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EDITORIAL

New therapeutic options in the management of chronic hypoparathyroidism

Nuevas opciones terapéuticas en el manejo del hipoparatiroidismo crónico

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Hypoparathyroidism is an endocrine disorder caused by insufficient production of parathyroid hormone (PTH), which leads to mineral metabolism alterations, notably hypocalcemia and hyperphosphatemia.[1,2] The most common form is transient postoperative hypoparathyroidism, which occurs after cervical surgery and usually resolves favorably in weeks or months. However, chronic hypoparathyroidism, whether of postoperative or non-surgical etiology (autoimmune, genetic, or other causes), is a disease with difficult clinical management for 2 reasons. The first is that it is a hormonal disorder that, through poorly understood mechanisms, increases the risk of multiple comorbidities (kidney disease, arterial and cerebral calcifications, cataracts, infections) and significantly affects patients' quality of life. The second is that conventional treatment does not adequately replace the actions of the missing hormone and only partially corrects some of the metabolic alterations.

The treatment recommended by the clinical practice guidelines[3] includes the administration of oral calcium and active vitamin D (calcitriol, alfacalcidol) supplements to maintain serum calcium near the lower limit of the reference range, as well as normalize serum phosphate concentrations and urinary calcium excretion. Occasionally, vitamin D (cholecalciferol, calcifediol), magnesium supplements, or thiazides are required. However, the lack of PTH decreases both calcium reabsorption and tubular phosphate excretion, which favors hypercalciuria and hyperphosphatemia, causing changes to bone microarchitecture. This is accompanied by an increased risk of renal complications and ectopic calcifications.[3] On the other hand, the titration of calcium and calcitriol is slow and imprecise, which means that patients need many medical consultations for medication adjustment and, in some cases, visits to the emergency department (ED) or hospital admissions. Finally, patients on conventional treatment frequently present changes to health-related quality of life affecting different domains.[4]

In response to these limitations of conventional therapy, new compounds have been developed in recent years that use PTH or its derivatives in different formulations to achieve better clinical, biochemical, and quality of life control in patients with hypoparathyroidism.

Parenteral administration of recombinant human PTH(1–34), the N-terminal fragment of the complete PTH(1–84) molecule, has proven effective to maintain serum calcium, reducing calciuria, and increasing phosphate excretion.[5] However, it presents the disadvantage of a short duration of action after subcutaneous administration, which requires 2 daily injections,[6] and has no recognized indication in hypoparathyroidism. Recombinant human PTH(1–84), on the other hand, is identical to the endogenous human hormone and exerts a longer-lasting calcemic action, allowing for once-daily administration.

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The Efficacy and safety of recombinant human parathyroid hormone (1–84) in hypoparathyroidism (REPLACE)[7] study had the primary endpoint of analyzing the proportion of hypoparathyroidism patients who, on week 24, achieved reductions ≥ 50% in their daily dose of calcium and active vitamin D, maintaining serum calcium ≥ baseline and below the upper limit of normal. This target was achieved in 53% of patients in the treated group vs only 2% of the placebo group. PTH(1–84) was authorized by the U.S. Food and Drug Administration (FDA) in 2015 and by the European Medicines Agency (EMA) in 2017, but the manufacturing laboratory made the decision to discontinue its production at the end of 2024 due to irresolvable supply problems.

With the aim of providing a more physiological approach to PTH deficiency, subcutaneous continuous infusion pumps with this hormone have been used. Compared to patients treated with 2 daily subcutaneous injections, patients treated with PTH(1–34) in continuous infusion showed normalization of serum calcium with smaller fluctuations in calcium, phosphorus, and magnesium concentrations and a reduction in calciuria, with normalization of bone remodeling markers.[8] A recent study[9] with 12 patients with hypoparathyroidism included the change from conventional therapy to daily injections of PTH(1–84) or PTH(1–34) and, subsequently, to an infusion pump of PTH(1–84) or PTH(1–34). Results showed that most patients experienced an increase in serum calcium with the infusion pump vs conventional therapy or subcutaneous injections. Ten of these patients showed a reduction in calciuria, and all reported a decrease in hypocalcemia symptoms with continuous infusion.

Palopegteriparatide (TransCon PTH) is a prodrug consisting of a carrier, a linker molecule, and an active drug, PTH(1–34), which is slowly released and allows for daily administration. The Pathway[10] trial was conducted to assess the effect of palopegteriparatide on serum calcium and therapeutic doses of active vitamin D and oral calcium in adults with hypoparathyroidism. During the 26 weeks of a placebo-controlled blind period, 79% (48/61) of participants on palopegteriparatide reached the primary endpoint of independence from conventional therapy, maintaining normocalcemia without an increase in the study drug dose in the last 4 weeks. This target was only achieved in 5% (1/21) of those on placebo. In addition, treatment with the active drug demonstrated a reduction in calciuria and a significant improvement in some aspects of health-related quality of life, measured with a psychometric questionnaire validated for patients with hypoparathyroidism. Palopegteriparatide has recently received EMA authorization for the treatment of adults with hypoparathyroidism.

Eneboparatide is a PTH receptor 1 (PTHR1) agonist with a novel mechanism of action designed to meet the therapeutic goals of hypoparathyroidism. Currently, we have data from an open-label phase 2 study with 28 patients with hypoparathyroidism treated for 3 months with subcutaneous injections of eneboparatide.[11] More than 88% of these patients achieved independence from conventional therapy with maintenance of serum calcium at the therapeutic target. The drug also induced a rapid and sustained reduction in calciuria and a slight increase in bone remodeling markers.

Different oral preparations have been developed for the treatment of hypoparathyroidism. Encaleret is an orally active calcium-sensing receptor antagonist (calcilytic) that has been used in type 1 autosomal dominant hypocalcemia, a disorder caused by a gain-of-function mutation in the gene encoding this receptor.[12] In an open-label study with 15 patients, 0.75 mg tablets of oral PTH(1–34) were administered 4 times a day for 16 weeks.[13] Results showed a mean reduction of 42% in oral calcium, and a reduction in phosphatemia and calciuria. In June 2024, data from a phase 1 clinical trial with EB612—an oral PTH(1–34) preparation—were presented in 15 healthy subjects who received 1.5 mg of this preparation in the morning and 2.5 mg 4 h after eating.[14] This regimen caused an increase in serum calcium (3.9%) and a decrease in phosphatemia (20.8%), along with a notable increase in 1.25-dihydroxyvitamin D levels (73.2%) and a decrease in endogenous PTH (43%).

The possible indications for changing from conventional to replacement therapy with the new preparations have been included in the clinical practice guidelines[1,2] and include patients with hypocalcemia, fluctuations between hypercalcemia and hypocalcemia, high doses of calcium or calcitriol, renal comorbidity, hyperphosphatemia, malabsorption due to digestive disorders or bariatric surgery, and decreased quality of life with conventional therapy. However, the definition of a patient not adequately controlled is not easy, and even more difficult is the decision on which patients should receive treatment with the new PTH formulations at this time. A recent multicenter study has shown a strikingly high prevalence of inadequately controlled patients in Spain.[15] There is suggestive data that the inadequacy is related to the comorbidities and complications of hypoparathyroidism, so it is important that clinicians, health authorities, the pharmaceutical industry, patient associations, and regulatory agencies take these facts into account to make the most appropriate decision on the future of replacement therapy for this hormonal deficiency.

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Declaration of competing interest

None declared.

References

1. Brandi ML, Bilezikian JP, Shoback D, Bouillon R, Clarke BL, Thakker RV, et al. Management of hypoparathyroidism: summary statement and guidelines. J Clin Endocrinol Metab. 2016;101:2273–83, http://dx.doi.org/10.1210/jc.2015-3907.
2. Khan AA, Bilezikian JP, Brandi ML, Clarke BL, Gittoes NJ, Pasieka JL, et al. Evaluation and management of hypoparathyroidism summary statement and guidelines from the second international workshop. J Bone Miner Res. 2022;37:2568–85, http://dx.doi.org/10.1002/jbmr.4691.
3. Khan AA, Guyatt G, Ali DS, Bilezikian JP, Collins MT, Dandurand K, et al. Management of hypoparathyroidism. J Bone Miner Res. 2022;37:2663–77, http://dx.doi.org/10.1002/jbmr.4716.
4. Büttner M, Locati LD, Pinto M, Araújo C, Tomaszewska IM, Kiyota N, et al. Quality of life in patients with hypoparathyroidism after treatment for thyroid can-

cer. J Clin Endocrinol Metab. 2020;105:dgaa597, http://dx.doi.org/10.1210/clinem/dgaa597.
5. Winer KK, Ye S, Ferré EMN, Schmitt MM, Zhang B, Cutler GB Jr, et al. Therapy with PTH 1-34 or calcitriol and calcium in diverse etiologies of hypoparathyroidism over 27 years at a single tertiary care center. Bone. 2021;149:115977, http://dx.doi.org/10.1016/j.bone.2021.115977.
6. Winer KK, Sinaii N, Peterson D, Sainz B Jr, Cutler GB Jr. Effects of once versus twice-daily parathyroid hormone 1-34 therapy in children with hypoparathyroidism. J Clin Endocrinol Metab. 2008;93:3389–95, http://dx.doi.org/10.1210/jc.2007-2552.
7. Mannstadt M, Clarke BL, Vokes T, Brandi ML, Ranganath L, Fraser WD, et al. Efficacy and safety of recombinant human parathyroid hormone (1-84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study. Lancet Diabetes Endocrinol. 2013;1:275–83, http://dx.doi.org/10.1016/S2213-8587(13)70106-2.
8. Winer KK, Zhang B, Shrader JA, Peterson D, Smith M, Albert PS, et al. Synthetic human parathyroid hormone 1-34 replacement therapy: a randomized crossover trial comparing pump versus injections in the treatment of chronic hypoparathyroidism. J Clin Endocrinol Metab. 2012;97:391–9, http://dx.doi.org/10.1210/jc.2011-1908.
9. Charoenngam N, Bove-Fenderson E, Wong D, Cusano NE, Mannstadt M. Continuous subcutaneous delivery of rhPTH(1-84) and rhPTH(1-34) by pump in adults with hypoparathyroidism. J Endocr Soc. 2024;8:bvae053, http://dx.doi.org/10.1210/jendso/bvae053.
10. Khan AA, Rubin MR, Schwarz P, Vokes T, Shoback DM, Gagnon C, et al. Efficacy and safety of parathyroid hormone replacement with TransCon PTH in hypoparathyroidism: 26-week results from the phase 3 PaTHway trial. J Bone Miner Res. 2023;38:14–25, http://dx.doi.org/10.1002/jbmr.4726.
11. Takacs I, Mezosi E, Soto A, Kamenický P, Figueres L, Galvez Moreno MA, et al. An open-label phase 2 study of eneboparatide, a novel PTH receptor 1 agonist, in hypoparathyroidism. J Clin Endocrinol Metab. 2024;109:2199–209, http://dx.doi.org/10.1210/clinem/dgae121.
12. Gafni RI, Hartley IR, Roszko KL, Nemeth EF, Pozo KA, Lombardi E, et al. Efficacy and safety of encaleret in autosomal dominant hypocalcemia type 1. N Engl J Med. 2023;389:1245–7, http://dx.doi.org/10.1056/NEJMc2302708.
13. Ish-Shalom S, Caraco Y, Khazen NS, Gershinsky M, Szalat A, Schwartz P, et al. Safety and efficacy of oral human parathyroid hormone (1-34) in hypoparathyroidism: an open-label study. J Bone Miner Res. 2021;36:1060–8, http://dx.doi.org/10.1002/jbmr.4274.
14. Burshtein G, Itin C, Hoppe A, Santora AC, Galitzer H, Pery D, et al. SAT-758. Phase 1 study results of EB612, a first-in-class oral PTH(1-34) analog for the treatment of hypoparathyroidism. ENDO. 2024 [accessed 8 Nov 2024]. Available from: https://www.abstractsonline.com/pp8/#!/11016/presentation/9825
15. Díez JJ, Anda E, Pérez-Corral B, Paja M, Alcazar V, Sánchez-Ragnarsson C, et al. Prevalence of chronic postsurgical hypoparathyroidism not adequately controlled: an analysis of a nationwide cohort of 337 patients. Front Endocrinol (Lausanne). 2024;15:1464515, http://dx.doi.org/10.3389/fendo.2024.1464515.