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Calcimimetic and calcilytic drugs for treating bone and mineral-related disorders

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The calcium-sensing receptor (CaSR) plays a pivotal role in regulating systemic Ca^{2+} homeostasis and is a target for drugs designed to treat certain disorders of bone and mineral metabolism. Calcimimetics are agonists or positive allosteric modulators of the CaSR; they inhibit parathyroid hormone (PTH) secretion and stimulate renal Ca^{2+} excretion. The first calcimimetic drug is cinacalcet, a positive allosteric modulator of the CaSR that is approved for treating secondary hyperparathyroidism (HPT) in patients on renal replacement therapy and for some forms of primary HPT characterized by clinically significant hypercalcemia. Cinacalcet is also being investigated as a therapy for other hypercalcemic conditions and certain hypophosphatemic disorders. Calcilytics are CaSR inhibitors that stimulate the secretion of PTH and decrease renal excretion of Ca^{2+}. Although calcilytics have failed thus far as anabolic therapies for osteoporosis, they are currently being evaluated as novel therapies for new indications involving hypocalcemia and/or hypercalciuria.

Introduction

About 25 years ago, it became apparent that parathyroid cells express a cell surface CaSR that enables these cells to detect and respond to small changes in the concentration of extracellular Ca^{2+}. Because extracellular Ca^{2+} is the principal physiological regulator of PTH secretion, the CaSR was

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thought to be a target for novel drugs potentially useful in treating certain disorders of bone and mineral metabolism.[1] Activators of the CaSR, which would inhibit secretion of PTH, were envisioned as medical therapy for primary hyperparathyroidism (HPT) and a new approach to treat secondary HPT in patients with chronic kidney disease (CKD). It was also becoming clear at that time that transient increases in circulating levels of PTH, achieved by the systemic administration of PTH fragments, stimulate new bone formation. A CaSR inhibitor would be expected to stimulate secretion of PTH and could provide an orally-active anabolic therapy for osteoporosis. The development of potent and selective activators and inhibitors of the CaSR has sustained some of these initial suppositions.

The first CaSR-active compound to enter clinical trials was the calcimimetic NPS R-568. This compound was shown to be safe and effective in patients with primary or secondary HPT but was replaced by cinacalcet because the latter had greater oral bioavailability.[1] This article focuses on the clinical results obtained with cinacalcet in patients with primary or secondary HPT and briefly discusses those obtained with calcilytic compounds.

Primary hyperparathyroidism

Several studies have addressed the safety and effectiveness of cinacalcet in the treatment of various forms of primary HPT. The first was a randomized, double-blind, placebo-controlled trial that enrolled 22 patients with mild primary HPT.[2] This study demonstrated transient decreases in plasma levels of PTH and sustained decreases in serum levels of Ca^{2+} after 15 days of twice daily administration of cinacalcet. Adverse events in this study were mild to moderate in severity and infrequent with the most common being paresthesias. Overall, both the tolerability of cinacalcet and the lowering and stability of the serum Ca^{2+} values in the study laid the groundwork for a larger Phase 3 trial.

That multicenter trial randomized 78 patients (21 men and 57 women) with mild to moderate primary HPT to treatment with cinacalcet or placebo twice daily for 52 weeks.[3] The primary endpoint was attaining normal total serum Ca^{2+} levels ($\leq$10.3 mg/dL)[d] with at least a 0.5 mg/dL reduction from the baseline level. Patients treated with cinacalcet had significantly lower serum Ca^{2+} values as early as 2 weeks after randomization, and significantly more patients treated with cinacalcet (73%) reached the primary endpoint compared to placebo (5%). The mean pre-dose decrease in plasma PTH values in patients treated with cinacalcet was 7.6% and was significantly lower than the 7.7% increase in PTH levels observed in patients treated with placebo. Serum phosphorus levels rose in cinacalcet-treated patients, compared to placebo, as expected from the fall in plasma PTH concentrations. Serum 1,25-dihydroxyvitamin D levels, while elevated at baseline in both groups, did not significantly change in response to cinacalcet. Biochemical markers of bone turnover [bone specific alkaline phosphatase (BSAP) and N-telopeptide (NTX)], which were normal at baseline, rose mildly but significantly in patients treated with cinacalcet compared to placebo. Bone mineral density (BMD) measurements at the lumbar spine, total hip and distal third of the radius did not change after treatment with cinacalcet for 52 weeks. Adverse events in both treatment groups were mild to moderate. The most common were nausea (28% cinacalcet, 16% placebo) and headache (23% cinacalcet, 41% placebo). Three patients in the cinacalcet-treated group did experience serum Ca^{2+} levels <8.0 mg/dL while receiving the lowest dose of study drug (30 mg).

The trial continued for an additional 4.5 years in an open-label extension enrolling 45 patients from the original cohort.[4] Patients previously on placebo and switched to cinacalcet treatment experienced the same degree of serum Ca^{2+} lowering as did those continuing on cinacalcet (Fig. 1). The percentage of patients who achieved serum Ca^{2+} levels of $\leq$10.3 mg/dL was 74–92% over years 2–5 of the extension study. When pre-dose plasma intact PTH levels were analyzed over the extension study, there was a significant lowering at years 4 and 5. Intact PTH levels never reached the normal range at the time-points sampled during the 4.5 year extension which was “pre-dose” - typically 12 h post-dosing (Fig. 1). Serum phosphorus levels rose with cinacalcet treatment into the low normal range and

[d] To convert serum total Ca^{2+} level expressed as mg/mL to serum ionized Ca^{2+} level in mmol/L divide by 8.0.