**The Case for Earlier/Targeted Treatment of Hyperparathyroidism with Cinacalcet: Calcimimetics Have Much to Offer the “Right” Patient**

By David Goldsmith, MD

In the therapy of hypertension, diabetes, or dyslipidemia or the attempt to prevent solid organ transplant rejection, it is a well recognized strategy to use a number of complementary pharmacologic approaches to address the fundamental goal, whether it is achieving better control of blood pressure (BP), blood sugar, or blood lipids, or long-term allograft survival. Monotherapy can work well, of course, in all of these settings, but usually only with milder disease states and only with good patient adherence and responsiveness to that single intervention. More often than not, we blend synergistic approaches, maximizing response while minimizing toxicity.

One has to wonder, just from first principles, whether in nephrology we have grasped this, or do we still think and prescribe largely in silos?

The use of vitamin D therapy is now well established in the medical management of secondary hyperparathyroidism. It has been part of good clinical practice for about three decades, and many guideline statements and other documents attest to its importance (1). However, it must be said that there is no evidence of worth anywhere that the use of vitamin D improves the quality and length of life in patients with chronic kidney disease (CKD) (2). Sadly, this is the rule and not the exception in nephrology. From the birth of the use of erythropoiesis-stimulating agents with epoetin in 1989 to 2009 and the TREAT Study (Trial to Reduce Cardiovascular Events with Aranesp Therapy), it had been regarded as self-evident that erythropoietin prolonged patients’ lives on the basis of spin and assertion, not relying securely on randomized, controlled trial data (3). We may well be in the same situation with vitamin D and its expensive analogues for exactly the same reasons. This is not, in 2017, a comfortable position to be in.

The Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events Trial, of course, has told us (or certainly me) that the use of cinacalcet in the attempt to prolong the life of CKD patients with mild to moderate secondary hyperparathyroidism was both expensive and futile (4). This is not the fault of cinacalcet but more of a failure to design and understand the way, however, that the regulatory pathways and some other influences compel innovators or new product manufacturers to work is to show that their product adds something of value to the previous gold standard. Although technically correct as an approach, this tends to lead to negation of the possibility that, by adding additional or novel therapies at an earlier stage in a chronic disease’s evolution, there could be longer-term benefit to the patient. Conditions that tend to progress with age or time, such as diabetes and complications of CKD, definitely fall into this category in my opinion. Therefore, with the introduction of cinacalcet, what was demanded by regulators was the demonstration of the ability of the drug to improve the biochemical profiles of patients already taking vitamin D but failing to meet guideline-recommended serum PTH concentrations. This is useful and valid information indeed, but the companies have also failed to do trials that accurately reflect real patients and always preferred to pretend that diverse biochemical or hematologic manipulations are somehow meaningful for patients.

I think there are three reasons we should consider cinacalcet to be of great value to nephrology and in the treatment of secondary hyperparathyroidism. The first is in the prevention, or at least delay, of surgical parathyroidectomy in patients truly not medically or psychologically fit enough for surgical intervention (the words that I have used are important here—I am not advocating the abandonment of parathyroid surgery) (6).

The second is in situations where patients show vitamin D sensitivity with hypercalcemia, hyperphosphatemia, and raised Ca x P product. Here, cinacalcet is really important to help restore some biochemical balance and permit ongoing vitamin D-based therapy (one is contemplating here that cinacalcet’s value is in being permissive of continued use of vitamin D) (7).

The third state where cinacalcet is of value is postrenal transplantation in controlling serum calcium and preventing major hypercalcemia (e.g., >3 mmol/L or 12 mg percent) (8). In these circumstances in the past, we were often forced to use big doses of intravenous bisphosphonates (with several short- and medium-term risks) or resorted to early post-renal transplant parathyroidectomy, which is associated with some loss of kidney function (bearing in mind that vitamin D itself can be so associated and that vitamin D doses after successful parathyroidectomy are often prodigious in the short term at least).

Cinacalcet in my view is “more sinned against than sinning,” and we should thus rethink its potential roles in nephrology more carefully now, rejecting the Lorelei siren calls coming from the commercial drive for more widespread, indiscriminate prescription. However, in selected patient groups for better bone and mineral metabolism control (for whatever reason), it is close to indispensable (pun not intended).

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References


