimimetic NPS R-568 decreases plasma PTH in rats with mild and severe renal or dietary secondary hyperparathyroidism. *Endocrine* 10:97-103, 1999
5. Yamaguchi T, Chattopadhyay N, Kifor O, et al: Expression of extracellular calcium-sensing receptor in human osteoblastic MG-63 cell line. *Am J Physiol* 280:C382-C393, 2001
6. Yamaguchi T, Kifor O, Chattopadhyay N, et al: Expression of extracellular calcium (Ca²⁺)-sensing receptor in the clonal osteoblast-like cell lines, UMR-106 and SAOS-2. *Biochem Biophys Res Commun* 243:753-757, 1998
7. Goodman WG, Hladik GA, Turner SA, et al: The calcimimetic agent

- AMG 073 lowers plasma parathyroid hormone levels in hemodialysis patients with secondary hyperparathyroidism. *J Am Soc Nephrol* 13:1017-1024, 2002
8. Lindberg JS, Moe SM, Goodman WG, et al: The calcimimetic AMG 073 reduces parathyroid hormone and calcium \times phosphorus product levels in hemodialysis patients with secondary hyperparathyroidism. *Kidney Int* 63:248-254, 2003
 9. Quarles LD, Sherrard DJ, Adler S, et al: The calcimimetic AMG 073 as a potential treatment for secondary hyperparathyroidism of end-stage renal disease. *J Am Soc Nephrol* 14:575-583, 2003
 10. Drüeke T, Cunningham J, Goodman WG, et al: Short-term treatment of secondary hyperparathyroidism with the calcimimetic agent AMG 073. *J Am Soc Nephrol* 12:764, 2001
 11. Shoback DM, Bilezikian JP, Turner SA, et al: The calcimimetic cinacalcet normalizes serum calcium in subjects with primary hyperparathyroidism. *J Clin Endocrinol Metab* 88:5644-5649, 2003