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**Appraisal of cinacalcet hydrochloride for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy**

As an endocrinologist with a particular interest in metabolic bone diseases, I principally see the skeletal impact of pathologically elevated parathyroid hormone concentrations, both in the context of primary and secondary hyperparathyroidism. Secondary hyperparathyroidism and its negative impact on skeletal health can be seen relatively early in the evolution of chronic renal impairment and in the setting of end-stage renal disease, secondary hyperparathyroidism is challenging and often unsatisfactorily managed using conventionally available therapies. Traditional therapies for secondary hyperparathyroidism have been targeted at correcting or replacing biochemical abnormalities rather than addressing the route cause of the problems. Cinacalcet offers a novel and effective means of treating the key pathogenic factor in secondary hyperparathyroidism in the context of chronic renal impairment.

Conventional therapies that take the form of active preparations of vitamin D, calcium supplementation, and phosphate restriction are only moderately effective in achieving acceptable clinical standards and are prone to unacceptable side-effects. These traditional therapies for secondary hyperparathyroidism can contribute to

hypercalcaemia and hyperphosphataemia that have been linked to mortality in end-stage renal disease (ESRD). Furthermore hyperphosphataemia and secondary hyperparathyroidism significantly increase the risk of fracture.

Bone diseases seen in the context of chronic renal impairment are complex and multifactorial and may range from high turnover states arising predominantly from excess PTH secretion to low turnover states of diverse etiology (including therapeutic use of vitamin D sterols that may overly suppress PTH) that are typically associated with normal or reduced plasma PTH levels. Both states are associated with increased fracture rates but the treatment for each to achieve a reduction in fracture rates is very different (anti-catabolic agents in high turnover states while anabolic agents may be more appropriate for low turnover states). Anti-catabolic agents used in low turnover states may actually increase fracture risk by further suppressing bone turnover.

The only effective way to differentiate high from low turnover states is with bone biopsy, an invasive procedure. Few patients with ESRD have bone biopsies performed to determine the specific form of renal bone disease. Thus patients with renal bone disease and increased fracture risk often are not treated with specific bone-active drugs for fear of exacerbating the underlying skeletal state and further increasing fracture risk. The personal and health economic impact of high fracture rates is self evident.

A more effective means of managing secondary hyperparathyroidism-induced renal bone disease is required that can supplant the issues of low and high turnover states in ESRD. Cinacalcet is able to suppress PTH hypersecretion and its use should supersede the requirement for use of vitamin D sterols and phosphate binders that can exacerbate the complex metabolic bone diseases seen in patients with secondary hyperparathyroidism and ESRD.

Another important subgroup of patients with ESRD are those that despite use of preparations of activated vitamin D have refractory hyperparathyroidism that leads to hypercalcemia, progressive bone disease, and the requirement for parathyroidectomy. Early and appropriate intervention with cinacalcet may see this subgroup diminishing.

In contrast with vitamin D, when using cinacalcet, the reduction in PTH secretion is accompanied by simultaneous reductions of the calcium/ phosphorus product, serum calcium, and phosphorus; all of which are hallmark features of increased risk of cardiovascular disease and mortality in patients with end-stage renal disease. Notwithstanding that the phase 2 and phase 3 clinical studies of cinacalcet were powered to answer questions related to biochemical end points and not morbidity such as fracture rates, from a physiological standpoint cinacalcet offers a far more preferable solution to the inevitable problem of secondary hyperparathyroidism in the context ESRD.

A small clinical study has demonstrated that suppression of PTH with cinacalcet can reverse bone loss in the proximal femur. Moreover, analysis of pooled safety data from 4 large randomized controlled trials has also showed a significant reduction in the risk of parathyroidectomy (RR 0.07, 95% CI 0.01–0.55) and fracture (RR 0.46, 95% CI 0.22–0.95) in cinacalcet versus placebo treated groups.

Cinacalcet offers an effective means of treating secondary hyperparathyroidism in ESRD. Current standard treatments for secondary hyperparathyroidism in ESRD exacerbate risks of fractures (and cardiovascular events). Use of cinacalcet in place of standard treatment should reduce this excess risk. While high quality data relating to clinically relevant end points are currently lacking, there are data suggesting an improvement in clinical outcomes including parathyroidectomy and fracture rates in addition to its desirable effects on PTH and mineral metabolism. There is clear clinical need for improved management of secondary hyperparathyroidism in ESRD and cinacalcet offers the opportunity to do this.

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