EDITORIAL

Treatments for secondary hyperparathyroidism in hemodialysis

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Secondary hyperparathyroidism (SHPT) is a common and serious progressive manifestation of chronic kidney disease (CKD), with negative effects on the outcomes of patients on hemodialysis. With current treatment approaches, a considerable proportion of patients have inadequately controlled parathyroid hormone (PTH), phosphorus, and calcium levels, with the values often falling outside the recommended ranges.[1] PTH is the primary regulator of calcium metabolism; it stimulates bone resorption, increasing serum calcium and phosphorus levels, and promotes vitamin D production.[2] These mineral disturbances can result in serious sequelae, such as an increased risk of renal osteodystrophy, osteitis fibrosa, progressive vascular calcification, and in turn, cardiovascular disease and death.[3]

Under normal physiological conditions, the principal regulator of parathyroid gland function and PTH secretion is the calcium-sensing receptor (CaSR).[4] Activation of the CaSR by increased serum calcium levels rapidly inhibits PTH expression, synthesis, and secretion, and parathyroid gland hyperplasia. Decreased serum calcium levels result in reduced CaSR activity, which promotes PTH synthesis and secretion. As SHPT progresses in patients with CKD–mineral and bone disorder, downregulation of the CaSR expression results in hyperplastic parathyroid glands and loss of sensitivity and responsiveness to blood calcium, which contributes to excess PTH levels observed in patients on dialysis. Furthermore, the CaSR influences PTH gene expression and may upregulate the vitamin D receptor (VDR). The parathyroid glands express high levels of the VDR, which when activated by vitamin-D binding decreases PTH gene transcription.[1] The VDR is expressed in ubiquity in tissues (including the intestines, kidneys, bone, and vessels).[3] Its activation in the gastrointestinal tract increases calcium absorption, thus elevating serum calcium levels and reducing parathyroid gland activity through CaSR activation.[4]

Both hyperphosphatemia and hypocalcemia, together with low calcitriol levels, which occur as kidney function declines, are key contributors to the pathogenesis of SHPT in patients with CKD.[5] Importantly, the compensatory downregulation of the CaSR and VDR in the parathyroid may play a central role in the development of SHPT.[6] Persistent alterations in the signaling of the CaSR and VDR, including the reduced expression of both, can eventually result in refractory SHPT, in which the parathyroid gland becomes insensitive to calcium- or calcitriol-mediated inhibition of PTH synthesis.[6] Continuous stimulation of the parathyroid glands by these derangements in mineral homeostasis promotes PTH synthesis and eventually parathyroid hyperplasia. Because of their integral roles in the pathogenesis of SHPT, the CaSR and VDR are biologically plausible targets for therapies in the treatment of this disorder.

In their study, Zawierucha et al[7] report the effects of SHPT treatment with paricalcitol alone versus paricalcitol plus cinacalcet in 64 patients on hemodialysis, with a follow-up of 6 months. In both groups, a significant decrease in serum PTH levels was observed, without major adverse events in terms of high/low levels of serum calcium or phosphorus (or both). This is an interesting study, but we would like to emphasize some critical points.

The current treatment for SHPT comprises 2 main strategies: control of PTH production by using active vitamin D analogues, and the use of calcimimetics, currently agents that allosterically modify the CaSR to enhance its activation in the presence of circulating calcium levels, thus reducing PTH levels.[8] Parathyroidectomy is usually a treatment strategy of last resort, after pharmacotherapy has failed. The goal of treatment is to maintain serum calcium, phosphorus, and PTH

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levels within accepted target ranges.[9] Because of the limitations associated with the standard-of--care treatment for SHPT, PTH targets are not met for many patients. In hemodialyzed patients affected by SHPT, active vitamin D (calcitriol and its analogue, paricalcitol) can suppress PTH levels, even if this therapeutic approach is not without risks. Active vitamin D replacement therapy could elevate calcium and phosphorus absorption, promoting hypercalcemia and hyperphosphatemia, when calcitriol or paricalcitol are used at high doses.[9]

In this study, Zawierucha et al[7] used 18 μg/wk of intravenous paricalcitol to control SHPT, and patients did not develop severe hypercalcemia or hyperphosphatemia. On the other hand, patients treated with cinacalcet (0.6 [0.3] mg/kg bw/d) did not have hypocalcemia.[7] Recent studies have evaluated whether paricalcitol might improve cardiovascular outcomes in SHPT. The phase 3 PRIMO trial,[10] a placebo-controlled randomized double--blind 48-week study, investigated the effect of paricalcitol treatment on ventricular mass in 227 patients with CKD and mild left ventricular hypertrophy but normal systolic function. Treatment with oral paricalcitol at a dose of 2 μg/d reduced PTH levels within 4 weeks and maintained them within the normal range throughout the study; however, nonsignificant increases were observed between the paricalcitol and placebo groups in the primary outcome measure (ie, the change in left ventricular mass). Moroever, reductions in PTH occurred in the context of significant elevations in serum calcium and phosphorus levels, and in the percentage of patients experiencing hypercalcemia in comparison with placebo (20.9% and 5.4%, respectively).[10]

Calcimimetics represent an additional option for the treatment of SHPT in patients with CKD receiving dialysis.[11] Unlike vitamin D analogues, cinacalcet does not elevate intestinal calcium and phosphorus absorption. Clinical evidence from subsequent trials suggests that cinacalcet, in combination with a low dose of active vitamin D analogues, is effective in lowering PTH levels.[11] In the 33-week open-label ACHIEVE trial,[14] 65% of patients receiving cinacalcet plus a low dose of active vitamin D had a reduction of 30% or higher in PTH levels from baseline, in comparison with 36% of those receiving active vitamin D alone.[12] In addition, in the 16-week open-label OPTIMA trial[13] in dialysis patients with poorly controlled SHPT, 71% of the patients receiving cinacalcet plus low-dose active vitamin D treatment achieved PTH levels of 300 pg/ml or less, as compared with 22% of patients receiving active vitamin D alone.

Hypocalcemia is a common, but easily managed, adverse event associated with cinacalcet therapy. In the placebo-controlled double-blind EVOLVE trial[14] in patients with moderate to severe SHPT receiving hemodialysis, patients received either cinacalcet or placebo. The primary composite endpoint of the study was based on the time until death, myocardial infarction, hospitalization for unstable angina, heart failure, or a peripheral vascular event. In this study, the majority of patients were already receiving phosphorus binder and vitamin D analogue therapy, but without a clinical benefit. In the primary analysis, no significant difference was detected between the cinacalcet and placebo arms in terms of the primary endpoint.[14] Nonetheless, the study results may have been influenced by the high drop-in and dropout rates of participants and the lower than expected event rate. Biochemical endpoints were achieved in a greater proportion of patients using cinacalcet.[15] However, cinacalcet was associated with a greater incidence of nausea and vomiting than placebo, and 12% of cinacalcet-treated patients developed hypocalcemia as opposed to 2% of placebo-treated ones.[14] Discontinuations due to adverse events occurred in 16% of patients in the cinacalcet group and in 12% of placebo-treated patients. Furthermore, the preplanned and exploratory sensitivity analysis suggested a nominally significant risk reduction in cardiovascular events and parathyroidectomy when imbalances in patient characteristics (eg, age) were accounted for at study entry.[14]

In summary, Zawierucha et al[7] are asking if it makes sense to combine paricalcitol with cinacalcet in SHPT treatment in patients on hemodialysis. Our answer is: "yes, it absolutely does make sense." In fact, vitamin D analogues, such as paricalcitol, selectively target the VDR, lowering PTH levels.[2] However, clinical data reveal that paricalcitol treatment can be associated with elevations in serum calcium and phosphorus, and a significant percentage of patients treated with paricalcitol experience hypercalcemia.[10] Calcimimetics, such as cinacalcet, reduce PTH and serum calcium and phosphorus levels when compared with vitamin D.[13] In addition, poor adherence has been observed among dialysis patients self-administering oral cinacalcet. Consequently, there has been interest in treating hemodialyzed patients affected by SHPT with the combination of cinacalcet and low doses of paricalcitol, to improve the efficacy and tolerability and further advance the treatment of SHPT.

The pharmacological management of SHPT has progressed in recent years. The introduction of targeted therapies, such as selective VDR and CaSR modulators, offers an increased opportunity to adequately control elevated PTH levels, especially in patients with CKD receiving dialysis.

Note The opinions expressed by the author are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

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