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Active vitamin D vs. calcimimetic as a first agent for secondary hyperparathyroidism

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The classic pathogenesis of secondary hyperparathyroidism (SHPT) in chronic kidney disease (CKD) begins with hypersecretion of parathyroid hormone (PTH) resulting from a physiological response to correct metabolic disorder of calcium (Ca), phosphorus (P), and vitamin D. In recent years, some new players have been introduced to play an important role in developing SHPT. Abnormalities of Ca-sensing receptor (CaSR) and vitamin D receptor (VDR) are known to be involved in the pathogenesis of SHPT, and fibroblast growth factor-23 has also been shown to be associated with the pathogenesis.

Current SHPT treatment commonly includes the use of phosphate binders, vitamin D receptor activators (VDRAs), and calcimimetics with surgical parathyroidectomy left for medically refractory cases. While VDRAs would be reasonable to use in the patients whose serum Ca values are lower than normal range with adequately controlled P levels, calcimimetics may be more suitable for the patients whose serum Ca values are higher than normal range and P values remain above target.

1. Active vitamin D

Because vitamin D deficiency is a very common problem in the patients with CKD, it is desirable to correct vitamin D deficiency from the early CKD stages. Current guidelines recommend oral supplementation of nutritional vitamin D in the patients with vitamin D deficiency and mild renal insufficiency. However, in advanced CKD, supplementation with vitamin D cannot overcome the reduced ability of the remnant kidney to produce active sterol calcitriol. Accordingly, in the patients with end-stage renal disease, it is necessary to use active vitamin D to achieve the desired result.

VDRAs suppress PTH by both a direct action on parathyroid VDR and an indirect action via serum Ca elevation. However, since parathyroid VDR expression is decreased as parathyroid cells proliferate from diffuse to nodular hyperplasia, the effect of VDRAs is limited in severe SHPT. Compared with calcitriol, paricalcitol suppresses PTH more efficiently with reduced risk of hypercalcemia. In observational studies, a favorable effect on patient mortality has been associated with therapy with active vitamin D. The revised KDIGO guidelines do not recommend routine use of VDRAs for patients with CKD 3-5 to avoid hypercalcemia and over-suppression of PTH, whereas administration of a VDRA is recommended for patients with progressive SHPT.

2. Calcimimetics

The main pharmacological characteristic of cinacalcet is its strong inhibitory effect on PTH secretion without affecting the severity of SHPT. Cinacalcet inhibits PTH within several hours, whereas VDRAs require a few days for suppression. Therapy with cinacalcet is often limited by nausea, which may limit compliance with this therapy. In EVOLVE study, the use of cinacalcet did not reduce either risk of death or risk of major cardiovascular events even though there was a significant reduction in PTH level in cinacalcet group.

Etelcalcetide is an intravenous calcimimetic and has a lower rate of adverse effects such as nausea and vomiting. This drug also has other advantages including its prolonged effect of PTH inhibition and fewer drug interactions since it is not a target of cytochrome P450. A new oral calcimimetic, evoalcet, has also been developed and is receiving much anticipation.

Currently, a combination of VDRA and calcimimetic is recognized as the optimal strategy for SHPT. A combination therapy is most effective for control of serum Ca and P as well as PTH. This may result from the fact that calcimimetics upregulate VDR as well as CaSR in parathyroid glands resulting in

enhancement of the actions of both receptors. The beneficial effect of this combination therapy on cardiovascular disease makes this approach optimal for SHPT treatment. However, treatment needs to be individualized because of the heterogeneity of the biochemical parameters, the burden of disease, and the severity of comorbid conditions.