End-Stage Renal Disease Related Hyperparathyroidism

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Changing landscape of the treatment of hyperparathyroidism related to end-stage renal disease – can we turn the clock backward?

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End-stage renal disease (ESRD) is often complicated by hyperparathyroidism (HPT), leading to high serum levels of PTH, calcium and phosphate. ESRD-related HPT is associated with an increased risk of (cardiovascular) mortality, mineral and bone disorders, and clinical features as abdominal pain, fatigue, and forgetfulness. These debilitating symptoms, in addition to the burden of chronic renal failure and its treatment, often lead to a decreased quality of life (QoL).

Historically, parathyroidectomy (PTx) has been the gold standard and has served as the only treatment for ESRD-related HPT. When vitamin D supplementation and phosphate binders were studied in the 1980s, PTx became a second line treatment.[1] For the ESRD patient, the resulting treatment algorithm has proven to be effective in improving both biochemical values as clinical outcomes.

In 2004, the calcimimetic agent cinacalcet entered the market, and the standards of practice changed immediately. Initial studies, many funded by the pharmaceutical industry that is involved in providing cinacalcet, showed promising results in decreasing PTH levels and improving serum calcium concentrations. In addition, its positive effect on biochemical outcomes, the use of cinacalcet was also associated with a decrease in the number of PTxs performed, the incidence of fractures, and rates of cardiovascular hospitalization.[2] However, a study comparing cinacalcet with PTx, the former gold standard, was never conducted. Despite the high costs of about $14,480 per patient per year, calcimimetics rapidly gained the dominant position in the guidelines of the Kidney Disease: Improving Global Outcomes Working Group.[3]

In the following years, many studies that investigated cinacalcet started to report the decreased rate of PTx as a positive outcome, implying that refraining from PTx as long as possible should be the preferred strategy. Yet, a surgical referral is physician dependent and can hardly be seen as an objective outcome measure. After all, PTx is a safe and reliable treatment option, not an adverse event that should be avoided, just because it represents an operation. Possibly, results from studies such as a nationwide retrospective analysis of dialysis patients in the United States undergoing PTx in 2015 encouraged caregivers to refrain from PTx; a procedure-related mortality rate of 2% was found, and during the first 30 days after PTx, 24% required rehospitalization.[4] A substantial proportion of these patients, however, were likely treated in low-volume centers. In contrast, many other studies worldwide showed a mortality rate of less than 1% and low postoperative complication rates. This discrepancy emphasizes the necessity to centralize these more complex patients with ESRD to high-volume (e.g., with an annual case load

≥20 patients) medical centers with experienced surgeons and nephrologists, leading to excellent outcomes; these fragile patients require multidisciplinary and experienced care postoperatively to prevent or substantially lower perioperative complications and to adequately treat the potential hungry bone syndrome.

After initial promising results, more recent studies investigating the efficacy of cinacalcet have raised the question of whether all ESRD patients truly benefit compared to PTx. In 2012, the primary outcome of the EVOLVE Trial (the risk of mortality or a nonfatal cardiovascular event), did not differ statistically compared to placebo-users during a follow-up of 60 months.[5] Furthermore, in almost 50% of patients, the use of cinacalcet was accompanied by various adverse events, such as nausea and diarrhea, compared to 19% in the placebo group. This observation led to a considerable number of patients discontinuing the study drug. Although a post hoc analysis suggested less vascular calcifications in the cinacalcet group, the number needed to treat might be high. Noncompliance and discontinuation of cinacalcet are likely the main reasons why a French prospective study found that cinacalcet was not successful in decreasing PTH levels.[6] Although never directly compared, PTx improves the QoL by effectively decreasing PTH levels, improving calcium-phosphorus homeostasis, ameliorating symptoms of bone pain and pruritis, and decreasing polypharmacy, whereas calcimimetics do not have these effects.[7] In addition to this, PTx is already cost-effective after 7.25 months of dialysis compared to cinacalcet.[8] In Australia, the unsatisfactory results led to the removal of cinacalcet from the reimbursed drug list in 2015, whereas in most countries, prescription patterns of calcimimetics are still on the rise. These successive changes in availability of cinacalcet led to an initial decrease in the rate of PTx during the cinacalcet era, followed by an increase after its banning (Figure 1).[9] Indeed, the most recent monodisciplinary Kidney Disease: Improving Global Outcomes guidelines advise prescribing cinacalcet initially together with vitamin D analogues and phosphate binders or even as monotherapy. Despite all recent favorable evidence of the efficacy of PTx, it has almost disappeared from the treatment algorithm.

HPT related to ESRD is a complex disease that requires patient-tailored treatment by a multidisciplinary team. Only when considering patient-specific factors, such as comorbidity, potential prompt kidney transplantation, patient preference, QoL, and the severity of disease, can physician and patient decide on the optimal treatment.

The best treatment of HPT related to ESRD remains disputable, but how cinacalcet gained such a dominant position without a randomized controlled trial comparing

cinacalcet with the former golden standard PTx is concerning. Current guidelines seem to be monodisciplinary and subordinate the limited clinical benefit of cinacalcet to the proven favorable effects of PTx. How this shift has happened is unclear. Therefore, we urge clinicians to discuss these complex patients in multidisciplinary meetings with input from an experienced endocrine surgeon. In the Netherlands we, therefore, founded the Dutch Hyperparathyroidism Study Group, a nationwide collaboration between all involved specialties to push the best care for these vulnerable patients to the next level. Weighing the aforementioned factors could lead to earlier identification, of which patients will likely benefit from PTx and for which patients pharmacologic treatment is sufficient. This approach will lead to a treatment algorithm in which cinacalcet and PTx can complement each other as clinically appropriate. Unfortunately, despite extensive research in medicine, it sometimes seems impossible to turn the clock backward.

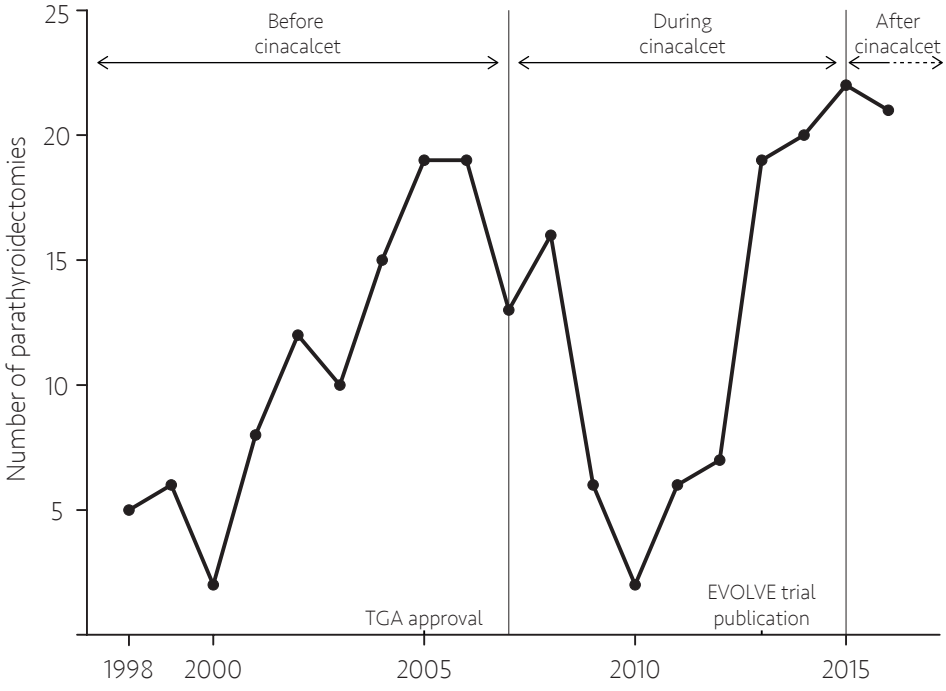

Figure 1 – Changing rates of parathyroidectomy according to the availability of cinacalcet[9]

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