Editorial

Recent advances in the management of Chronic Hypoparathyroidism

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Hypoparathyroidism (hypoPT) is a common Endocrine problem, dealt by the Endocrionlogists all over the world. Diagnosis requires either undetectable or inappropriately low PTH (Parathormone) levels in the context of hypocalcemia. Most patients with post-surgical hypoparathyroidism are diagnosed immediately after the surgery causing hypoPT, whereas a diagnostic delay may be seen in patients with non surgical or idiopathic hypoPT.[1] Patients having family members with 22q11DS (DiGeorge), HDR or Autoimmune polyglandular Syndrome -1 (APCED) are at risk of developing hypoPT.[2] Genetic testing should be offered to the patients with idiopathic hypoPT especially in young patients or when genetic form of hypoPT is suspected or patient having family history of nonsurgical hypoPT.[3]

The commonest complications of hypoPT are Cataract (17%), Infections (11%), Nephrocalcinosis (15%), renal insufficiency (12%), seizures (11%), depression (9%) and Ischemic heart disease (7%).[4] A US base cohort study,[5] reported that patients with hypoPT have 3x more often kidney stones and subsequent development of renal insufficiency. The data from Canadian National hypoPT and Italian National HypoPT registries, showed that significant bone fragility in post-menopausal women with chronic hypoPT, and a large percentage of men above 50yrs of age develop osteoporosis.[6,7]

The conventional treatment is mostly first line therapy with oral calcium with activated vitamin D3. The limitations of this therapy include wide fluctuations in the serum calcium, hyperphosphatemia, hypercalciuria, high pill burden, poor quality of life and risk of renal complications.[8] The goals of treatment for hypoPT, include relief of symptoms of hypocalcemia, avoiding hypercalcemia, normalization of phosphate and urine calcium, preservation of renal function and avoidance of nephrocalcinosis and ectopic calcifications.[8]

When conventional therapy is deemed unsatisfactory, use of recombinant PTH or PTH analogues is recommended [8]. PTH therapy for hypoPT provides blood PTH levels within the normal physiological range and restore downstream calcitriol and normalizing biochemical abnormalities, skeletal health and quality of life.

TransCon PTH (palopegteriparatide) is an investigational prodrug of PTH (1-34), administrated subcutaneously once daily, with sustained release of active PTH that provides PTH levels in the physiological range for 24hours a day in adults with hypoPT.[9] It is different from PTH (1-84), which had shorter half life of 3hours and complex dosing protocols.[10] Phase 3 trial of TransCon PTH has shown promising results in the normalization of serum calcium with less fluctuations, reductions in the urine calcium, improvement in BMD, mean increase of eGFR of 8.9mL/min/1.73m^2 and significant reduction in the vitamin D intake with 98.4% patients who were able to stop vitamin D.[9]

Eneboparatide, a long acting PTH/PTHrP (1-36) hybrid analogue, is also under trails and currently not yet FDA approved. It acts by targeting the R^0 conformation of PTHR1, and induces a long-active effect on serum Calcium mainly through a potent and sustained Calcium reabsorption effect at the kidney level, with neutral impact on Bone in multiple studies. It was well tolerated, had a good safety profile and usage results in discontinuation of oral calcium and active vitamin D intake in most of the patients, whereas maintaining serum calcium in the target range.[11]

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Encalaret, is an investigational oral Calcilytic drug, targets hypocalcemia and hypercalciuria in patients with autosomal dominant hypocalcemia type 1 (ADH1). Over the 18 month of therapy, Encalaret normalized mean iPTH and blood calcium with reduction in the urinary calcium.[12] It was well tolerated and also decreased mean blood phosphate and increase mean magnesium levels. It is not FDA approved yet.

In conclusion, the treatment of chronic hypoPT has evolved over years and the new drugs, mentioned above, have shown better and sustained normalization of normocalcemia and avoidance of long term complications, which were seen earlier with conventional treatment.

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