Calcimimetics: A Promise Unfulfilled

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Only rarely is a medication introduced with the potential to fundamentally alter care for patients receiving maintenance dialysis. In the history of nephrology, or at least of dialysis, the most impactful of these was surely epoetin alfa. Not until cinacalcet, the first-in-class allosteric modulator of the calcium sensing receptor (CaSR) introduced in 2004, did a medication of even remotely similar potential importance appear. Although secondary hyperparathyroidism (SHPT) does not constitute as grave a threat as severe anemia, allosteric modulators of the CaSR offered an exciting new mechanistic pathway with which to treat SHPT, complementing use of vitamin D sterols.

Such was the enthusiasm for cinacalcet that the rate of parathyroidectomies decreased in the United States in apparent anticipation of the drug becoming available. In the context of growing recognition of the dangers of vascular calcification and the deleterious effects of fibroblast growth factor 23 (levels of which are increased by vitamin D sterols), some suggested that CaSR agonists should become a mainstay of SHPT treatment, perhaps even displacing vitamin D sterols as first-line treatment. However, as any practicing nephrologist knows, cinacalcet never became as widely used as vitamin D sterols. The major reasons, at least anecdotally, for its limited use include the drug’s cost, gastrointestinal side effects, apparent preferential use in patients with the most advanced SHPT, and its use often for relatively short periods, ostensibly in an attempt to “rescue” patients from severely elevated parathyroid hormone (PTH) levels, rather than as long-term maintenance therapy akin to antihypertensive agents.

There is renewed interest in calcimimetics with the introduction of a new generation of CaSR agonists, namely etelcalcetide and, in Japan, evocalcet. Because the first published studies of these new agents occurred circa 2015, there is an acute need to examine the breadth and depth of the evidence for use of calcimimetics.

In this issue of *AJKD*, Palmer et al provide a timely and rigorous review of the effects of calcimimetics for SHPT treatment. Using advanced analytical techniques of a network meta-analysis, an approach by which more than 2 interventions can be compared at once, these investigators, highly experienced in meta-analyses, build on their previous work from the pre-etelcalcetide era. The authors now examine all known published trials involving any calcimimetic, including trials in which calcimimetics were tested against each other. The populations studied comprised, as might be expected, primarily maintenance hemodialysis patients, but studies enrolling peritoneal dialysis patients, those with chronic kidney disease not requiring kidney replacement therapy, and even kidney transplant recipients, although much rarer, were also included.

The authors conclude that all 3 agents are more effective than placebo in lowering PTH levels to target ranges, which is precisely how they are widely used in protocolized approaches for SHPT. Etelcalcetide appeared to be the most potent, albeit at a cost of presenting the highest risk for hypocalcemia. Cinacalcet, although potent in lowering PTH levels to target, was the worst for nausea but presented lower risk for hypocalcemia than etelcalcetide. Evolcalcet was associated with less risk for nausea and hypocalcemia but appeared to be the least potent in reducing PTH levels to a target range.

Some of the article’s findings deserve comment. Comparing calcimimetics to “placebo” means, in most cases, comparing calcimimetics to a vitamin D sterol–based therapeutic approach to SHPT. Thus, importantly, patients who receive “placebo” are not left untreated for their SHPT. Interestingly, in some trials of calcimimetics versus a vitamin D sterol–only approach, doses of vitamin D sterols increase, perhaps due to the need to combat calcimimetic-induced hypocalcemia or attain superior phosphate control (which in turn permits prescribers to increase doses of vitamin D sterols). In contrast, in some other trials, doses of vitamin D sterols decrease, presumably due to the superior PTH level control afforded by the calcimimetic.

A second major finding is that the risk for and severity of hypocalcemia appear to be directly related to the potency of the drug in reducing PTH levels, an intuitive concept, but one nevertheless elegantly displayed across the 3 calcimimetics studied.

A third major finding, concerning nausea, also merits comment. Although the nausea caused by cinacalcet was originally hypothesized to be the result of a combination of the local effects on the gastric mucosa, effects on gastrointestinal motility (a process partially regulated by the CaSR), and central effects induced by the passage of the drug across the blood-brain barrier, nausea was also relatively common in trials of etelcalcetide. The cause of etelcalcetide’s gastrointestinal effects are unknown at present, given that the drug does not appear to cross the blood-brain barrier. These effects are a substantial disappointment to many and a barrier to etelcalcetide’s use in dialysis patients, for whom nausea and poor appetite are relatively common concerns.
Finally, there is no evidence that the drugs decrease mortality. As Palmer et al make clear, most trials of calcimimetics are short-term studies of perhaps 6 months in duration. The EVOLVE trial was the only study specifically designed to investigate whether a calcimimetic (cinacalcet) could confer a mortality benefit. Unfortunately, as the renal community knows, the trial’s findings were as controversial as its aspirations were ambitious, despite several tantalizing sensitivity analyses and alternative approaches, and did not demonstrate unequivocal evidence of a mortality benefit. Although one might wish for trial evidence conclusively demonstrating that CaSR agonists (or any SHPT therapy) can affect mortality, it is extraordinarily unlikely that any such evidence will be forthcoming.

These present findings provide key insights about the use of calcimimetics, but the findings must be considered within the context of the reimbursement environment, which in the United States constitutes a limitation on calcimimetic use. From 2018 to the present, both cinacalcet and etelcalcetide, while technically within the End-Stage Renal Disease Prospective Payment System (the “bundle”), are reimbursed under what is known as the Transitional Drug Add-On Payment Adjustment (TDAPA). Use of the drugs therefore results in the payment of an additional sum to dialysis providers. However, that sum is fixed and is not dependent on the cost of the drug, which has the effect of incentivizing use of the least expensive drug. As such, many US dialysis providers heavily encourage the use of cinacalcet over etelcalcetide because drug contracts for the former can reduce the per-pill costs of cinacalcet to extremely low levels. When calcimimetics are removed from the TDAPA program altogether, as is likely in the near future, strong incentives to use generic cinacalcet over etelcalcetide will remain, at least in the United States.

In this reimbursement environment, many major US dialysis providers have imposed protocols requiring intensive dose escalation of vitamin D sterols before the use of calcimimetics, a process often limited by hyper-phosphatemia, and when calcimimetics are required, cinacalcet is preferred. Calcimimetics therefore are not truly a therapy that can be used at liberty, the way that vitamin D sterols can, at least in the United States. This is unfortunate because many patients would likely benefit from the nephrologists’ ability to titrate the 2 drugs in combination at will.

Given that calcimimetics are often used in patients with the most severe SHPT, most typically those for whom monotherapy with vitamin D sterols has failed, parathyroidectomy constitutes a particularly interesting comparator. Parathyroidectomy, as would be expected, results in better control of PTH levels than current pharmacologic options. However, parathyroidectomy cannot truly be called a “definitive” therapy since PTH levels remain high for about a third of patients a year after the procedure, while roughly one in ten experience levels that are extremely low. Perhaps most daunting, a 30-day mortality rate of 2% has been reported, a particularly ominous finding given that parathyroidectomy is an elective procedure. Furthermore, only a subset of dialysis patients are candidates for surgery on the neck, meaning it is not a practical alternative to either calcimimetics or vitamin D sterols for many.

In conclusion, Palmer et al, in their rigorous study of all known calcimimetic trials, have provided convincing evidence that these drugs are generally highly effective at lowering PTH levels. They are not as effective as parathyroidectomy, but are obviously far less invasive with lower risk. However, as Palmer et al demonstrate, hypocalcemia and nausea are daunting untoward effects that pose the greatest clinical threats to routine use of these agents. Additionally, in the United States, as in many other countries, financial incentives (and disincentives) play a major role in how drugs are used. For these reasons, despite their considerable theoretical appeal, it remains uncertain whether calcimimetics can ever fulfill their potential as mainstays of treatment for SHPT in real-world treatment environments.

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