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Teriparatide (rhPTH 1-34) treatment in the pediatric age: long-term efficacy and safety data in a cohort with genetic hypoparathyroidism.

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ABSTRACT

Background: Hypoparathyroidism is characterized by the absence or inadequately low circulating concentrations of the parathyroid hormone, resulting in hypocalcemia, hyperphosphatemia and elevated fractional excretion of calcium in the urine. The use of activated vitamin D analogues and calcium supplements represent conventional therapy. Subcutaneous recombinant human parathormone [rhPTH(1-34)] has been proposed as a substitutive treatment, even to avoid side effects of vitamin D and calcium.

Objective: To assess the long-term safety and efficacy of rhPTH(1-34) in a pediatric cohort of patients with genetic hypoparathyroidism.

Methods: The study is a 9.2-year self-controlled study of 6 pediatric patients (4 males and 2 females, aged 9.4 ± 5.2) with DiGeorge, Hypoparathyroidism-Deafness-Renal dysplasia (HDR) or Autoimmune-Candidiasis-PolyEndocrinopathy-Ectodermal-Dysplasia (APECED) syndrome, associated with autoimmune intestinal malabsorption in a patient. The presence of clinical signs of hypocalcemia and biochemical parameters, such as calcium, phosphate, alkaline phosphatase in the blood and calcium-creatinine ratio in urine, were compared during conventional treatment and rhPTH (1-34) (teriparatide, 12.5 μg twice daily).

Results: The rhPTH(1-34) treatment allowed a reduction, although not always a complete suspension, of calcium supplementation and a slight reduction of calcitriol therapy. The number of tetanic episodes was reduced in 4 patients during rhPTH(1-34) treatment. Mean blood calcium, alkaline phosphatase and phosphate did not significantly change, while a significant reduction of the urinary calcium-to-creatinine ratio (0.55±0.32 vs. 0.16±0.09, p=0.03) was obtained. Renal ultrasound examination showed a worsening in 3 patients, while it did not change in the remaining 3 subjects during the follow-up.

Conclusion: in children with syndromic hypoparathyroidism presented here, replacement therapy with rhPTH(1-34) allowed to maintain adequate levels of calcium and phosphate in the blood, normalize urinary calcium excretion and reduce tetanic episodes. In patients with low compliance to conventional therapy or intestinal malabsorption, the use of rhPTH(1-34) could be considered, also to reduce the side effects of treatment with vitamin D and calcium.

INTRODUCTION

Hypoparathyroidism is characterized by the absence or the inadequately low circulating concentrations of parathyroid hormone (PTH) resulting in hypocalcemia, hyperphosphatemia and elevated fractional excretion of calcium in the urine (1). The clinical manifestations, mainly caused by hypocalcemia, can involve almost any organ systems and include paresthesia, tingling, brain fog, muscle cramps, seizure, positive Chvostek and Trousseau signs, laryngospasm, cardiac arrhythmias [1-2]. Activated vitamin D analogues and calcium supplement represent the conventional treatment for hypoparathyroidism [3], even if they do not replace physiologically the PTH actions and can be associated with short-term and long-term complications as hypocalcemia, hypercalcemia, increased urinary calcium excretion, nephrocalcinosis, impaired renal function and reduced quality of life [1]. Furthermore, in the different periods of the pediatric age it can be difficult to

balance the risk of under- or over-treatment and, in addition, the compliance to the chronic treatment may be poor as children have to take oral drugs three to four times a day.

Theorically, the most physiologic treatment is represented by the hormonal replacement of PTH. In 2002 a recombinant human PTH(1-34) [rhPTH(1-34), teriparatide, Forsteo, Eli Lilly, IN, USA] was approved by the U.S. Food and Drug Administration (FDA) for osteoporosis in postmenopausal women (and later in men) at high risk for fracture, with restrictions in duration of therapy (18–24 months) [4].

In 2015 the Food and Drug Administration (FDA) and in 2017 the European Medicine Agency (EMA) approved the use of rhPTH(1-84) [rhPTH(1-84), Natpara, Shire-NPS Pharmaceuticals, MA, USA] in adults with hypoparathyroidism which cannot be well controlled with the standard therapy [5-6].

Actually both are considered as “off—label” for the use in pediatric age but in recent years several studies have reported the effects of rhPTH(1-34) treatment for hypoparathyroidism in adults, children and also in newborns [7-24]. Since a lower risk of complications related to hypoparathyroidism or significant improve in the quality of life compared to the conventional therapy has not been documented so far, its routine use in hypoparathyroidism is not recommended [3]. To date no data have been produced on the use of rhPTH(1-84) in children [25-26].

Most of the attention on the safety of rhPTH is related to the toxicity data emerging from the rat models and show the development of bone tumors (osteoma, osteoblastoma and osteosarcoma) in a dose-dependent manner for rhPTH (1-34) and rhPTH (1-84) when high doses are used (3 to 71 times higher than those used in humans) [27-30]. However, some papers discuss whether toxicity data on rat models can be transferred directly to humans, mainly due to the important differences in skeletal physiology between rodents and primates, due to the long duration of treatment used in rats, corresponding to 80 -90% of its lifespan, and for very high doses, above-physiological, used doses [27-31]. Furthermore, primates who received high doses of rhPTH(1–34) for 18 months showed no osteosarcoma or bone proliferative lesions [32]; also, in patients with long-standing hyperparathyroidism, chronically elevated PTH levels are not associated with the development of osteosarcomas [33] and in patients with hypoparathyroidism or osteoporosis treated with rhPTH(1–34) there was no evidence of an increase in the rate of osteosarcoma, although most of them have only been treated for 2 years [4, 34].

In a previous study we analyzed the data of short-term (2.5 years) rhPTH(1-34) treatment in 6 pediatric patients with syndromic hypoparathyroidism; compared to conventional treatment, the rhPTH(1-34) regimen allowed a reduction in the calciuria-creatininuria ratio (CaU/CrU) and tetanic episodes in 4 patients, while the average levels of calcium, phosphorus and alkaline phosphatase in the blood did not they have changed significantly [18].

The aim of this study is to evaluate teriparatide long-term safety and efficacy in the same small pediatric cohort affected by syndromic hypoparathyroidism.

SUBJECTS AND METHODS

The subjects enrolled are the same as those of our previous cohort (18): six young patients suffering from syndromic hypoparathyroidism, four males and two females, currently aged 9.4 ± 5.2 (3.4-18.6).

The etiology of hypoparathyroidism has been genetically confirmed; 3 patients have an APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy) (P3 and P4 are brother and sister), 2 a DiGeorge (hypoparathyroidism, congenital cardiac malformation, thymic aplasia, cleft palate) and 1 a HDR (hypoparathyroidism, deafness, renal dysplasia) syndrome.

At the time of diagnosis of hypoparathyroidism all of them had typical clinical signs and symptoms and low blood calcium levels (1.7±0.2 mmol/L), high blood phosphate (2.9±0.7 mmol/L), undetectable urinary calcium excretion (CaU/CrU <0.02); low PTH values (6.4–8.5 ng/L) were present in 3 patients and undetectable values (<3 ng/L) in the remaining 3 subjects. Alkaline phosphatase, serum magnesium, 25-OH vitamin D, and 1,25-OH vitamin D were normal in all subjects. Kidney sonographic evaluation at diagnosis showed abnormalities in 3 out 6 patients: right kidney hypodysplasia and bilateral hyperechogenicity in P1, bilateral hyperechogenicity in P2, right kidney agenesis in P5. Complete clinical, genetic and sonographic data at diagnosis are reported in Table 1.

The study represents a self-controlled trial conducted at Regina Margherita Children's Hospital in Turin, Italy. All the patients were included in the Piedmont Regional Network for Rare Diseases which allows clinicians to use off-label drugs, approved and covered by the Italian National Health Service. Teriparatide treatment has been approved by the pharmacological board and Ethics Committee of our institution. Patients and parents have given their written informed consent.

From the time of the diagnosis, all patients had received conventional treatment with oral calcium and vitamin D for 4.8±4.1 years. This was progressively discontinued in all patients admitted to hospital and therefore teriparatide was administered subcutaneously, twice a day and with a maximum dose of 25 μg / day. Twelve hours after the last conventional treatment, blood calcium, phosphate, magnesium, alkaline phosphatase, PTH, 25-OH vitamin D, 1-25-OH vitamin D, ALT, AST, creatinine have been evaluated, as well as urinary calcium, phosphate and creatinine collected in 24 hours. The drug was administered subcutaneously by administering 0.3 ml of the insulin syringes filled from the pen of teriparatide which contains 600 μg of rhPTH (1–34) in 2.4 mL and delivers 2.5 μg at each release (0.3 ml of the syringe for insulin, which has 30 notches and in which 1 notch equals to 0.01 ml of product, contains 2.5 μg of teriparatide). The initial dose was 2.5 μg bid and was subsequently progressively increased to maintain serum calcium above 2 mmol/L (with a maximum dose of 12.5 μg bid) [18]. The evaluation of blood calcium, phosphate and alkaline phosphatase, of the urinary calcium/creatinine ratio on spot has been performed daily for 5 days, then weekly for 3 weeks, monthly in the first year, and then every three months or more frequently, depending on the clinical and metabolic conditions.

Clinical and auxological follow-up every three months included the assessment of height, weight, and growth velocity, according to Tanner standards and clinical evaluation of any bone pathology.

Renal ultrasound was performed before starting treatment with teriparatide and repeated every year. At the same intervals, bone mass density (BMD) was evaluated with phalangeal quantitative ultrasound (QUS; DPM sonic BP, IGEA, Carpi, Italy) [BMD: amplitude-dependent speed of sound SD score (Ad-Sos SDS); bone transmission time SDS (BTT SDS)]

Fatigue, bone pain, arthralgia, cramps at the upper and lower limb, numbness, tingling and adverse events have been investigated. Tetanus crises were considered those manifested with trismus or carpal and pedal spasm or generalized convulsions, while tingling, numbness and muscle cramps were not included.

RESULTS

CONVENTIONAL TREATMENT

Follow-up during conventional treatment with oral calcium (1–2.5 g daily) and calcitriol (0.25–0.5 μg daily) lasted 4.8±4.1 years. At the last evaluation before switching to rhPTH (1–34) treatment (Table 2), blood PTH was in range in 2 out 6 (11.3–13.1 ng/L) and undetectable in 4 out 6 subjects (<3 ng/L). Mean blood calcium was 2.10±0.26 mmol/L, phosphate 2.01±0.23 mmol/L, alkaline phosphatase 154±62 UI/L. High urinary calcium levels were detected, with a urinary calcium/creatinine ratio 0.55±0.32 mg/mg. Tetanus episodes were observed in 4 out 6 subjects. The last ultrasound evaluation of the kidney before starting treatment with teriparatide was not modified with respect to the diagnosis in all patients (kidney hypodysplasia and bilateral hyperechogenicity in P1, bilateral hyperechogenicity in P2, right kidney agenesis in P5).

TERIPARATIDE TREATMENT

The teriparatide dose employed was 0.68±0.23 μg/kg/day (range 0.31-0.82 μg/kg/day) divided in 2 doses. All subjects reached the maximum dose of 25 μg/day during the first year of therapy. Follow-up during teriparatide treatment lasted 9.2±0.2 years.

The mean blood calcium value was 2.23 ± 0.13 mmol/L, that of phosphate 1.69 ± 0.21 mmol/L, alkaline phosphatase 176 ± 63 IU/L and urinary calcium/creatinine ratio 0,16 ± 0.09 (Table 3). Four subjects presented tetanic episodes (the total number of episodes per year was 0.16). The renal ultrasound evaluation at the end of the follow-up showed nephrocalcinosis in P2 and P3, hyperecogenicity in P1 and P4; P5 and P6 had normal echographic results. During treatment with teriparatide, some patients showed some new signs, mainly related to the natural history of their respective syndrome (Table 3).

TERIPARATIDE AND CONVENTIONAL TREATMENT COMPARISON

During teriparatide treatment all subjects restarted oral calcium and vitamin D, based on blood levels monitoring, except for P1, who took calcium therapy only during intercurrent illnesses for few days. In particular, P2 required oral calcium only in the last nine months of observation, at the age of 17.4; P3 after 6 months of rhPTH treatment, for only 2 months and then started oral calcium again 8 years after onset of teriparatide (at the age of 11.4); P4 after 5.4 years of treatment (at the age of 13.7); P5 after 2 months for 6

months and then after 1.8 years (at 20.4 years); P6 after 6.3 years (at the age of 12.7). The conventional and teriparatide treatment timeline is represented in Figure 2.

In general, during treatment with teriparatide, calcium supplementation was required for 32.3±29.7% (3.5-84.5%) of the overall observation time: the average dose over the entire period was lower than the conventional treatment (1006±290 mg vs 1417±534 mg, ***p=0.15***; 26 mg/kg vs 58 mg/kg, ***p=0.04***).

Vitamin D analogue was also restarted to maintain calcium levels above 2 mmol/l in all the patients: after 6 months in P5, after 1 year in P1, P3 and P4, after 4 years in P2 and 5 years in P6. Overall, the vitamin D analogue was administered for 75.2±23.2% of the observation time, with no dose differences compared to the conventional treatment (calcitriol 0.016±0.008 mcg/kg vs 0.015±0.011 mcg/kg, p=0.86).

During teriparatide treatment blood calcium increased but not significantly (2.10±0.25 vs 2.23±0.13; p=0.43) whereas blood phosphate decreased (1.69±0.21 vs 2.01±0.23, p=0.06) (Figure 1).

With conventional treatment and teriparatide, the urinary calcium-to-creatinine ratio was 0.55±0.32 mg/mg and 0.16±0.09 mg/mg, respectively (p=0.03).

Alkaline phosphatase remained in the normal range with both treatment options and the number of tetanic crises per years was reduced in the 4 patient who experienced crises during conventional treatment; only P4 had tetanic crisis during the treatment with teriparatide. The overall mean frequency of tetanic crisis in the 6 patients during rhPTH(1-34) and conventional treatment was 0.16 and 0.65 episodes/year respectively (p=0.18).

The mean height Z-scores (calculated considering age, gender and pubertal stage) at the beginning and at the end of rhPTH(1-34) study were -0.39±0.70 and -1.24 ±1.23 (p=0.2).

Phalangeal ultrasonographic evaluation showed no significant differences in BMD during conventional treatment and during teriparatide.

Kidney ultrasound worsened in 3 patients (with nephrocalcinosis in 2 patients) and was unmodified in 3 patients.

TERIPARATIDE LONG TERM SAFETY

Along the 9.2 years of follow-up during teriparatide treatment, no local cutaneous or subcutaneous dystrophy nor allergic reactions have occurred; nor systemic symptoms (nausea, headache, vertigo, joint pain, dyspnoea, fever, urticaria, etc.); nor derangements in the hepatic or renal function (not even in those children with pre-existing hepatopathy); nor clinical evidence of bone lesions.

DISCUSSION

Few studies have so far focused the attention on the comparison between rhPTH(1-34) and conventional treatment in hypoparathyroidism in adult [8, 10] and children [15, 17, 18]. The present study reports one of the longest follow up in children receiving rhPTH(1-34), and also includes the youngest patient with hypoparathyroidism so far treated.

The reduction of urinary calcium excretion during teriparatide treatment is the main result found in this 9 years observational study. The increased calciuria is one of the most severe adverse effects of conventional treatment because it can lead to nephrocalcinosis, kidney stones and impaired renal function. In subjects with syndromic hypoparathyroidism, kidneys are often involved, with hypo/dysplasia or agenesia, conditions that predispose to an increased risk of chronic renal failure, which can be aggravated by hypercalciuria.

The effect of rhPTH(1-34) therapy in reducing urinary calcium excretion as compared with conventional therapy have been already highlighted in previous studies [8, 10, 17, 18]. Despite the decrease in calciuria, nephrocalcinosis developed in two patients of this study, not associated with renal failure. It is likely that the cumulative effect of chronic calcium intake or acute administration of calcium during emergency department visits for tetany and that the intermittent, non-physiological, replacement of PTH is unable to clear the risk of nephrocalcinosis in these patients, as also suggested by other studies on treatment with teriparatide [17].

Since treatment with PTH(1-34) twice a day seems more effective than the once-daily regimen [7, 19] more physiological replacement therapy by continuous subcutaneous infusion of the infusion pump has been proposed for hypoparathyroidism [9, 14, 16, 20] which might further correct renal calcium excretion.

The initial dose of 2.5 μg bid was decided on the basis of the minimum dose that could be administered with our device and on the basis of data from previous studies on patients with similar clinical features and ages [15], by also considering the exact effects of teriparatide on calcium-phosphorus metabolism; the treatment was started in a safe hospitalization regimen.

In our cohort, during teriparatide, blood calcium levels were in the low-normal range or just below. Five patients resumed calcium supplementation with lower doses than conventional treatment, for different periods, after 11 years of age. To maintain adequate calcium values, vitamin D was also given during treatment with teriparatide; only in the first two years it was completely suspended or significantly reduced.

These data could be explained by the increase in calcium requirements with weight gain or during puberty, combined to our decision to maintain the daily dose of rhPTH(1-34) up a maximum of 25 μg (mean 0.68 μg/kg/day with range of 0.31-0.82 μg/kg/day). Although other Authors have used higher doses, we have decided not to exceed the maximum dose of 25 μg for the awareness of the association of high dose of teriparatide with the onset of osteosarcoma in murine models. Other studies that compared rhPTH(1-34) with conventional treatment on pediatric cohorts used higher rhPTH(1-34), up to 1.2 μg/kg/die (approximately 54 μg) [15], with a maximum of 1.5 μg/kg/die (108 μg) with total discontinuation of conventional therapy, but a worsening rate of nephrocalcinosis of 41.6% (5/12) [17].

The second remarkable result found in our cohort is that related to the mean levels of phosphate in the blood, which have dropped to high-normal range or just above, lower than those detected with conventional treatment; however, we are aware that this result could be partially influenced by the physiological decline of phosphate levels with increasing age.

At the end of the rhPTH(1-34) study, height Z-scores had decreased in all patients, even if without statistical significance. We believe that this finding may be unrelated to the rhPTH(1-34) treatment itself, but explained by the severe comorbidities and the multi-system involvement of the genetic forms of hypoparathyroidism

affecting our patients, which may have influenced their growth; moreover, normal linear growth has previously been reported in hypoparathyroid children treated with teriparatide [15, 17].

It is noteworthy that one of subjects of the study developed an autoimmune intestinal malabsorption during the follow up; the teraparatide treatment in this case have allowed to maintain the blood calcium levels stable, notwithstanding the reduced absorption of the oral conventional therapy, indicating that the subcutaneous teriparatide treatment in such cases might represent the best solution [16].

The presented data on a follow up lasting more than 9 years indicate that PTH (1-34) given by twice-daily subcutaneous injection is safe and effective, it is able to keep blood calcium levels in the low-normal range or just below, to reduce phosphate levels and, overall, to reduce hypercalciuria. During the follow up period, the hypocalcemic crises decreased, although the number of patients and episodes are too small to achieve statistical significance.

Indeed, during treatment with teriparatide, long-term side effects have to be strictly monitored, with particular attention to bone diseases. Osgood-Schlatter disease, an inflammation of the patellar ligament at the tibial tuberosity which is a common cause of knee pain in growing adolescents, and gouty arthritis, an inflammation caused by uric acid crystal deposits, have been the only osteoarticular involvement diseases recorded in our subjects. The other comorbidities evidenced during our study with PTH (1-34) may be related to the patients' syndromes.

CONCLUSIONS

In recent years rhPTH(1-34), a drug approved in 2002 by the FDA for post-menopausal osteoporosis, has also been used in the management of adults and children with hypoparathyroidism, as a replacement treatment. To date, there are few data on the efficacy and safety of its use in children after many years of follow-up; they show a significant reduction in renal calcium excretion, an increase in blood calcium levels and a decrease in blood phosphate, despite the suspension or significant reduction of conventional therapy, without treatment-related adverse events or significant complications.

Even if the same results have been found also in the present study, to reinforce these efficacy and safety data, to further investigate the effects of the PTH treatment on BMD and linear growth, to assess which are the most appropriate therapeutic doses, even using rhPTH (1-84), the new drug so far approved from the FDA and the EMA only for the adult hypoparathyroid population, further studies are needed on large cohorts of pediatric patients with long-term follow-up and rigorous monitoring of possible late side effects, particularly related to bone.

Compliance with Ethical Standards:

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Conflict of Interest: All Authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethical approval: This article does not contain any studies with animals performed by any of the authors.

Informed consent: Informed consent was obtained from all parents of the individual participants included in the study.

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