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Second Chances to Improve ESRD Outcomes With a Second-Generation Calcimimetic

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Disturbances of mineral metabolism are among the most challenging clinical problems for patients with end-stage renal disease (ESRD). Beginning in its early stages, chronic kidney disease increases circulating concentrations of fibroblast growth factor 23 (FGF23), which triggers calcitriol (ie, 1,25-dihydroxy vitamin D₃) deficiency, lowers serum calcium concentrations, and secondarily increases parathyroid hormone (PTH) levels.¹ Simultaneously, progressive declines in glomerular filtration rate reduce phosphate excretory capacity, which further exacerbates FGF23 excess and secondary hyperparathyroidism. As advanced chronic kidney disease progresses to ESRD, hyperphosphatemia ensues, and FGF23 and PTH levels increase exponentially as they futilely work to overcome the impediments to normal mineral homeostasis imposed by loss of kidney function.

Beyond the monthly dialysis laboratory report, elevated levels of PTH, FGF23, and phosphate are independent risk factors for mortality and cardiovascular disease, including arterial and valvular calcification and uremic cardiomyopathy.^{2–5} Poorly controlled secondary hyperparathyroidism also increases risk of fractures and other musculoskeletal complications that accelerate disability in ESRD.^{6,7} As a result, disordered mineral metabolism is thought to contribute significantly to the 10- to 20-fold higher risk of mortality among patients with ESRD vs the general population.⁸ A major aspiration in clinical nephrology is to identify strategies to treat disordered mineral metabolism in an effort to prolong survival and enhance quality of life of patients with ESRD.

Currently approved treatments for disordered mineral metabolism in ESRD include phosphate binders to treat hyperphosphatemia and active vitamin D analogs and cinacalcet to lower PTH levels. Cinacalcet is an oral “calcimimetic” that targets the calcium-sensing receptor on the parathyroid glands to inhibit PTH secretion by mimicking the effect of extracellular calcium.⁹ Unlike calcium-based phosphate binders, high-dialysate calcium concentrations, and vitamin D analogs, which all lower PTH levels in part by supplying additional calcium, cinacalcet lowers PTH without calcium loading. This is viewed as a potential advantage because prolonged exposure to exogenous calcium loading in patients with ESRD can promote soft tissue and arterial calcification.¹⁰ Because cinacalcet

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simultaneously lowers PTH, serum phosphate, and FGF23 levels,¹¹ there was further hope that calcimimetics could become the cornerstone of a pharmacological armamentarium to improve survival in patients with ESRD by controlling multiple aspects of disordered mineral metabolism.

The Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial randomized 3883 patients with ESRD and secondary hyperparathyroidism who were undergoing hemodialysis to receive daily cinacalcet vs standard therapy but found that cinacalcet did not significantly reduce the risk of death or major cardiovascular events.¹² However, the trial was hampered by several unanticipated problems, including failure of randomization to prevent a significant age gap between treatment groups that favored standard therapy. In addition, the clinical availability of cinacalcet enabled a high rate of cinacalcet “drop-ins” (off-protocol use) into the standard care group, whereas nausea, vomiting, and other adverse effects led to a high rate of “dropouts” from the cinacalcet group, both of which led to gradual loss of separation between the treatment groups and biased the results toward the null. Acknowledging these shortcomings, optimists might anticipate that a follow-up trial using a stricter study design and a second-generation calcimimetic with fewer adverse effects than cinacalcet and enhanced adherence could prove, for the first time, that successful treatment of disordered mineral metabolism can indeed deliver elusive cardiovascular and mortality benefits to patients with ESRD.

This issue of *JAMA* presents 2 reports of randomized clinical trials of the new second-generation calcimimetic etelcalcetide. As a novel intravenous formulation with pharmacokinetics that allows thrice-weekly dosing at the time of dialysis, etelcalcetide was developed to improve efficacy and adherence and reduce gastrointestinal adverse effects relative to cinacalcet. In the first report, Block and colleagues present the virtually identical results of 2 separate 27-week multinational placebo-controlled trials.¹³ In aggregate, 1023 patients (508 in one trial and 515 in the other trial) with ESRD and severe secondary hyperparathyroidism (defined as PTH greater than 400 pg/mL already treated with calcium, phosphate binders, or vitamin D analogs) were randomized to receive etelcalcetide or placebo 3 times weekly with conventional hemodialysis schedules. Compared with placebo, etelcalcetide-treated patients were more likely to reach the primary end point of achieving more than a 30% reduction in PTH concentrations during weeks 20 through 27 of the trials (74.0% with etelcalcetide vs 8.3% with placebo in one trial and 75.3% vs 9.6% in the other; $P < .001$ for both). Etelcalcetide also lowered serum phosphate and FGF23 concentrations significantly.

The second report, also by Block and colleagues, presents the results of a single randomized trial that compared the PTH-lowering efficacy and safety of etelcalcetide vs cinacalcet in 683 patients undergoing hemodialysis who had PTH concentrations greater than 500pg/mL despite concurrent therapies.¹⁴ This double-blind, double-dummy trial was primarily designed to demonstrate the noninferiority of etelcalcetide compared with cinacalcet at reducing PTH concentrations by at least 30% from baseline to weeks 20 through 27. Not only was etelcalcetide noninferior to cinacalcet in reducing PTH concentrations by 30% (68.2% with etelcalcetide vs 57.7% with cinacalcet), it also proved to be statistically

significantly superior in all secondary efficacy analyses, including likelihood of achieving more than 30% or 50% reductions in PTH.

In all 3 trials, off-protocol treatment with cinacalcet was prohibited and local PTH measurements were suspended for the duration of the trials while titration of study drugs was performed centrally in response to PTH measurements that were not shared with site investigators. These design elements maintained per-protocol separations between the comparator and treatment groups. In contrast, serum calcium levels were reported locally and investigators were encouraged to respond by modifying usual clinical care at their discretion. This approach enabled a clear determination of the effect of etelcalcetide on serum calcium values. Whereas investigators reported decreased serum calcium concentrations in more than two-thirds of patients receiving etelcalcetide and in nearly as many patients receiving cinacalcet, most telling was the clinical significance that investigators attributed to the hypocalcemia that they encountered. Patients treated with etelcalcetide across all 3 trials were more likely to receive therapies to increase their serum calcium levels, including increases in dialysate calcium concentrations, oral calcium supplements, calcium-based phosphate binders, and active vitamin D analogs. Nevertheless, serum calcium values remained lower and muscle spasms and hypotension were more common in etelcalcetide-treated vs placebo-treated patients. In addition, etelcalcetide-treated patients were more likely than placebo-treated patients to exhibit prolongation of corrected QT intervals. Because hemodialysis patients are exposed to rapid electrolyte shifts and other medications that can prolong the QT interval and promote sudden cardiac death,^{15,16} longer-term trials are needed to fully assess the cardiac safety of etelcalcetide.

One of the main theoretical benefits that drove the development of calcimimetics was the ability of these agents to lower PTH levels directly without precipitating positive calcium balance. However, the observation that many patients tolerated etelcalcetide and cinacalcet only if they were cotreated with therapies to increase serum calcium levels raises the question of whether the frequent requirement for calcium supplementation may undermine some of the potential benefits of etelcalcetide. It is possible that the hypocalcemic effect of etelcalcetide will ultimately prove to be most pronounced at the onset of treatment, when PTH is highest and bone is most demineralized, similar to the severe hypocalcemia that immediately follows successful surgical parathyroidectomy in patients with ESRD. As a corollary, it is possible that the severity of hypocalcemia might be attenuated when patients initiate treatment with etelcalcetide earlier in their course of ESRD when they have less advanced secondary hyperparathyroidism, unlike the current trials that specifically enrolled patients with long-standing ESRD and poorly controlled secondary hyperparathyroidism. Additional clinical trials will be needed to conclusively answer these questions.

The reports in this issue of *JAMA* by Block et al^{13,14} raise several other critical new questions. Will etelcalcetide prolong the lives of patients? Several observational studies reported that patients with PTH concentrations greater than 600 pg/mL are at significantly higher risks of death and cardiovascular events than patients with PTH levels of 150 to 300 pg/mL.² Although it may be tempting to assume that lowering individual patients' PTH levels by 30% to 50% or more (and simultaneously lowering serum phosphate and FGF23

levels) will result in commensurate reductions in risk, only randomized trials with hard clinical end points, including mortality, can provide clear answers.

Will etelcalcetide improve the quality of life for patients with ESRD? Despite bypassing the gut, intravenous etelcalcetide did not mitigate the gastrointestinal adverse effects associated with cinacalcet. Thus, the high rates of nausea and vomiting induced by both drugs appear to be a systemic rather than local gastrointestinal class effect of calcimimetics, perhaps mediated by activating the calcium-sensing receptor in the nonparathyroid targets that elicit nausea and vomiting in response to hypercalcemia. On the other hand, because etelcalcetide can be administered by dialysis facilities, the quality of life of patients with ESRD may improve from enhanced adherence to a beneficial treatment and from shifting the burden of medication costs to commercial dialysis organizations. However, given the bundled reimbursement of dialysis care in the United States, widespread adoption of etelcalcetide will likely occur only after health economics studies confirm that the up-front premium cost of etelcalcetide vs alternative medications is offset by downstream savings that would accrue from avoiding costs related to uncontrolled secondary hyperparathyroidism, including care for fractures, parathyroid surgery, and cardiovascular complications.¹⁷ Modeling these end points requires knowledge of the numbers needed to treat, which, again, requires randomized trials with clinical outcomes.

How will the addition of etelcalcetide advance the field? Because etelcalcetide potently reduces PTH, phosphate, and FGF23 concentrations via a route of administration that could increase adherence, it offers the best opportunity yet for a future clinical trial to demonstrate that enhanced biochemical control of disordered mineral metabolism translates into improved clinical outcomes. Such a trial would clearly influence ESRD management directly. Indirectly, it could also provide the proof-of-concept confidence needed to fuel a new wave of pharmaceutical innovation to target disordered mineral metabolism when it is first established in earlier stages of chronic kidney disease, perhaps most amenable to treatment, and (currently) free from restrictions imposed by bundled reimbursement.

All of these pressing questions will be best answered by randomized trials, which begs a final question: Can nephrologists soon expect a randomized trial of etelcalcetide with hard clinical end points? Demonstration of the efficacy of etelcalcetide for improving biochemical end points like PTH and serum phosphate is the low bar that must be overcome to secure regulatory approval for new treatments of disordered mineral metabolism in ESRD. This low-cost regulatory pathway enables more rapid introduction of new agents into ESRD practice but also serves as a powerful disincentive to conduct costly outcomes trials that are rightfully required in other therapeutic areas and thereby perpetuates the outcomes trial-deprived culture that permeates and stifles nephrology. Regulatory authorities should reconsider their approval processes to incentivize hard end-point trials in ESRD, and the manufacturer of etelcalcetide should conduct a rigorous second-generation trial to evaluate the effects of this promising second-generation calcimimetic for reducing mortality and major cardiovascular events and improving quality of life for patients with ESRD.

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