



Treatment of Hypoparathyroidism by Re-Establishing the Effects of Parathyroid Hormone

Lars Rejnmark

Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark

The conventional treatment of hypoparathyroidism (HypoPT) includes active vitamin D and calcium. Despite normalization of calcium levels, the conventional treatment is associated with fluctuations in calcium levels, hypercalciuria, renal impairment, and decreased quality of life (QoL). Replacement therapy with parathyroid hormone (PTH)(1-84) is an option in some countries. However, convincing beneficial effects have not been demonstrated, which may be due to the short duration of action of this treatment. Recently, palopegteriparatide (also known as TransCon PTH) has been marketed in Europe and is expected also to be approved in other countries. Palopegteriparatide is a prodrug with sustained release of PTH(1-34) designed to provide stable physiological PTH levels for 24 hours/day. A phase 3 study demonstrated maintenance of normocalcemia in patients with chronic HypoPT, with no need for conventional therapy. Furthermore, this treatment lowers urinary calcium and improves QoL. Another long-acting PTH analog with effects on the parathyroid hormone receptor (eneboparatide) is currently being tested in a phase 3 trial. Furthermore, the treatment of autosomal dominant hypocalcemia type 1 with a calcilytic (encaleret) is also being tested. All in all, improved treatment options are on the way that will likely take the treatment of HypoPT to the next level.

Keywords: Hypoparathyroidism; Parathyroid hormone; Hypocalcemia; Therapeutics

INTRODUCTION

Hypoparathyroidism (HypoPT) is a disease involving hypocalcemia due to insufficient levels of parathyroid hormone (PTH). Most often, HypoPT occurs following surgery to the anterior part of the neck, causing damage to the parathyroid glands (postsurgical HypoPT), but in 20% to 25% of cases the disease is non-surgical [1]. Different mechanisms may be responsible for non-surgical HypoPT with impaired synthesis or secretion of PTH, including genetic or autoimmune causes [2].

PTH normally affects the renal handling of calcium and phosphate. PTH is known to stimulate both the renal tubular reabsorption of calcium (thereby lowering renal calcium excretion)

and the renal excretion of phosphate (thereby lowering plasma phosphate concentrations and the calcium phosphate [CaxP] product). Accordingly, in addition to hypocalcemia, HypoPT is often associated with both hypercalciuria and high plasma phosphate levels with a high CaxP product.

Post-surgical and non-surgical HypoPT are treated in similar manners with conventional therapy being activated vitamin D and calcium supplements, thereby aiming at normalizing plasma calcium levels and relieving symptoms associated with hypocalcemia [3]. Despite achieving normocalcemia in response to conventional therapy, patients often experience unpredicted fluctuations in plasma calcium levels causing hypo- or hypercalcemic symptoms. Furthermore, the disease is associated with

Received: 30 December 2023, **Revised:** 1 February 2024,
Accepted: 19 February 2024

Corresponding author: Lars Rejnmark
Department of Endocrinology and Internal Medicine, Aarhus University
Hospital, Palle Juul-Jensens Boulevard 99, Aarhus 8200, Denmark
Tel: +45-7845-5475, **E-mail:** rejnmark@clin.au.dk

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numerous complications, including an increased risk of renal insufficiency and extra-skeletal (including renal) calcifications; additionally, patients with HypoPT are at increased risk of having neuropsychiatric diseases and an impaired quality of life (QoL). It is unknown whether this is due to the disease itself (lack of PTH) or the treatment used (calcium supplements and active vitamin D) for HypoPT [4]. In recent years, several studies have reported on the treatment of HypoPT with replacement therapy with the missing hormone (i.e., PTH) or drugs that act in a similar manner (Table 1).

TREATMENT WITH PTH(1-84)

Treatment with PTH, as a daily subcutaneous injection with recombinant human PTH(1-84) (rhPTH[1-84]), was marketed in 2015 for adults with chronic HypoPT that cannot be well controlled by treatment with calcium supplements and active forms of vitamin D alone. The treatment was approved based on the findings of the REPLACE study, which was a double-blind phase 3 controlled trial randomizing adult patients with chronic HypoPT of ≥ 18 months duration ($n=134$) to treatment with rhPTH(1-84) or placebo for 24 weeks [5]. The starting dose of rhPTH(1-84) was 50 $\mu\text{g}/\text{day}$, and doses could be up-titrated to 75 $\mu\text{g}/\text{day}$ and then 100 $\mu\text{g}/\text{day}$ (or similar placebo) while treatment with active vitamin D plus calcium supplements were down-titrated according to plasma calcium levels.

The primary endpoint was the proportion of patients at week 24 who achieved a 50% or greater reduction from baseline in their daily dose of oral calcium and active vitamin D while maintaining a serum calcium concentration greater than or the same as baseline concentrations and less than or equal to the upper limit of normal. The primary endpoint was achieved by 53% of the patients in the rhPTH(1-84) group compared with only 2% in the placebo group, which was a highly significant difference ($P<0.0001$). In addition to maintaining normocalcemia, treatment reduced the concentrations of serum phosphate and the CaxP product. However, despite replacement therapy with rhPTH(1-84), the randomized controlled trial did not show a significant reduction in renal calcium excretion, although a subsequent open-label study with up to 8 years of treatment with rhPTH(1-84) did suggest beneficial effects in response to treatment on renal calcium excretion [6]. Since being launched in 2015, rhPTH(1-84) has been used in several countries for the treatment of chronic HypoPT, but it has not been available in the USA since 2019 due to issues related to rubber particles breaking off from the rubber septum used in the drug-dispensing cartridge. Consequently, the manufacturer has decided to stop producing the drug worldwide at the end of 2024.

After an injection, rhPTH(1-84) has a relatively short plasma half-life and if injected once a day, PTH will not be present in the circulation throughout a 24-hour time period to bind to its receptors.

Table 1. Drugs Approved or Being Investigated in Randomized Trials for the Treatment of Hypoparathyroidism by Reestablishing the Effects of PTH

Drug ^a	Mode of administration	Use in clinical practice	Duration of action	Effects on 24-hour urinary calcium	Effects on QoL
PTH(1-34)	SC of infusion	Off-label	Very short (few hours)	Only reduced with continuous infusion	Open-label studies have suggested improved QoL.
rhPTH(1-84)	SC	Approved by FDA and EMA	Short (some hours)	Observational analyses suggest a reduced 24-hour U-Ca, but this has not been documented in RCTs	Observational analyses suggest an improved QoL, but this has not been documented in RCTs.
Palopegteriparatide	SC	Approved by EMA	Long (several days)	RCTs have shown reduced 24-hour U-Ca (normalized)	RCTs have shown improved QoL.
Eneboparatide	SC	Investigational drug	Long (several days)	A phase 2 trial suggests reduced 24-hour U-Ca	NA
Encalret	Oral	Investigational drug	Short (BID)	A phase 2 trial suggests reduced 24-hour U-Ca	NA

PTH, parathyroid hormone; QoL, quality of life; SC, subcutaneous injection; rhPTH, recombinant human PTH; FDA, U.S. Food and Drug Administration; EMA, European Medicines Agency; U-Ca, urinary calcium; RCT, randomized clinical trial; NA, not available; BID, *bis in die* (twice a day administration).

^aAll drugs cause increased levels of plasma calcium while reducing (abolishing) needs for conventional therapy with calcium supplements and active vitamin D.

Although the pharmacodynamic half-life is longer than the pharmacokinetic half-life, this is a likely explanation for the REPLACE study not showing a significant reduction in 24-hour renal calcium excretion in response to once-a-day treatment with rhPTH(1-84). Moreover, treatment has been shown to cause fluctuations in calcium levels, with an increase immediately after an injection followed by a decline during the last part of a 24-hour treatment period.

TREATMENT WITH PTH(1-34)

Similar to PTH(1-84), PTH(1-34) contains the N-terminal part of the PTH molecule, which is important for the physiological action of the hormone. However, PTH(1-34) has an even shorter plasma half-life than PTH(1-84), and studies have shown that PTH(1-34) has to be injected twice a day in children and adults to maintain normocalcemia in patients with HypoPT [7,8]. In addition, compared to a once-daily injection, twice-daily injections allowed for a reduction in the total daily PTH(1-34) dose required to maintain normocalcemia. Further studies have shown that administration of PTH(1-34) as a continuous infusion by an insulin pump causes even more stable plasma calcium levels, reduces urinary calcium, and enables a further reduction in the total dose of PTH(1-34) needed to maintain normocalcemia [9,10].

PALOPEGTERIPARATIDE

As an alternative to providing PTH(1-34) by an insulin pump, palopegteriparatide (also known as TransCon PTH) has been developed. It is a prodrug with sustained release of PTH(1-34) designed to provide stable PTH levels in the physiological range for 24 hours/day. A linker binds PTH(1-34) to a carrier molecule that efficiently shields PTH from binding to its receptor and prolongs the peptide's half-life in circulation. Under the influence of skin temperature and physiological pH, PTH is released from the carrier and free PTH(1-34) is released, mimicking endogenous PTH secretion, while the carrier molecule is excreted by the kidney [11]. The treatment is administered as a once-a-day subcutaneous injection. In addition to maintaining plasma calcium levels within the target range throughout the day with no need for treatment with active vitamin D or calcium supplements, renal calcium excretion is reduced in response to treatment with palopegteriparatide [12,13]. Furthermore, a phase 3 trial demonstrated an improved QoL in response to treatment with palopegteriparatide compared to conventional treatment

[13]. The disease-specific Hypoparathyroidism Patient Experience Scale showed improvements in HypoPT-related symptoms, functioning, and well-being for participants treated with palopegteriparatide including an improvement compared with placebo in physical and cognitive domain scores. Furthermore, health-related QoL as measured by the 36-Item Short-Form Health Survey (SF-36, version 2) also improved significantly in response to treatment compared with the placebo for the physical functioning subscale score.

Palopegteriparatide has recently received marketing authorization from the European Medicines Agency, and this medicine is now authorized for the treatment of adults with chronic HypoPT in the European Union. Presumably, it will also soon be authorized in additional countries, including the U.S. Food and Drug Administration for use in the USA.

ENEBOPARATIDE

Eneboparatide is a long-acting PTH analog that acts as a PTH receptor 1 agonist, which through a novel mechanism of action activates a specific conformation of the receptor [14]. Data from a phase 2 trial showed that eneboparatide was well tolerated in patients with HypoPT, and daily subcutaneous administration enabled most patients to discontinue conventional therapy with active vitamin D and calcium supplements. Moreover, treatment seems to cause a reduction in renal calcium excretion and a stable bone mineral density. A multinational phase III clinical trial is currently ongoing [15].

ENCALERET

Autosomal dominant hypocalcemia type 1 (ADH1) is a monogenic form of non-surgical HypoPT caused by a gain-of-function variant in the gene encoding the extracellular calcium-sensing receptor (CaSR) [16]. PTH secretion and urinary calcium are largely regulated by the CaSR. Gain-of-function variants of CASR increase the sensitivity of CaSR to plasma calcium levels causing the receptor to record plasma calcium levels as being higher than they are. As a result, PTH secretion is low and renal calcium excretion is high. Encaleret is an oral CaSR antagonist (calcilytic), thereby addressing the underlying molecular pathophysiological mechanism. A recently published phase 2 clinical trial including 13 adults with ADH1 showed beneficial effects of encaleret. Treatment corrected hypocalcemia and reduced hypercalciuria, with increased PTH levels [17]. A multinational phase 3 clinical trial with a larger group of patients with ADH1

is currently ongoing.

CONCLUSIONS

Despite normalizing plasma calcium levels, thereby alleviating severe symptoms of hypocalcemia, conventional treatment of HypoPT with active vitamin D and calcium supplements is associated with unpredictable fluctuations in plasma calcium levels, hypercalciuria, and several complications, including an increased risk of impaired kidney function and impaired QoL. Substitution with the missing hormone using rhPTH(1-84) or PTH(1-34) has been shown to reduce the need for conventional therapy; however, due to the short duration of action, replacement therapy with these analogues is not ideal. Palopegteriparatide is a prodrug with sustained release of PTH(1-34) designed to provide stable PTH levels in the physiological range for 24 hours/day and has recently been approved for treatment of chronic HypoPT in Europe. Treatment with eneboparatide and encalaret also seems to cause long-acting effects on the calcium-PTH axis, and phase 3 clinical trials are currently ongoing aiming to demonstrate a normalization of calcium homeostasis in response to treatment of patients with chronic HypoPT.

CONFLICTS OF INTEREST

Lars Rejnmark has received speakers fee/research contracts/grants and/or consulting from Takeda Pharmaceuticals, Kyowa Kirin, Ascendis Pharma, Calcilytix Therapeutics, and/or Amolyt.

ORCID

Lars Rejnmark <https://orcid.org/0000-0002-2152-4247>

REFERENCES

- Harslof T, Rolighed L, Rejnmark L. Huge variations in definition and reported incidence of postsurgical hypoparathyroidism: a systematic review. *Endocrine* 2019;64:176-83.
- Mannstadt M, Bilezikian JP, Thakker RV, Hannan FM, Clarke BL, Rejnmark L, et al. Hypoparathyroidism. *Nat Rev Dis Primers* 2017;3:17055.
- 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.
- Bollerslev J, Rejnmark L, Zahn A, Heck A, Appelman-Dijkstra NM, Cardoso L, et al. European expert consensus on practical management of specific aspects of parathyroid disorders in adults and in pregnancy: recommendations of the ESE educational program of parathyroid disorders. *Eur J Endocrinol* 2022;186:R33-63.
- 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.
- Tay YD, Tabacco G, Cusano NE, Williams J, Omeragic B, Majeed R, et al. Therapy of hypoparathyroidism with rhPTH (1-84): a prospective, 8-year investigation of efficacy and safety. *J Clin Endocrinol Metab* 2019;104:5601-10.
- 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.
- Winer KK, Yanovski JA, Sarani B, Cutler GB Jr. A randomized, cross-over trial of once-daily versus twice-daily parathyroid hormone 1-34 in treatment of hypoparathyroidism. *J Clin Endocrinol Metab* 1998;83:3480-6.
- 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.
- Winer KK, Fulton KA, Albert PS, Cutler GB Jr. Effects of pump versus twice-daily injection delivery of synthetic parathyroid hormone 1-34 in children with severe congenital hypoparathyroidism. *J Pediatr* 2014;165:556-63.
- Holtén-Andersen L, Pihl S, Rasmussen CE, Zettler J, Maitro G, Baron J, et al. Design and preclinical development of TransCon PTH, an investigational sustained-release PTH replacement therapy for hypoparathyroidism. *J Bone Miner Res* 2019;34:2075-86.
- Khan AA, Rejnmark L, Rubin M, Schwarz P, Vokes T, Clarke B, et al. PaTH forward: a randomized, double-blind, placebo-controlled phase 2 trial of TransCon PTH in adult hypoparathyroidism. *J Clin Endocrinol Metab* 2022;107:e372-85.
- 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.
- Shimizu M, Joyashiki E, Noda H, Watanabe T, Okazaki M, Nagayasu M, et al. Pharmacodynamic actions of a long-act-

- ing PTH analog (LA-PTH) in thyroparathyroidectomized (TPTX) rats and normal monkeys. *J Bone Miner Res* 2016;31:1405-12.
15. Kamenicky P, Takacs I, Mezosi E, Soto A, Figueres L, Lemoine S, et al. OR23-04 Treatment of chronic hypoparathyroidism with eneboparatide (AZP-3601), a novel PTH 1 receptor agonist: results from a phase 2 trial. *J Endocr Soc* 2023;7(Supplement 1):bvad114-562.
 16. Toka HR, Pollak MR. The role of the calcium-sensing receptor in disorders of abnormal calcium handling and cardiovascular disease. *Curr Opin Nephrol Hypertens* 2014;23:494-501.
 17. Gafni RI, Hartley IR, Roszko KL, Nemeth EF, Pozo KA, Lombardi E, et al. Efficacy and safety of encalaret in autosomal dominant hypocalcemia type 1. *N Engl J Med* 2023; 389:1245-7.