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Cinacalcet: Addressing the Unmet Clinical Need in the Management of CKD-Mineral and Bone Disorder in Infants on Dialysis

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Kidney Int Rep (2024) **9,** 2332–2334; https://doi.org/10.1016/j.ekir.2024.06.014

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Since the introduction of the first pediatric renal replacement therapy program in the 1960s, the number of infants and young children started on renal replacement therapy has gradually increased, and is currently 28.0 to 32.1 per million age-related population.[S1] Despite significant improvements in the care of infants and young children on dialysis, registry data highlight that the mortality risk remains the highest in this particular age group.[S2] Indeed, infants on dialysis face several challenges such as a longer waiting time on dialysis before kidney transplantation, higher rates of hospitalizations, and a high prevalence of severe comorbidities such as bone fractures, infections, and failure to thrive.[1,2] Multiple factors contributing to the systemic disease of children with kidney failure have been identified. These factors include dysregulation of homeostasis; accumulation of toxic organic metabolites; treatment-specific symptoms related to dialysis; disease-related symptoms, for example due to syndromic causes; and disturbance in renal endocrine function leading to anemia and chronic kidney disease- mineral and bone disorder (CKD-MBD).[3]

From registry data, we have learned that inadequate CKD-MBD control is prevalent in infancy. In a study from the International Pediatric Dialysis Network Registry, including 890 children on peritoneal dialysis from 24 countries, less than 20% of children had parathyroid hormone (PTH) levels within the Kidney Disease Outcomes Quality Initiative limits. Moreover, PTH level above twice the upper normal limit was found in 39% of infants and 54% of children aged between 1 and years.[4] High quality studies comparing patient outcomes in infants and young children in relation to various PTH targets are lacking. Therefore, the general consensus is maintaining the balance between too high and too low PTH by following temporal trends rather single time-point values and considering other biochemical parameters of CKD-MBD such as calcium, phosphorus, bicarbonate, 25 hydroxyvitamin D, and alkaline phosphatase levels.[5] Of note, in the International Pediatric Dialysis Network Registry study, only half of the children younger than 5 years had calcium and phosphorus levels within the Kidney Disease Outcomes Quality Initiative recommendations.[4]

The management strategies of hyperparathyroidism in infants and young children on dialysis include native and activated vitamin D analogues, dietary and pharmacological control of hypophosphatemia and hyperphosphatemia, adjustments of dialysis prescription, and parathyroidectomy in highly selected cases as a last resort option. In the past decennia, calcimimetics, cinacalcet and more recently, etelcalcetide have emerged as efficient pharmacological options in lowering PTH. Cinacalcet is an allosteric modulator of the calcium-sensing receptor expressed in the parathyroid glands (Figure 1). It enhances the calcium-sensing receptor sensitivity for extracellular Ca, resulting in reduced serum PTH, Ca, and P levels, allowing better control of secondary hyperparathyroidism.[6] In adults, the use of calcimimetics aids in maintaining PTH within targets and reduces fibroblast growth factor 23 levels, whereas the results on the effects on the all-cause mortality and cardiovascular mortality are inconclusive.[7] Beside the effects of cinacalcet on PTH and fibroblast growth factor 23, animal studies (i.e., uremic rats) have also shown that the combined treatment of

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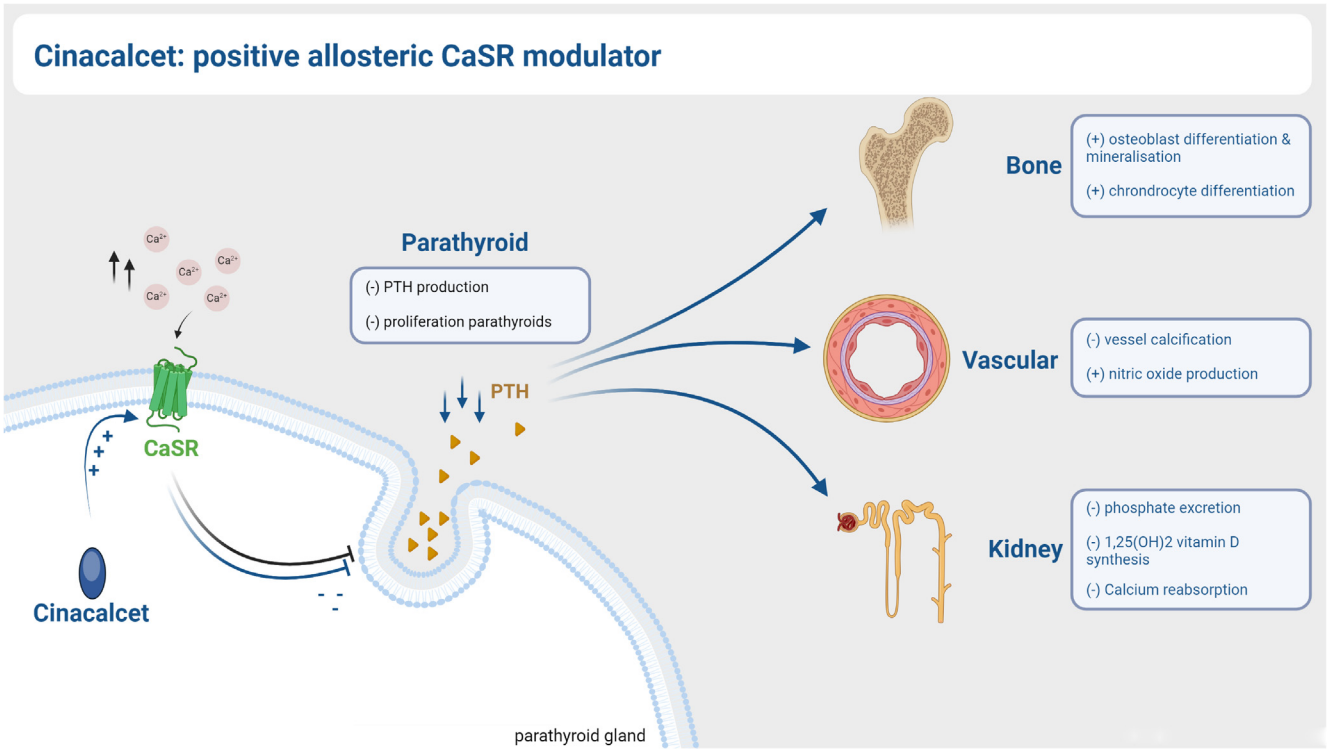

Figure 1. Mechanism of action of cinacalcet.[S6, S7] CaSR, calcium sensing receptor; PTH, parathyroid hormone. The figure was created by Evelien Snauwaert using Bio.Render.

cinacalcet and activated vitamin D analogues resulted in an increased number of osteoblasts, and a decreased osteoid along with over 50% decrease in vascular calcification in comparison to activated vitamin D analogues alone.[S3]

There is also some evidence on the use of cinacalcet in pediatric patients, including 2 randomized controlled trials, prospective observational studies, and retrospective reports.[6] In 2017, the European Medical Agency approved the use of cinacalcet in children on dialysis with refractory secondary hyperparathyroidism; and in 2020, the position statement for cinacalcet use in children was issued by the European Society for Paediatric Nephrology and the Chronic Kidney Disease-Mineral and Bone Disorders Working Group of the ERA-EDTA.[6]

Infants and young children on dialysis constitute a small, but a very challenging group of patients due to their intensive skeletal growth and specific dietary requirements, including sufficient calcium supply. Considering the growing life expectancy, complications of deranged CKD-MBD parameters may carry major repercussions on cardiovascular morbidity and mortality. The recent paper of Bernardor *et al.*[8] adds to the existing evidence by providing clinical and biochemical data on 26 children younger than 3 years treated with cinacalcet. Although Bernardor *et al.*[8] reported that treatment with cinacalcet resulted in a significant reduction in PTH levels, there was a considerable proportion of children with side effects such as hypocalcemia and precocious puberty. Although the authors report no significant improvement in height *z*-score under cinacalcet therapy, these findings should be interpreted with caution, given that 7 out of 26 patients were concomitantly treated with recombinant growth hormone and the fact that in this particular age group nutrition is the essential factor impacting statural growth. In line with the authors' concern, attention should be drawn to the high proportion of children with hypophosphatemia both at cinacalcet initiation (77%) and at their 1-year follow-up (79%). Infants have high demands for both calcium and phosphorus to ensure a positive mineral balance and endochondral ossification and prevent skeletal deformities, bone pain, and growth delay.[S4] Hypophosphatemia is a recognized risk factor for mineralization abnormalities and rickets, and maintaining phosphorus levels within normal range for age is essential in the management of CKD-MBD during infancy.

Along with the presence of hypophosphatemia, more than half of the patients (58%) in the study were deficient or insufficient for vitamin D and a small group of children (12%) were hypocalcemic

at cinacalcet initiation, which poses the question of if hypocalcemic complications could have been prevented in infants with optimal vitamin D status, normophosphatemia, and plasma calcium levels within the (higher) normal range for age prior to initiation of cinacalcet. An additional risk of potentially life threatening hypocalcemic complications in infants treated with cinacalcet might also lay in its starting dose. In the retrospective case series of Bernardor *et al*.[8] the average initial starting dose was 2 times above the recommended starting dose, and the cinacalcet dose was higher in patients experiencing hypocalcemic episodes.

Further research is needed to identify the benefits and potential harms of cinacalcet in infants and young children, with a particular focus on relevant outcomes beyond the surrogate marker PTH, such as the fracture risk, cardiovascular disease, statural growth, bone mineralization, and vascular calcification.

Taken together, these data clearly indicate the clinical need to standardize the management of CKD-MBD in the youngest children and by extension in other understudied populations such as predialysis children or pediatric kidney transplant recipients.[9,S5] The high prevalence of hypocalcemic episodes in the reported cohort suggests the potential benefit of using cinacalcet with low to moderate doses of activated vitamin D analogues.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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