Rev Osteoporos Metab Miner. 2022 [Ahead of published issue]

Teriparatide in the substitutive treatment of chronic hypoparathyroidism. About a case

Morán López JM[1], Crespo Gutiérrez J[2], Puech de Oriol M[5]
1 Endocrinology, Diabetes and Nutrition. Virgen del Puerto Hospital. Plasencia. Caceres (Spain)
2 Family and Community Medicine. Virgen del Puerto Hospital. Plasencia. Caceres (Spain)

Date of receipt: 10/01/2022 - Date of acceptance: 06/07/2022

Summary
Objetive: To report experience in the use of teriparatide as an effective replacement therapy for chronic hypoparathyroidism.
Material and methods: The clinical case of a patient with post-surgical chronic hypoparathyroidism who previously presented difficult control with conventional treatment (calcium salts and calcitriol) is presented, for which teriparatide was started as a substitute treatment.
Results: The patient presented analytical values of phosphocalcic metabolism compatible with normality from the 4th week of treatment with teriparatide, allowing the suspension of previous treatments and maintaining good control one year after the change in therapy.
Conclusions: Teriparatide is an effective option for treating chronic hypoparathyroidism. We have observed a latency phase until the hormonal effect begins, so we recommend frequent analytical monitoring and gradually reduce treatment with calcitriol and calcium salts for adequate control.

Key words: teriparatida, hipoparatiroidismo, crónico, postquirúrgico, tratamiento.

Introduction
The clinical management of chronic hypoparathyroidism (using calcium salts and active vitamin D analogs) is currently less common than other hormone replacement treatments in endocrinological deficits, where treatment is based on deficient hormone administration. The treatment objectives indicated in the clinical practice guidelines mark albumin-adjusted calcium target levels at or slightly below the lower limit of the reference range (0.5 mg/dL) in order to avoid chronic complications derived from conventional chronic treatment (hypercalciuria due to the lack of effect of PTH on renal calcium reabsorption), with associated nephrolithiasis and calcifications at various levels (central nervous system, ophthalmological, renal,etc)[1,2].

In the past two decades, studies have been carried out to establish the effectiveness and safety of replacement therapy for hypoparathyroidism with PTH 1-84 (parathyroid hormone) and PTH 1-34 (teriparatide) due to poor clinical and biochemical control of chronic hypoparathyroidism with conventional treatment[3-5]. However, NATPAR® (PTH 1-84) has received the resolution of NO FINANCING IN SPAIN[6].

Clinical case report
We present the case of a 28-year-old man with postoperative chronic hypoparathyroidism since the age of 17 after total thyroidectomy for T4N1bM1 papillary thyroid carcinoma.

He was treated with calcium carbonate, a dose ranging between 6 and 8 grams of elemental calcium, calcitriol with a dose ranging between 0.5 and 1.5 mcg per day, cholecalciferol in a variable dose to maintain calcidiol levels between 20-30 ng/ml and magnesium salts, between 8 and 16 mEq of magnesium element daily. As initial complications, he suffered several crises of tetany

Correspondence: Jenifer Crespo Gutiérrez (jennifercrespogu@gmail.com)

secondary to discontinuing treatment. Once compliance with calcium salts and active vitamin D analog stabilized, he presented high phosphate levels (around 5.8-7.2 for reference values of 2.5-4.5 mg/dl), with calcium phosphorus above 55 on more than one occasion. Hyperphosphataemia was controlled by reducing the doses of calcitriol and spacing calcium carbonate doses to every 4 hours, managing to optimize its chelating effect. It appeared, however, due to the interference of calcium salts in the absorption of levothyroxine, great difficulty in adjusting the suppressive dose despite administering it weekly to minimize the effects of calcium salts on the intestinal absorption of thyroid hormone.

In this context, the indications of Brandi et al.[2] to start parathormone replacement therapy were reviewed and it was decided in 2018 to request PTH 1-84 as compassionate use treatment in this patient, which was not authorized after the 2019 AEMPS resolution.

Alternatively, and after reviewing the existing scientific evidence[3,4] it was decided to use subcutaneous (sc) teriparatide as an alternative. In these studies, the replacement dose reportedly ranged between 0.3 and 0.8 mcg/kg day.

Prior to commencing treatment, the patient was being treated with calcitriol 0.5 mcg daily, calcium carbonate 2g/8h, magnesium 16 mEq daily with the following analytical control: calcium adjusted to albumin 7.64 mg/dl (8.2-10.2), phosphate 5.9 mg/dl (up to 4.5), phosphocalcium: 46.02

Following the REPLACE[5] study indications and the technical data sheet for PTH 1.84[7] treatment was started with teriparatide 20 mcg sc at night, reducing the dose of calcitriol by 50% (to 0.25 mcg/day) and calcium carbonate (to 1 g every 8 hours) and the magnesium salt dose to 4 mEq daily. Analytical controls were carried out every 72 hours, experiencing a significant decrease in albumin-adjusted calcaemia (6.4 mg/dl) during the first week, maintaining similar levels of phosphate (5.7 mg/dl) and with normal figures. of magnesium (1.83 mg/dl), so the dose of teriparatide was doubled to 20 mcg sc every 12 hours. According to a recent study, a dose of 20 mcg teriparatide does not seem to be enough to control the condition[8].

With the change, there was a progressive rebound in the analytical values, presenting the following analytical values 7 days after starting teriparatide 20-0-20 (mcg): albumin-adjusted calcium 8.8 mg/dl (8.4 -10.2), phosphate 4.8 mg/dl (2.4-4.4), magnesium 1.62 mg/dl (1.6-2.6) with detectable urinary magnesium, normal renal function and calcitriol 32.7 ng/dl. It was decided at that time to suspend calcitriol and magnesium salt, leaving the patient under treatment with teriparatide 20 mcg sc every 12 hours and calcium carbonate 1 g/8 hours orally. After four weeks, he presented a practical normalization of the analytical values, so the calcium carbonate was suspended, leaving only teriparatide 20 mcg sc every 12 hours. In the following controls, the patient presented analytical values of phosphocalcic metabolism compatible with normality until reaching the year of treatment without presenting adverse effects, presenting a good tolerance of the drug with the 20 mcg/12h dose (table 1).

Discussion

Replacement treatment for chronic hypoparathyroidism with intact parathyroid hormone (PTH 1-84) or its active fraction (PTH 1-34) represents a novel aspect in managing this condition. The PTH 1-84 molecule has a complete clinical development (phases I, II, III, IV) based on the REPLACE studies and FDA approval for its use, while the management of chronic hypoparathyroidism with teriparatide lacks a similar clinical development, with only phase III studies to date. Knowledge about its effects in the management of this disease is based on results in series of patients with congenital hypoparathyroidism. There are no clinical studies directly comparing both molecules. In our case, teriparatide dose escalation was necessary to maintain calcaemia within target ranges, maintaining a replacement dose within the ranges described in the literature

Table 1. Evolution of the different parameters studied according to the prescribed treatment

Treatment followed	Time	Calcium (mg/dL)	Albumin (mg/dL)	Ca ajusted albumin (mg/dL)	Phosphate (mg/dL)	Magnesium (mg/dL)	FG (mL/min/ 1.73m²)
Calcitriol 0.5 mcg daily + Calcium carbonate 2 g/ 8h, + Magnesium salt 16 mEq/day	**0**	7.8	4.2	7.6	5.9	1.72	90
Teriparatide 20 mcg/24h SC + Calcitriol at 0.25 mcg/day + Calcium carbonate at 1 g every 8 hours + Magnesium salt 4 mEq/day	**1st week**	6.7	4.4	6.4	5.7	1.83	90
Teriparatide 20 mcg/12h SC + Calcium carbonate at 1 g every 8 hours	**5th week**	8.8	4.3	8.5	4.8	1.62	90
Teriparatide 20 mcg/12h SC	**10th week**	9.1	4.3	8.8	4.5	1.68	90
Teriparatide 20 mcg/12h SC	**Year**	9.1	4.2	8.9	3.9	1.63	90

(0.3-0.8 mcg/kg/day). This dose escalation was also seen in the REPLACE study for PTH 1-84 (77% of patients needed to increase the dose of PTH 1-84 from 50 mcg daily to 75 or 100 mcg daily to achieve the primary objective (reduction of the dose of calcitriol and calcium salts by 50%, maintaining good biochemical control). Independence from conventional treatment is also described with both molecules (43% of the patients treated with PTH 1-84 in the REPLACE study were able to discontinue the treatment with calcitriol maintaining calcium supplements providing less than 500 mg of elemental calcium per day).

Indeed, our patient responded well to treatment with teriparatide that allowed us to progressively suspend the calcitriol and magnesium salt treatment until finally suspending calcium carbonate and maintaining a normalization of the analytical values, remaining only with teriparatide 20 mcg sc every 12 hours. In the following controls, the patient presented analytical values of phosphocalcic metabolism compatible with normality until reaching the year of treatment.

As a limitation of our study, we note that the effect of teriparatide on calciuria in our patient has not been quantified, an aspect of great clinical relevance in managing these patients. Furthermore, the effects of teriparatide on bone and mineral density and markers of bone remodeling have not been evaluated.

Conclusions

Teriparatide has been an effective option for the replacement treatment of chronic hypoparathyroidism using a dose that corresponds to that described in the literature (0.5 mcg/kg/day, divided into two doses). A latency period has also been observed until the full effect of the medication is reached, which has allowed us to completely suspend the previous treatment, requiring frequent monitoring and gradual de-escalation of treatment with calcitriol and calcium salts for adequate control.

Conflict of interests: The authors declare no conflict of interest.

Bibliography

1. Bollerslev J, Rejnmark L, Marcocci C, Shoback DM, Sitges-Serra A, van Biesen W, et al. European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol. 2015;173(2):G1-20.
2. 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(6):2273-83.
3. Winer KK, Ko CW, Reynolds JC, Dowdy K, Keil M, Peterson D et al. Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. J Clin Endocrinol Metab. 2003;88(9):4214-20.
4. 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(2): 391-9.
5. 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(4):275-83.
6. Agencia española de medicamentos y productos sanitarios. Informe de Posicionamiento Terapéutico de parathormona (Natpar®) en el tratamiento del hipoparatiroidismo crónico. 2019. Disponible en: https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-parathormona-Natpar-hipoparatiroidismo.pdf?x23109. (Accedido el 1 Octubre de 2021).
7. Agencia española de medicamentos y productos sanitarios. Ficha Técnica NATPAR 50 microgramos/dosis polvo y disolvente para solución inyectable. Disponible en: https://cima.aemps.es/cima/dochtml/ft/1151078002/FT_1151078002.html (Accedido el 1 Octubre de 2021).
8. Marcucci G, Masi L, Cianferotti L, Giusti F, Fossi C, Parri S et al. Chronic hypoparathyroidism and treatment with teriparatide. Endocrine. 2021;72 (1):249-59.