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DRUG EVALUATION

Natpara for the treatment of hypoparathyroidism

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ABSTRACT

Introduction: Hypoparathyroidism is a rare endocrine disorder characterized by hypocalcaemia and hyperphosphatemia, due to absent or inappropriately low parathyroid hormone levels. For management of chronic hypoparathyroidism, current treatment options involve oral calcium and vitamin D. This standard treatment cannot resolve all problematic aspects of the disease, such as abnormal bone remodeling and reduced quality of life, and is associated with long-term complications, including nephrolithiasis, nephrocalcinosis, renal impairment, cataracts and cerebral calcifications.

Areas covered: In 2015, the FDA (Food and Drug Administration) approved rhPTH (1–84), named Natpara®, a bioengineered recombinant human PTH, for the management of hypoparathyroidism of any etiology, except Autosomal Dominant Hypocalcemia, not well controlled with calcium and active vitamin D. Herein, the authors review its chemistry, pharmacodynamics, pharmacokinetics and clinical efficacy for hypoparathyroidism.

Expert opinion: Replacement therapy with rhPTH (1–84) is a fundamental step in the treatment of chronic hypoparathyroidism in cases not well controlled by standard therapy, providing the natural hormone that is lacking for the maintenance of normal calcium levels, and reducing long-term risks associated with conventional therapy. Nevertheless, given the chronic nature of the disease, in the future, further studies will have to be performed to evaluate long-term efficacy and safety of the drug.

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Hypoparathyroidism; parathyroid hormone (PTH); rhPTH (1–84); hypocalcemia

1. Introduction

Hypoparathyroidism is a rare endocrine disease characterized by hypocalcaemia and hyperphosphatemia, due to absent or inappropriately low parathyroid hormone (PTH) levels [1,2]. This disorder can be acquired or hereditary. It results from a surgical procedure in approximately 75% of patients, and in the remainder is due to genetic, autoimmune, or unknown etiologies. The most common acquired form of hypoparathyroidism in adults, caused by surgery, is due to inadvertent or unavoidable removal of the parathyroid glands or damage to the parathyroid glands and/or their blood supply [3]. The second most common cause in adults is autoimmune disease, either affecting only the parathyroid glands, or multiple other endocrine glands, such as autoimmune polyglandular syndrome type 1-3-4 (APS-1-3-4) or rarely APS-2 [2]. Other forms of genetic hypoparathyroidism can be in association with other organ defects or an isolated disorder. Syndromic genetic forms of hypoparathyroidism include: DiGeorge's syndrome, hypoparathyroidism–deafness–renal dysplasia syndrome, Kenny–Caffey syndrome, hypoparathyroidism–retardation–dysmorphism syndrome, Kearns–Sayre syndrome, and mitochondrial encephalopathy, lactic acidosis, and stroke-like episode syndrome. Non-syndromic isolated genetic forms include: familial isolated hypoparathyroidism with autosomal dominant, recessive or X-linked inheritance, and autosomal dominant hypocalcemia with hypercalciuria type 1 and 2 [1]. Autosomal dominant hypocalcemia with hypercalciuria type 1 is caused by heterozygous activating mutations of calcium sensing receptor (CasR), resulting in a decrease of PTH, with consequent hypocalcemia with relative or absolute hypercalciuria. The recently identified autosomal dominant hypocalcemia with hypercalciuria type 2 is caused by heterozygous gain-of-function missense mutations of the guanine nucleotide binding protein (G protein) Alpha 11 (GNA11), increasing the sensitivity to changes in Cao^{2+} [4]. The remaining cases of acquired hypoparathyroidism include rare infiltrative diseases in which the parathyroid glands are affected by metastatic disease or copper or iron overload, or ionizing radiation exposure [1,2].

Most signs and symptoms of hypoparathyroidism are due to low serum ionized [Ca^{2+}], altering neurologic, cognitive, muscular, and cardiac functions [1,2]. The clinical features due to hypocalcaemia result in highly variable manifestations, such as neuromuscular irritability (e.g. tetany, muscle cramping, paraesthesias, laryngo-, and bronchospasm), central nervous system alterations (seizures, and altered mental status), cardiac complications (e.g. congestive heart failure, and prolonged QT interval), other complications (e.g. calcifications of the basal ganglia, abnormal dentition, and cataracts) or no symptomatology [2]. Moreover, hypoparathyroidism is characterized by a state of marked low bone turnover with an increased bone mass. The abnormally low bone

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Box 1. Drug summary

Drug name	Natpara®
Phase	Launched
Indication	Hypoparathyroidism
Pharmacology description	Parathyroid hormone receptor 1 agonist
Route of administration	Subcutaneous injection
Pivotal trial(s)	REPLACE (23), REPEAT (24); RACE (NCT01297309) (ongoing, but not recruiting participants)

remodeling and dense bone suggests that, in the case of PTH deficit, bone is hypermature and potentially more subject to fracture than bone with appropriate PTH levels [5]. Patients affected by hypoparathyroidism frequently report symptoms suggesting impaired quality of life, including cognitive symptoms such as 'brain fog' and inability to concentrate, depression and/or anxiety, in addition to fatigue, muscle spasms, pain, and paresthesia [1].

For management of chronic hypoparathyroidism, current treatment options involve oral calcium and vitamin D (its metabolites and analogs) supplementation, and thiazide diuretics, which reduce urinary calcium excretion. Patients affected by chronic hypoparathyroidism often require large amounts of calcium and active forms or metabolites of vitamin D to maintain normal serum calcium levels. Apparently, normalization of serum calcium levels in response to conventional therapy with calcium and active vitamin D does not restore the normal physiology of calcium homeostasis, and induces hypercalciuria and hyperphosphatemia in absence of the renal calcium reabsorption and phosphaturia normally promoted by PTH [2]. Therefore, standard treatment increases the risk of extra-skeletal calcification and long-term kidney complications [6]. In addition, due to the lack of PTH, bones typically have abnormal remodeling, and many patients with hypoparathyroidism complain of reduced quality of life, despite conventional therapy [7]. These problematic aspects have directed scientific research to find different therapeutic options.

The first treatment of hypoparathyroidism with use of bovine PTH extract was attempted 50 years ago in humans, but failed due to the development of neutralizing antibodies after several weeks of injection [8]. No further studies were performed until it became possible to produce PTH by recombinant DNA technology. There are two formulations of PTH that have been studied in hypoparathyroidism: the full-length molecule, PTH (1–84), and the N-terminal biological active fragment of the molecule, PTH (1–34), named teriparatide. Both formulations have been studied as a subcutaneous injection. Generally, for different pharmacokinetics, PTH (1–84) is required once daily, while PTH (1–34) is administered by multiple injections per day [9,10]. PTH has been investigated as a therapy for hypoparathyroidism in several studies since 1996, in children, and in adults in which hypoparathyroidism occurred as a thyroid surgery complication, or could be due to autoimmune disease or genetic mutations. Over the past two decades, studies of replacement therapy with PTH have ushered in a new era in the management of this disease, with an improvement of calcium homeostasis and quality of life, particularly for those who require large amounts of calcium and active vitamin D. To date, only in the United States, the Food and Drug Administration (FDA) has approved recombinant human (rh)PTH (1–84) [rhPTH (1–84)], named Natpara® (see Box 1), a bioenginerred recombinant human PTH, for the management of hypoparathyroidism in 2015 [11]. The FDA indication for this drug is for subjects with hypoparathyroidism of any etiology, with the exception of Autosomal Dominant Hypocalcemia, which cannot be well controlled on calcium and active vitamin D. rhPTH (1–84), indeed, has not been studied in patients with hypoparathyroidism caused by mutations of CasR. These individuals may have normal levels of PTH but hypocalcemia, representing a steady state of the abnormally sensitive CaSR. In these cases, future therapies might employ calcilytics, which directly modulate the CaSR.

In particular, in accordance with the most recently published guidelines, therapy with rhPTH (1–84) is recommended in case of: oral calcium/vitamin D medications required to control the serum calcium or symptoms that exceed 2.5 g of calcium or >1.5 μg of active vitamin D or >3.0 μg of the 1-alpha vitamin D analog; hypercalciuria, renal stones, nephrocalcinosis, stone risk, or reduced creatinine clearance or eGFR (<60 ml/min); hyperphosphatemia and/or calcium–phosphate product that exceeds 55 mg^2 dL^2 (4.4 $mmol^2$ L^2); gastrointestinal tract disorder that is associated with malabsorption; and, finally, reduced quality of life [8].

This article reviews the pharmacological features, clinical efficacy, safety, and tolerability of this drug in patients affected by chronic hypoparathyroidism.

2. rhPTH (1–84) replacement therapy in hypoparathyroidism

2.1. Chemistry

Natpara® is a synthetic rhPTH (1–84), identical to the full-length human 84-amino acid protein. It is produced by recombinant DNA technology using a strain of *Escherichia coli*. This molecule of 84 amino acids is composed by an amino (N)-terminal structure (34 amino acids) and a carboxyl (C)-terminal structure (50 amino acids), with a molecular weight of 9425 Da [11].

2.2. Physiological role of PTH

Physiologically, the major function of PTH is to regulate circulating ionized calcium. The effects of PTH on the bone, kidneys, and intestine are necessary to maintain serum calcium within a tight range. PTH also has a reciprocal effect on phosphate metabolism [12,13], and acts in concert with fibroblast growth factor 23 (FGF23) and klotho. In the bone, PTH stimulates the expression of receptor activator of nuclear factor k-B ligand (RANKL) by osteoblasts, which induces osteoclastogenesis and osteoclastic bone resorption, and reduces the expression of osteoprotegerin (a RANKL decoy receptor), mobilizing calcium and phosphorus into the circulation [13]. In the kidneys, PTH favors conversion of 25-hydroxyvitamin D [25(OH)D] to $1,25(OH)_2D$, and promotes calcium reabsorption and phosphate excretion. $1,25(OH)_2D_3$, in turn, increases intestinal calcium and phosphate absorption [2,13].

2.3. Pharmacodynamics

rhPTH (1–84) increases serum calcium concentrations in a dose proportional manner [14]. Clarke et al. investigated a single subcutaneous injection of rhPTH (1–84) in patients affected by hypoparathyroidism, with a dose-escalating study of single subcutaneous administration of 50 µg and then 100 µg. Each patient received a single 50-µg rhPTH (1–84) dose, had at least a 7-day washout interval, and then received a single 100-µg rhPTH (1–84) dose. Compared with calcitriol, rhPTH (1–84) 50 µg reduced 24-h calcium excretion and calcium-to-creatinine ratios by 12% and 23%, respectively, and rhPTH (1–84) 100 µg reduced them by 26% and 27%. Compared with calcitriol, rhPTH (1–84) 50 µg increased urinary phosphate excretion and phosphate-to-creatinine ratios by 53% and 54%, respectively, and rhPTH (1–84) 100 µg increased them by 45% and 42% [14,15].

Sikjaer et al. performed a 24-h monitoring study, analyzing the effects of rhPTH (1–84) in 38 patients with hypoparathyroidism who had previously completed a 6-month randomized study on effects of treatment with a fixed rhPTH (1–84) dose of 100 µg/day or similar placebo as an add-on to conventional treatment. rhPTH (1–84) changed the diurnal rhythms of ionized calcium levels and $1,25(OH)_2D$ levels, with rising levels following injection. In 71% of the rhPTH (1–84) treated patients, asymptomatic hypercalcemia was seen. Compared with placebo, 24-h urinary calcium, phosphate, and magnesium did not change, although the diurnal variation in renal excretion rates changed significantly in response to treatment. In this study a 100-µg daily dose of rhPTH (1–84) appeared to be too high in some patients, suggesting a need for a device allowing for individual dose adjustments [9].

In contrast to the effect of rhPTH (1–84) treatment in patients with osteoporosis, in hypoparathyroidism it causes a decrease in bone mineral density (BMD) and a marked increased bone turnover, with a pathological state of overmineralized bone and, during long-term treatment, may determine a more physiologic bone metabolism [16]. A study showed effects of rhPTH (1–84) (100 mg/day subcutaneously) on bone microstructure, as assessed by micro-computed tomography (mCT), with iliac crest bone biopsies of patients with hypoparathyroidism after 24 weeks of treatment. Compared with placebo, PTH caused a 27% lower trabecular thickness ($p < 0.01$), a 4% lower trabecular bone tissue density ($p < 0.01$), and connectivity density was 34% higher ($p < 0.05$). The number of Haversian canals per area, at cortical bone, was 139% higher in the group treated with rhPTH (1–84), with an increased cortical porosity. Areal BMD (aBMD) and volumetric BMD (vBMD), at different subregions of the hip, decreased significantly by 1–4% in the patients treated with rhPTH (1–84), as assessed by dual-energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT). However, at the lumbar spine, aBMD decreased by 1.8% ($p < 0.05$), whereas vBMD increased by 12.8% in the group treated with PTH compared with the placebo group [17]. Moreover, Rubin et al. showed that rhPTH (1–84) stimulated the increase of the number and maturity of circulating osteogenic cells and histomorphometric indices of bone formation in patients affected by hypoparathyroidism, thus explaining, at least in part, the role of the PTH bone anabolic [18,19].

2.4. Pharmacokinetics

Peak plasma concentration (mean T_{max}) after single subcutaneous injections of rhPTH (1–84) at 50 and 100 µg in subjects affected by hypoparathyroidism occurs within 5–30 min, and a second usually smaller peak at 1–2 h [14,15]. PTH levels become undetectable by 12 or 24 h [15]. The plasma AUC increases in a dose-proportional manner from 50 to 100 µg, and the apparent terminal half-life ($t_{1/2}$) is 3.02 and 2.83 h for the 50 and 100 µg dose, respectively. One 100-µg dose of rhPTH (1–84) provides a 24-h calcemic response in hypoparathyroidism subjects [14].

rhPTH (1–84) administered subcutaneously has an absolute bioavailability of 53%, and a volume of distribution of 5.35 L at steady state. Physiologically, once secreted, PTH is rapidly cleared from plasma through uptake, principally by the liver and kidney, where PTH (1–84) is cleaved into amino- and carboxyl-terminal fragments that are then cleared by the kidney [20]. Currently, no dose adjustment for rhPTH (1–84) is required for patients with mild to moderate renal or hepatic impairment, and no studies were conducted in patients with severe renal impairment or in renal impairment patients on dialysis [14]. Pharmacokinetic analyses have shown that age, sex, race, and body weight did not significantly affect the pharmacokinetics of this drug [14].

The recommended starting dose is 50 µg and, based on calcemic response, can be titrated at 2–4-week intervals upward to doses of 75 µg and then 100 µg. It is intended to be self-administered once daily by subcutaneous injection into alternating thighs [11].

3. Clinical efficacy

3.1. Phase II study

In a Danish randomized controlled, double-blind study, rhPTH (1–84) or placebo was administrated in a fixed dose of 100 µg in 62 patients for 24 weeks. Compared with placebo, patients treated with rhPTH (1–84) reduced their daily dose of calcium and active vitamin D significantly, by 75% and 73%, respectively, without developing hypocalcemia. However, hypercalcemia occurred frequently during the down titration of calcium and active vitamin D. Plasma phosphate and renal calcium and phosphate excretion did not change. Furthermore, this treatment significantly increased plasma levels of bone turn-over markers, whereas BMD decreased at the hip, lumbar spine, and whole body, but not at the forearm [16].

3.2. Phase III studies

Further data from five studies, have been published on effects of replacement therapy with rhPTH (1–84) in hypoparathyroidism [21–25].

Rubin et al. investigated the use of the rhPTH (1–84) in a fixed dose of 100 µg every other day by subcutaneous injection in 30 subjects with hypoparathyroidism in an open-label study for 24 months, with monitoring of calcium and vitamin D supplementation requirements, serum, and 24 h urinary

calcium excretion, and BMD by DXA. Requirements for supplemental calcium decreased significantly by 45%, as did requirements for supplemental $1,25(OH_2)D_3$, by 41%. Serum calcium levels and 24 h urinary calcium excretion were mostly unchanged at 24 months. BMD increased at the lumbar spine by 2.9 ± 4% from baseline, while femoral neck BMD remained unchanged and distal one third radial BMD decreased by 2.4 ± 4% [21].

Similarly, Cusano et al. [22] studied the effect of 4 years of rhPTH (1–84) treatment in 27 adults with hypoparathyroidism. Replacement therapy reduced supplemental calcium requirements by 37% and active vitamin D by 45%. Seven subjects were able to stop $1,25(OH_2)D_3$ completely. Serum calcium levels remained stable, and urinary calcium and phosphorus excretion decreased. Lumbar spine BMD increased by 5.5 ± 9% at year 4. Femoral neck and total hip BMD remained stable. At year 4, distal radius BMD was not different from baseline. Bone turnover markers increased significantly, reaching a threefold peak from baseline values at 6–12 months, subsequently declining to steady-state levels at 30 months. This is the first study to report the extended use of any PTH therapy in a well-described cohort over 4 years. Subsequently, Cusano et al. demonstrated that rhPTH (1–84) therapy is not only associated with improvement in biochemical and skeletal indices, but also in mental and physical health as determined by the RAND 36-Item Short Form (SF-36) Health Survey [26,27].

In REPLACE, a double-blind, placebo-controlled, randomized phase 3 study [23], 134 patients with hypoparathyroidism were randomly assigned to 50 µg per day of rhPTH (1–84) or placebo for 24 weeks. Active vitamin D and calcium were progressively reduced, while rhPTH (1–84) could be titrated up from 50 to 75 µg and then 100 µg. Compliance with injection was excellent for both groups, with 80% or higher compliance in 88 (98%) of 90 patients in the rhPTH (1–84) group and 42 (96%) of 44 patients in the placebo group. The primary endpoint of the study 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 concentration and less than or equal to the upper limit of normal. This endpoint was achieved by 53% of patients in the rhPTH (1–84) group compared with 2% in the placebo group. In the rhPTH (1–84) group, the mean dose of oral calcium supplementation and active vitamin D decreased respectively by 52% and 78%, and, in the hip region, there was also a significant decline in BMD. In the rhPTH (1–84) group, albumin-corrected serum calcium concentrations increased at the start of treatment, despite large reductions in both oral calcium and active vitamin D doses, whereas urinary calcium excretion showed a slight decrease. In the placebo group, on the other hand, total serum calcium concentrations fell rapidly and remained close to the lower end of the target range for the duration of the study; mean urinary calcium excretion rate also decreased. Mean serum phosphate levels were similar (at the upper limit of normal) in both groups at baseline, but decreased in the group treated with rhPTH (1–84) and remained lower than in the placebo group. This is the first study to use a flexible dosing regimen of rhPTH (1–84) and a rigorous algorithm for titration of oral calcium and active vitamin D [23].

Subsequently, it has been conducted a 24-week, open-label, flexible-dose extension study of REPLACE, named REPEAT. Patients who previously completed or enrolled in REPLACE received rhPTH (1–84), 50 µg/day, escalated to 75 and then to 100 µg/day, if required. The primary endpoint was ≥50% reduction in oral calcium (or ≤500 mg/day) and active vitamin D (or calcitriol ≤0.25 µg/day or alfacalcidol ≤0.50 µg/day), maintaining normocalcemia. Twenty-four patients, of which 16 previously treated with rhPTH (1–84), and 8 rhPTH (1–84)-naïve, were enrolled and completed the study. At study end, 75% of patients achieved the study endpoint, and 58% eliminated oral calcium and active vitamin D. Urinary calcium, serum phosphate, and calcium–phosphate product decreased by the study end, and mean serum bone turnover markers increased with rhPTH (1–84, [24]).

Rubin et al. have recently published an important prospective open-label study of 33 subjects with hypoparathyroidism, treated with rhPTH (1–84) subcutaneous (starting dose of 100 µg every other day) for 6 years [25]. This study reports the longest clinical experience with PTH treatment available so far in the management of hypoparathyroidism. The use of a long-term, continuous therapy with rhPTH (1–84), in this population, has been associated with a significant reduction of supplemental calcium and calcitriol requirements, maintaining stable serum calcium levels, reducing urinary calcium excretion and with a good safety profile. Serum phosphate decreased significantly from baseline at years 4 and 5, but year-6 levels were similar to baseline values. Lumbar spine and total hip BMD increased, whereas femoral neck BMD remained stable and the distal one-third radius decreased. Bone turnover markers increased significantly, and subsequently declining but remaining higher than pretreatment values [25].

Table 1 shows the results of the studies shown so far.

4. Safety and tolerability

The REPLACE study tested, in addition to efficacy, also safety and tolerability of a once-daily flexible dose (50, 75, or 100 µg) regimen of rhPTH (1–84) in adults with hypoparathyroidism [23]. All 134 patients were included in the safety analyses, and the overall incidence of adverse events was similar in both groups, treated with rhPTH (1–84) and placebo group. Ten (11%) of the patients in the rhPTH (1–84) group and four (9%) in the placebo group had serious adverse events. In the rhPTH (1–84) group, only one serious adverse event, characterized by hypercalcemia, was regarded as treatment related. In both groups, no significant changes in cardiovascular variables (blood pressure, heart rate, or QTc interval), or renal variables, such as serum creatinine or estimated creatinine clearance, were described. During the treatment period, hypocalcaemia was reported as an adverse event in 23 (26%) patients in the rhPTH (1–84) group (43 events) compared with nine (21%) patients in the placebo group (nine events). The rhPTH (1–84) treatment was generally well tolerated. Data derived by the cohort study of subjects treated through 4 years have not raised any safety concerns [22], although

Table 1. Studies on effects of replacement therapy with rhPTH (1–84) in hypoparathyroidism.

Study	Participants	Trial	Outcomes		Trials	
Reference	Subjects Age (years)	Study design PTH peptides Dosage Duration	*Serum* calcium *Urinary* calcium BTM BMD	Results in treated rhPTH (1–84)	Strength	Limitation
Rubin et al. [21]	30 adult Age: 25–68 years	Open label Every other day PTH (1–84) s.c. (100 µg) 2 years	Calcium dose 1–25(OH)$_2$ D dose *S*-calcium *U*-calcium BTM BMD	↓ ↓ = = N/A ↑ Lumbar spine ↓1/3 distal radius = Femoral neck	Duration	No control arm, open label
Sikjaer et al. [16]	62 adult age: 25–80 years	Double-blind Randomized, Placebo-controlled Once per day PTH (1–84) s.c. (100 µg) vs. Calcium and 1–25(OH)$_2$ D 24 weeks	Calcium dose 1–25(OH)$_2$ D dose *S*-calcium *U*-calcium BTM BMD	↓ ↓ = = ↑ ↓ Lumbar spine, hip, femoral neck	Large number, double blind	Duration
Cusano et al. [22]	27 adult age: 25–68 years	Open label Every other day PTH (1–84) s.c. (starting dose 100 µg) 4 years	Calcium dose 1–25(OH)$_2$ D dose *S*-calcium *U*-calcium BTM BMD	↓ ↓ = ↓ ↑ ↑ Lumbar spine = Hip, femoral neck, distal radius	Duration	No control arm, open label
Mannstad et al. [23]	134 adult age: 18–85 years	Double-blind Randomized Placebo-controlled Once per day PTH (1–84) s.c. (starting dose 50 µg) vs. calcium and 1–25(OH)$_2$ D 24 weeks	Calcium dose 1–25(OH)$_2$ D dose *S*-calcium *U*-calcium BTM BMD	↓ ↓ = = N/A N/A	Flexible dosing and titration algorithm, large number, double blind	Short term Defined-dose schedule
Lakatos et al. [24]	24 adult Age: 18–85 years	Open-label, flexible-dose extension study of REPLACE once per day PTH (1–84) s.c. (starting dose 50 µg) 24-weeks	Calcium dose 1–25(OH)2 D dose *S*-calcium *U*-calcium BTM	↓ ↓ = ↓ ↑	Flexible dosing and titration	No control arm, open label
Rubin et al. [25]	33 adult age: 45–49 years	Prospective open-label study, every other day PTH (1–84) s.c. (starting dose 100 µg,) 6 years	Calcium dose 1–25(OH)$_2$ D dose *S*-calcium *U*-calcium BTM BMD	↓ ↓ = ↓ ↑ ↑ Lumbar spine, total hip = Femoral neck ↓ Third radius	Duration	No control arm, open label

BTM: bone turn-over markers; BMD: bone mineral density; *S*: serum; *U*: urinary; ↑: increase; ↓: decrease; N/A: not available.

further long-term data are necessary. With regard to hypercalcemia, it may occur early in the treatment course and is easily remedied by reducing supplemental calcium and active vitamin D [23]. Subsequently, the extension study REPEAT did not show serious adverse events [24].

The longest experience with the therapeutic use of PTH [25] for 6 years has demonstrated, although in a small sample, safety regarding the control of calcium homeostasis (12 hypercalcemic events in 9 subjects; 2.5% of all values), without hypercalcemic events requiring hospitalization. Moreover, many adverse events (i.e. nausea, headache, musculoskeletal, fatigue, dizziness, neurologic, mental and mood, paresthesia, and increased urination) seemed to diminish after the first year of therapy. The most common serious adverse event was hypocalcemia (five times in three patients), and other adverse events included eight fractures in six patients [25]. Therefore, the hypercalcemic and hypocalcemic events described have been very uncommon.

In a study, osteosarcoma has occurred in rats treated with PTH, given subcutaneously at doses of 10, 50, and 150 µg/kg/day [14,27,28]. These doses were respectively 3–71 times higher than systemic exposure described in humans following a subcutaneous dose of 100 µg/day based on AUC. In addition to dose, bone metabolism in the rat differs from that in humans, and the different physiology may account for the increased incidence of osteosarcoma in rats [29]. Therefore,

the relevance of these animal findings to humans is uncertain. Moreover, with over 10 years of clinical post-approval experience with PTH (1–34) and 7 years with rhPTH (1–84) for treatment of osteoporosis, no adverse signals of osteosarcoma have been observed [29,30]. Results from clinical trials with cumulative numbers of 16,000 subjects treated with up to 3 years of continuous therapy have not reported any skeletal malignancies [31–33]. The 'black box' warning for rhPTH (1–84) thus reiterates this cautionary note although rhPTH (1–84) has no therapeutic time limit for treatment.

No effect on fertility was described in male and female rats given PTH at doses up to 1000 µg/kg/day (120 times systemic exposure after a clinical dose of 100 µg/day).

However, no adequate studies in women exist for the use of rhPTH (1-84) during pregnancy and lactation. A peri-/post-natal study in pregnant rats treated with the drug (100, 300, 1000 µg/kg/day, subcutaneous) observed developmental effects from organogenesis through lactation, while entire stillborn litters were described in the 300 µg/kg/day group (34 times the 100 µg/day clinical dose based on AUC) [17]. In pups from litters in the 100 µg/kg/day group (10 times the 100 µg/day clinical dose based on AUC) was observed an increased incidence of morbidity associated with dehydration, broken palate and palate injuries related to incisor misalignment and mortality [17]. Since animal studies are not always predictive of human response, and actually the effects of rhPTH (1-84) during pregnancy and breastfeeding are unknown, the drug should be not used during pregnancy or lactation.

At last, safety and efficacy in patients less than 18 years of age has not been established, and the use of rhPTH (1–84) is to be avoided in case of pediatric and young adult patients with open epiphyses, considering the increased baseline risk for osteosarcoma [14].

5. Conclusions

Conventional therapy of hypoparathyroidism cannot resolve all problematic aspects of this disease, such as, in some cases a not adequate control of serum and urinary calcium homeostasis, an abnormal bone remodeling (low abnormal bone turnover, with impairment of bone quality), a poor compliance to therapy, and a consequent reduced quality of life. Moreover, large doses of calcium and active vitamin D supplements are associated to long-term risks of nephrolithiasis, nephrocalcinosis, renal impairment, cataracts, and cerebral calcifications.

The recent FDA approval of rhPTH (1–84) is a fundamental step in the treatment of hypoparathyroidism, for patients not well controlled with standard treatment. This drug provides the natural hormone, which is lacking in this disease and permits major reductions in the need for calcium and active vitamin D supplements, maintaining normal calcium levels. In the studies conducted so far on rhPTH (1–84) for hypoparathyroidism, it indeed, has shown an improved calcium homeostasis, a reduction of 24-h calcium excretion, and an improvement in quality of life. Moreover, therapy with rhPTH (1–84) tends to reverse the state of low bone turnover with a marked increased bone turnover and restoration of normal bone physiology. Finally, the drug has a potential preventive role for other complications such as nephrolithiasis, nephrocalcinosis, cataracts, and cerebral calcifications, given, of course, the drug effect on calcium–phosphorus homeostasis.

Nevertheless, in the future further studies will have to be performed to evaluate long-term efficacy and safety of the drug, given the chronic nature of the disease.

6. Expert opinion

The key findings in the research done in this field, so far, are the evident demonstration of a good control of calcium homeostasis by rhPTH (1–84), an important reduction of calcium and active vitamin D requirements, and a reversal of the state of low bone turnover typical of hypothyroidism.

On the other side, the weaknesses in the research done so far are the duration of the studies carried out until now, given the chronic nature of the disease and the need for PTH therapy over years, the numerousness of samples, the lack of the clarification of the effect on the control of serum phosphorus levels, the limitation of the outcomes assessed such as long-term complications, including extra-skeletal calcifications, nephrolithiasis and nephrocalcinosis, bone strength, and fracture risk.

Furthermore, long-term effects regarding quality of life and neurocognitive function require further studies. Impairment of well-being probably results directly from PTH deficiency without the involvement of changes in calcium homeostasis. It is known that PTH, specifically, binds to the PTH2 receptor, expressed in several brain regions, however, another brain-specific ligand to the PTH2 receptor, a hypothalamic neuropeptide (tuberoinfundibular peptide of 39 residues), has been described [34,35]. Moreover, the expression of 25-hydroxyvitamin D-1 alpha-hydroxylase has recently been demonstrated in brain tissue [36]. Therefore, its role in the central nervous system remains to be determined.

With regard to the effect of drug on BMD, the longest experience of continuous therapy for 6 years with rh PTH (1–84) has showed that BMD at lumbar spine and total hip, above average at baseline, increased throughout the study period, whereas BMD at the femoral neck was unchanged. BMD at the distal one third radius site progressively decreased [25]. As cited by the authors, these densitometric results are explainable considering the differential effects of PTH at these different sites (predominantly cortical or trabecular). Furthermore, histomorphometric analysis of bone biopsies after 2 years showed that trabeculae were thinner and more numerous, and showed an increase of cortical porosity [25]. It is possible that the salutary effects on microarchitecture and bone size could provide biochemical advantages at cortical bone despite a decrease in BMD, but further long-term investigations should be performed on microstructural features of bone tissue in patients treated with rhPTH (1–84). Moreover, it should be clarified whether the fracture events, described in this study, were associated to natural history of hypoparathyroidism, rather than due to rhPTH (1–84) treatment.

Data based on available studies up to now show a good safety profile of PTH in replacement therapy, but the FDA has approved rhPTH (1–84) with a 'black box' warning because of the history of rat osteosarcoma using all forms of PTH that have been studied so far, without limit of the duration of use.

In particular, the use of rhPTH (1-84) should be avoided in patients who have risk factors for osteosarcoma unless the benefits of using rhPTH (1-84) in these patients are determined to outweigh this potential risk. In future years, considering this potential long-term risk of osteosarcoma for humans, additional safety data should be collected.

rhPTH (1–84) has the advantage, due to its pharmacokinetics, that it can be administered just once a day. However, the ultimate goal of future research in this filed is to identify the optimal treatment regime, that actually require further clarifications. In particular, further investigations are necessary regarding ideal dosages and administration regimens for PTH, such as other delivery systems that do not require subcutaneous injection, or more physiologic delivery systems, such as continuous delivery by pump.

At last, in the coming years, thanks to the recent FDA approval of rhPTH (1–84), it will be possible to perform studies on larger patient samples, divided by type of hypoparathyroidism, severity, duration of disease, with a longer duration than what has been done so far, allowing to clarify all the above mentioned clinical outcomes and profile of safety of long-term medication.

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Declaration of interest

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