Recombinant parathyroid hormone for hypoparathyroidism in children: a narrative review
Rekombinowany parathormon w leczeniu niedoczynności przytarczyc u dzieci. Praca poglądowa

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The conventional management of hypoparathyroidism in children involves the use of calcium and vitamin D analogs. This therapy effectively increases the serum calcium levels but worsens hypercalciuria and its consequences such as nephrocalcinosis and renal insufficiency. Although replacement with the missing parathyroid hormone (PTH) is ideal and available for more than 2 decades, the reported concerns of osteosarcoma prohibited its use in children with open epiphyses. Nevertheless, the data accumulated over the past several years suggests that the fears of bone malignancies were probably overstated. With an aim to review the available data on recombinant PTH (rhPTH) use, we performed a literature search using international databases and identified 15 studies involving approximately 70 children with hypoparathyroidism due to various etiologies who received rhPTH1-34 for durations between 1 day and 13.5 years. All the studies appear to indicate that rhPTH1-34 therapy is an effective short and long-term strategy for treatment of hypoparathyroidism with better metabolic control, lesser effects on renal function and improved quality of life as compared to conventional therapy. A more significant conclusion is the safety of long-term use of rhPTH1-34 with no observed adverse skeletal effects so far. However, all studies mention the importance of a continued surveillance for adverse effects in the treated patients. This narrative review discusses the experience of rhPTH1-34 use exclusively in children.

Key words:
recombinant parathyroid hormone, rhPTH1-34, hypoparathyroidism, conventional therapy, children.
Introduction

Pediatric hypoparathyroidism (HPT) is an uncommon disorder of calcium and phosphate metabolism caused by defects in the synthesis or secretion of parathyroid hormone (PTH), end-organ resistance, or inappropriate regulations of PTH by calcium-sensing receptor (CaSR). These defects can be inherited or acquired. The common causes of HPT in children include the impaired or non-development of the parathyroid glands due to genetic or chromosomal alterations, abnormal signalling of the CaSR and autoimmune processes involving parathyroid glands [1]. The biochemical hallmarks of HPT are hypocalcemia and hyperphosphatemia. Unlike adults, HPT in children is often symptomatic because of high skeletal requirements of calcium and is frequently diagnosed due to clinical symptoms of hypocalcemia such as muscle spasms, laryngospasm, seizures, stridor and tetany. Non-specific manifestations include cognitive and or motor delay, slowness, dystonia, and uncial, dental and skin anomalies [1, 2]. Children with HPT suffer from several complications related to the disease itself or its treatment that include extracellular calcifications in the basal ganglia, posterior subcapsular cataracts, renal dysfunction, nephrocalcinosis, nephrolithiasis, and low bone turnover and increased bone density [1]. The mainstay of long-term management is calcium supplements and vitamin D analogs. The conventional therapy is aimed at amelioration of clinical symptoms, keeping the serum calcium concentrations at low-normal range, and avoiding hyperphosphatemia and hypercalcemia [3]. This management is often challenging and requires additional therapies such as thiazide diuretics, phosphate binders etc in order to prevent the long-term complications [1, 3]. Even with optimum conventional treatment, children often develop renal impairment and other complications [3]. The availability and the recent evidence of efficacy of recombinant PTH (rhPTH) offers hope for effective treatment of HPT in children [1, 3]. The US Endocrine Society guidelines recommend considering the use of rhPTH in the subset of adults patients of HPT who show inadequate control of serum calcium concentrations, require high doses of oral calcium and vitamin D, develop hypercalcemia, renal stones, nephrocalcinosis, reduced creatinine clearance or eGFR, hyperphosphatemia or high calcium-phosphate product, have evidence of malabsorption or reduced quality of life [1, 3]. No such guidelines exist for the use of rhPTH in children.

Pathophysiology of pediatric hypoparathyroidism

The production and secretion of mature PTH, an 84-amino acid protein, are regulated by a G protein-coupled CaSR, tightly regulated by the intracellular concentrations of calcium which mirror the serum concentrations. The net effects of PTH action are an increase in the serum calcium and a decrease in serum phosphate concentrations [4]. These effects are mainly achieved by stimulation of bone resorption to release calcium and phosphate and by decreasing calcium clearance and phosphate reabsorption by the kidneys. It also stimulates calcium and phosphate absorption by the gut by stimulating renal 1-alpha-hydroxylase activity and increasing the serum concentrations of 1,25-dihydroxy vitamin D [4]. The increase in serum phosphate concentrations as a result of enhanced bone resorption and gut absorption are neutralized by the phosphaturic effect of PTH. The deficiency of PTH results in the loss of direct effects of PTH on bone and the kidney, and indirect effects on the gut. The net result is hypocalcemia due to impaired calcium release from bone and restricted absorption from the gut. Hyperphosphatemia develops due to impaired urinary phosphate reabsorption. Calcium occurs despite hypocalcemia due to impaired renal calcium reabsorption. Biochemically, the albumin-corrected serum calcium and 1,25-dihydroxy vitamin D are low and serum phosphorus concentrations are elevated. The intact PTH is typically low but may be inappropriately normal for the degree of hypocalcemia [4]. Urinary calcium may initially be normal, high or low depending on calcium intake and bone turnover and often increases after initiation of calcium supplementation. The morbidity and mortality in HPT is related to the direct consequences of hypocalcemia as well as the abnormal calcium-phosphate product [5].

Conventional therapy

The standard treatment of HPT is aimed at controlling hypocalcemia. Severe manifestations such as seizures, laryngospasm and altered sensorium often require calcium infusions [3]. The long-term management consists of using large doses of oral calcium along with vitamin D analogs [3]. The doses of calcium and calcitriol need frequent adjustments with an aim to achieve freedom from symptoms, low normal serum calcium concentrations and avoidance of hypercalcemia. In addition, hyperphosphatemia needs to be controlled by using phosphate binders, Sevelamer and a diet low in phosphate content [1]. Thiazide diuretics are often used as adjuvant therapy to reduce hypercalcemia [3].

Concerns with conventional therapy

Poor metabolic control

Despite large doses of oral calcium, the control of hypocalcemia poor in many patients with HPT related probably to wide swings in supplementation requirements over time [5]. During conventional therapy, the patients remain at risk of hypocalcaemia with undertreatment and hypercalcaemia, hypercalciuria, hyperphosphatemia and associated complications with overtreatment [6]. Patients often develop severe symptoms while on standard therapy and require acute management with attendant risks of intravenous calcium administration and hospitalization.

Need for additional therapies

Additional therapies such as phosphate binding agents and thiazide diuretics are often necessary for optimum metabolic control as well as to prevent long-term complications.
Hypercalciuria and nephrocalcinosis

Absence of PTH in the renal tubules results in hypercalciuria which increases after the start of calcium supplementation. Over-treatment with conventional drugs augments hypercalciuria and nephrolithiasis. Thiazide diuretics are often inadequate to counteract the effects of hypercalciuria and nephrolithiasis. Mitchell et al. found 2- to 17-fold higher rates of chronic kidney disease Stage 3 or higher in patients with HPT as compared to normal individuals followed for 7 years [7]. Additionally, the urinary calcium excretion and hypercalciuria was seen in 50% and 25% of these patients [7]. In another study, nephrocalcinosis was detected in 31% and renal impairment in 2–17% of patients [8]. In children with HPT on standard therapy for a median duration of 7.4 years, nephrocalcinosis was observed in 38% and reduced eGFR in 45% [9].

Renal impairment

Standard therapy of HPT is unable to halt the progression of renal disease secondary to the combined effects of hypercalciuria and calcium phosphate product on kidneys. A majority of patients with HPT develop renal failure after prolonged conventional treatment and require repeated dialysis or renal transplantation [6]. Mitchell et al. found 2- to 17-fold higher rates of chronic kidney disease Stage 3 or higher in patients with HPT as compared to normal individuals followed for 7 years [7]. Additionally, the urinary calcium excretion and hypercalciuria was seen in 50% and 25% of these patients [7]. In another study, nephrocalcinosis was detected in 31% and renal impairment in 2–17% of patients [8]. In children with HPT on standard therapy for a median duration of 7.4 years, nephrocalcinosis was observed in 38% and reduced eGFR in 45% [9].

Ectopic calcifications

Standard treatment is insufficient to prevent the elevation of calcium phosphorus product which increases the risk of posterior subcapsular cataracts as well as soft tissue and brain calcifications [1]. The consequences of basal ganglia and intracerebral calcifications such as extrapyramidal movement disorders and psychosis have been reported in some studies [1, 2]. Additionally, elevations of calcium phosphorus product are associated with increased risks of cardiac arrhythmias and cardiovascular diseases in adults [1, 7].

Bone metabolism

The physiological aspects of HPT such as metabolic bone abnormalities remain unaddressed during conventional therapy. Patients with HPT typically have several abnormalities of bone remodelling such as greater cancellous bone volume, trabecular width, cortical width, bone mineral density and connectiv-ity density as compared to controls, and suppressed dynamic skeletal indices such as mineralizing surface and bone formation [10, 11]. Bone mineral density (BMD) is high due to low bone turnover [1]. Although the risk of fractures despite higher BMD is uncertain, a recent study indicated an increased risk of upper extremity fractures [12].

Quality of life

The lack of PTH is presumed to directly influence the patients’ quality of life. Most patients with HPT experience bone pain during conventional therapy [1]. In addition, they report physical, mental, and emotional symptoms, and a reduced quality of life in comparison to norm-based populations or matched controls [13].

Studies on rhPTH use in pediatric HPT

The use of rhPTH for management of HPT offers several advantages over conventional therapy. These include a lesser need for calcium and vitamin D supplements with a consequent decrease in urinary calcium excretion and ectopic soft tissue calcification, and improvement in bone remodeling dynamics and quality of life. There are two rhPTH molecules available for human use; the less studied full-length rhPTH1-84 and the intensively researched rhPTH1-34 analogue, Teriparatide which contains the first 34 amino-terminal amino acids of the natural PTH molecule that are important for binding to receptor and exert its actions. Although PTH1-34 was sequenced in 1972, the research on its role as replacement therapy of HPT was not pursued for the next 2 decades. Despite the availability of several short and long-term studies of the efficacy of rhPTH1-34 conducted in adults and children, its use is uncommon in clinical practice. In fact, HPT remains the only classic endocrine deficiency disease for which the missing hormone is not routinely used. Several excellent recent reviews have summarized the studies on the efficacy and safety of rhPTH1-34 with the primary focus on its use in chronic HPT in adults [14, 15]. In this narrative review, we will discuss the available research studies and the reported experience of rhPTH1-34 use in children with HPT.

The first effective use of PTH in children dates back to 1929 when Albright et al. administered parathyroid extract in a 14-year-old boy with idiopathic HPT who had severe life-crippling symptoms of hypocalcemia [16]. A 3-day initial course of PTH provided complete relief from symptoms and increased serum calcium and decreased serum phosphate. For recurrence of symptoms, he received PTH four times during a 27-day hospitalisation. The experiment provided the first proof of the normalisation of metabolic abnormalities of HPT with the administration of the missing hormone [16].

Table I depicts the salient features of the reported experience with the use of rhPTH1-34. Shichira et al. treated a 9-year-old boy having severe HPT due to activating mutation of CaSR with rhPTH1-34 for 3 days and demonstrated a rise in serum calcium concentrations and a fall in urine calcium creatinine ratio [17]. They concluded that this therapy was effective in correcting serum and urine calcium and phosphate levels [17]. A 17-month use of rhPTH1-34 by Mittelman et al. in a 3-wk-old infant with CaSR mutation helped preventing further serious hypocalcemic episodes and markedly decreased urinary calcium excretion [18]. A year later, a single dose of rhPTH1-34 in a neonate with severe hypocalcemia due to HPT was reported to be a safer alternative to commonly used methods to raise serum calcium levels [19].

Winer et al. compared the response of once-daily versus twice-daily rhPTH1-34 in 14 children with chronic HPT in a 28 week randomized cross over trial [20]. The mean 24-hour urine calcium excretion normalized on both treatment schedules. The metabolic control was achieved with half the rhPTH1-34 dose during the twice-daily regimen compared with the once-daily regimen (25 ±15 µg/d vs. 58 ±28 µg/d; p < 0.001). The authors concluded that the twice-daily rhPTH1-34 regimen was
Table I. Reported experience with the recombinant parathyroid hormone (rhPTH1–34) use in children

<table>
<thead>
<tr>
<th>S.no</th>
<th>Authors, country, year</th>
<th>Patients’ characteristics</th>
<th>Dose, route and dosing frequency</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Shiohara et al. [17] Japan, 2006</td>
<td>9-year-old boy with CaSR mutation</td>
<td>0.9 μg/kg/d, s.c., twice daily</td>
<td>3 days</td>
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<td>2.</td>
<td>Mittelman et al. [18] USA, 2006</td>
<td>3-week-old boy with CaSR mutation</td>
<td>5 μg, s.c., twice daily</td>
<td>17 months</td>
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<tr>
<td>3.</td>
<td>Newfield [19] USA, 2007</td>
<td>17-day-old neonate with idiopathic HPT</td>
<td>5 μg</td>
<td>Single dose</td>
</tr>
<tr>
<td>4.</td>
<td>Winer et al. [20] USA, 2008a</td>
<td>14 children (10 boys, 4 girls) aged 4–17 years: 1 had CaSR mutation, 1 post-surgical, 5 APS-1 and 7 idiopathic HPT</td>
<td>25 ±15 μg/d, s.c., twice daily</td>
<td>28 weeks (cross-over trial)</td>
</tr>
<tr>
<td>5.</td>
<td>Sanda et al. [21] USA, 2008</td>
<td>2 year 8 month-old-girl with CaSR mutation</td>
<td>7.5 μg/d s.c. daily</td>
<td>20 months</td>
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<td>6.</td>
<td>Theman et al. [22] USA, 2009</td>
<td>1 girl aged 6.2 year with CaSR mutation</td>
<td>0.4–1.7 μg/kg/d, s.c., twice daily</td>
<td>13.5 years</td>
</tr>
<tr>
<td>7.</td>
<td>Winer et al. [23] USA, 2010b</td>
<td>12 children (9 boys, 3 girls) aged 7–14 year: 1 with CaSR mutation, 2 APS and 4 idiopathic HPT</td>
<td>0.6 ±0.5 μg/kg/d, s.c., twice daily</td>
<td>3 years</td>
</tr>
<tr>
<td>8.</td>
<td>Linglart et al. [24] France, 2011</td>
<td>3 boys aged 8–13 years: 2 having APS, 1 idiopathic HPT</td>
<td>5–15 μg/d, continuous s.c. infusion</td>
<td>3 years</td>
</tr>
<tr>
<td>9.</td>
<td>Cho et al. [25] Australia, 2012</td>
<td>2-week-old neonate with HRD syndrome</td>
<td>1 μg/kg/d s.c. twice daily</td>
<td>12 days</td>
</tr>
<tr>
<td>10.</td>
<td>Winer et al. [26] USA, 2014c</td>
<td>12 children aged 7–20 years: 5 with APS and 7 CaSR mutation</td>
<td>0.32 ±0.04 μg/kg/d Pump delivery</td>
<td>26 weeks (cross-over trial)</td>
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<td>11.</td>
<td>Matarazzo et al. [27] Italy, 2014</td>
<td>6 children (4 boys, 2 girls), mean age 9.8 ±5.1 year. 3 had APS, 2 DiGeorge and 1 HDR syndrome</td>
<td>12.5 μg twice daily</td>
<td>2.5 year</td>
</tr>
<tr>
<td>12.</td>
<td>Fox et al. [28] UK, 2016</td>
<td>4-year-old boy with CaSR mutation</td>
<td>2–6 μg twice daily</td>
<td>9 months</td>
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<td>13.</td>
<td>Mishra [29] India, 2016</td>
<td>2 girls, 10 and 12 year-old, 1 having APS and 1 post thyroid surgery HBS</td>
<td>20 μg once and twice daily respectively</td>
<td>3 and 7 days respectively</td>
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<td>14.</td>
<td>Saraff et al. [30] UK, 2018</td>
<td>4 children, aged 8–13 years, 3 having APS and 1 idiopathic HPT</td>
<td>continuous s.c. infusion</td>
<td>3–8 years</td>
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<tr>
<td>15.</td>
<td>Winer et al. [31] USA, 2018</td>
<td>14 children aged 7–16 years, 9 had CaSR mutation and 5 APS</td>
<td>0.75 ±0.15 μg/kg/day, s.c., twice or thrice daily</td>
<td>1.5–10 years</td>
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HPT – hypoparathyroidism; APS – autoimmune polyglandular syndrome type-1; HDR – hypoparathyroidism-deafness-renal dysplasia syndrome; HBS – hungry bone syndrome; CaSR – calcium sensing receptor; s.c. – subcutaneous

*Some patients were common in these studies.*
more efficacious compared with once-daily treatment because it reduced the variation in serum calcium levels and accomplished this at a lower total daily rhPTH1-34 dose. They recommended that rhPTH1-34 should be used as a twice-daily regimen, and not as once-daily regimen, for an improved metabolic control [20]. Sanda et al. reported a 2 year 8 month old girl having autosomal dominant HPT due to CaSR mutation who manifested with severe hypocalcemia and hypomagnesemia [21]. Although hypomagnesemia required adjunctive therapy with subcutaneous magnesium, the use of rhPTH1-34 not only helped to correct the hypocalcemia but also increased serum magnesium by increasing its gastrointestinal absorption and bone resorption [21].

In a long-term observation spanning over 13.5 years, The-eman et al. showed an improved metabolic control in a girl with HPT caused by activating mutation of CaSR gene with replacement rhPTH1-34 therapy [22]. There were no recurrences of hypocalcemia, and hyperphosphatemia and urinary calcium excretion improved. Although nephrocalcinosis persisted, the renal function showed improvement. Significantly, bone densitometry and histomorphometric studies did not show changes other than those expected in osteoporotic patients on PTH therapy. Her data including the bone biopsies were compared with one age-, sex-, and length of HPT-matched control not on PTH and two sex-matched autosomal dominant HPT controls before and after 1 year of PTH. The authors concluded that long-term rhPTH1-34 replacement in the treatment of chronic HPT was efficacious and safe [22].

In a landmark trial, Winer et al. assessed the efficacy and safety of long-term rhPTH1-34 versus conventional therapy in 12 children with HPT [23]. The serum and urinary calcium and phosphorus levels as well as the bone densitometry parameters remained comparable between the 2 groups at various time points during the study. Although bone turnover markers were at the upper limit of normal or elevated in the PTH-treated patients, the difference in these parameters was not associated with a difference in bone mineral accrual or linear growth, which appeared to proceed normally in both the groups [23]. No PTH related adverse events were noted during the study period. The authors thus concluded that rhPTH1-34 therapy was safe and effective in maintaining stable calcium homeostasis in children with HPT and allowed normal skeletal development over the 3-year observation period.

In another long-term study, Linglart et al. reported the results of continuous rhPTH1-34 infusion in three boys, two of whom were resistant to conventional therapy [24]. The pump therapy not only allowed near normalization of serum and urine calcium but also corrected the severe manifestations of hypocalcemia that disrupted these children’s lives daily. The bone densitometry and growth parameters remained normal throughout the 3 year study period and the therapy was considered generally safe [24].

The use of rhPTH1-34 in the neonatal age was also described by Cho et al. [25]. The patient was refractory to usual therapy with calcium, cholecalciferol, calcitriol and magnesium and the addition of rhPTH1-34 promptly corrected the metabolic abnormalities of HPT.

The PTH pump therapy was also compared to the twice daily subcutaneous injections by Winer et al. [26]. The authors reported that rhPTH1-34 delivered via pump achieved near normalization of mean serum calcium and mean urine calcium excretion, and significantly reduced markers of bone turnover. The serum and urine calcium concentrations showed a biphasic pattern during twice-daily injection as compared to minimal fluctuation during pump delivery. Significantly, the rhPTH1-34 dose requirement was less during pump delivery (0.32 ±0.04 vs. 0.85 ±0.11 μg/kg/d, p < 0.001). The pump therapy was considered to provide more physiologic calcium homeostasis and bone turnover in children with congenital HPT [26].

Six children with syndromic HPT were treated with rhPTH1-34 by Matarazzo et al. [27]. The PTH therapy allowed complete calcium and vitamin D withdrawal in two patients, calcium withdrawal in three and reduction of vitamin D dose in two. Although the mean blood calcium, phosphorus, and alkaline phosphatase were not significantly modified, a significant reduction of urine calcium creatinine ratio (0.55 ±0.31 vs. 0.1 ±0.1, p = 0.02) was achieved. The control of symptoms was better during rhPTH1-34 therapy. No significant adverse events were reported. The authors concluded that substitutive treatment with rhPTH1-34 maintains adequate blood calcium levels and allows prompt normalization of urinary calcium excretion [27].

Fox et al. effectively used rhPTH1-34 therapy in a young boy with HPT who had continued to have tetanic episodes on conventional therapy [28]. The PTH therapy improved the metabolic control, relieved his symptoms and allowed reductions in the doses of calcium and alfalcacidol supplements. No PTH related adverse effects such as hypercalcemia were observed during the 9-month period [28].

A short term use of rhPTH1-34 by Mishra et al. in 2 patients was shown to promptly improve severe hypocalcemia which had failed to respond adequately to conventional treatment [29]. The authors concluded that rhPTH1-34 therapy can accelerate normalization of serum calcium and phosphate, reduce the need for calcium infusions, and shorten the period of hospitalization in the acute care settings [29].

Saraff V et al studied the role of continuous subcutaneous rhPTH1-34 infusion in 4 patients with HPT who were resistant to conventional therapy of hypocalcemia due to associated malabsorption [30]. Serum calcium normalized, phosphate decreased and alfalcacidol could be weaned off in all patients. Only one patient remained on a reduced dose of oral calcium supplements. The initially elevated urinary calcium creatinine ratio normalized during the first year of treatment. More importantly, no significant side effects were noticed in the short or long term of upto 8 years with patient-reported preference of pump therapy over conventional treatment [30]. The remarkable work on the use of rhPTH1-34 in children carried out by Winer et al. has been reported recently [31]. Their study included 14 children with HPT who were given rhPTH1-34 for a mean duration of 6.9 ±3.1 years. The mean height velocity and bone accretion velocities remained normal throughout the study.
Serum alkaline phosphatase levels also remained normal and correlated with the rhPTH1-34. The metabolic control was good with mean serum and 24-hour urine calcium levels remaining within the normal ranges. Although nephrocalcinosis was seen to progress in five of 12 patients, their renal function remained normal. An important conclusion of this study was the safety of the rhPTH1-34 use over a long observation period [31].

**rhPTH1-34 versus rhPTH1-84**

Although treatment with the native missing hormone, rhPTH1-84 has been approved for adults with chronic HPT, there are no head-to-head comparison studies with rhPTH1-34 [3]. There is a single report by Stögmann et al. on the use of rhPTH1-84 in children [32]. They treated a boy aged 14 years with autoimmune HPT and a girl aged 17½ years having idiopathic HPT with rhPTH1-84. A daily administration of rhPTH1-84 resulted in hypercalcemia in the first patient. Subsequently an alternate day dosing of rhPTH1-84 was found to be effective in maintaining serum calcium levels in both patients without any side-effects [32].

**Safety concerns**

**General side effects**

These include hypo and hypercalcemia, muscle spasms, fatigue, nausea, headache, paraesthesias, hypesthesia, arthralgias, dizziness, mental and mood alterations, increased urination, hypercalciuria, and hypertension [33]. These adverse effects are uncommon, usually transient and tend to decrease during treatment.

**Risk of osteosarcoma and black box warning**

The use of rhPTH carries a theoretical risk of bone tumours particularly osteosarcoma. Based on the risk estimated from animal studies, the Food and Drug Administration (FDA) had issued a black box warning that prohibits the use of rhPTH when epiphyses are still open. However, the osteosarcoma risk has been a matter of intense debate as it remains unconfirmed in human studies. In the first animal study, 50% of the Fisher rats who received the highest doses of 75 μg/kg developed osteosarcoma [34]. Another study which used even higher PTH doses of up to 150 μg/kg/day reported a similar risk of osteosarcoma [35]. Interestingly, these doses were 3–71 times higher than the systemic exposure described in humans following a subcutaneous dose of 100 μg/day based on AUC [33, 35]. Subsequently, a non-carcinogenic dose of 10 μg/kg/day and a “no-effect” dose of 5 μg/kg/day for neoplasm formation were defined [33–36].

The doses used in humans for clinically relevant effects are far below the defined non-carcinogenic doses in animal studies. The FDA’s warning itself has come under criticism. Elrayyah et al. scrutinized the evidence that led to the warning and concluded that the warning was based on very low-quality evidence derived primarily from animal studies [37]. Subbiah et al., highlighted the divergent risks of PTH-induced osteosarcoma in humans and mice while reporting the second patient of osteosarcoma out of more than 430,000 users who were under a postmarketing surveillance program [38]. The Osteosarcoma Surveillance Study did not find a single patient who had a prior history of PTH treatment amongst 1448 osteosarcoma cases diagnosed between 2003 and 2009 [39]. The Forteo Patient Registry which has linked 63,270 rhPTH treated patients to 42 US cancer registries since 2009 reported no cases of rhPTH induced osteosarcoma amongst 5268 osteosarcoma cases diagnosed in the registries [40]. Furthermore, the relevance of results of animal studies to human skeletal physiology is uncertain. The bone metabolism in the rats differs significantly from that in humans and is characterised by bone growth that keeps occurring throughout their life span which may account for the increased incidence of osteosarcoma in rats [32]. No adverse signals of osteosarcoma have been reported even after 10 years of clinical experience in patients with osteoporosis who received rhPTH for at least 3 years [39]. Reassuringly, the long-term rhPTH treatment studies in children have not reported the occurrence of bone tumours [31].

**Summary, conclusions and future directions**

Despite the limitations of the studies included in the current review as mainly observational, small number of patients studied and short duration of follow up, an important inference that the use of rhPTH1-34 in children with HPT has not been observed to be associated with significant side-effects especially bone malignancies, can be drawn. Treatment with rhPTH thus presents an attractive option to children with chronic HPT who either have failure of conventional therapy or are prone for disease or treatment related complications. Although rhPTH1-84 is more physiological replacement than rhPTH1-34 due to a longer effective half-life, the experience in children is limited. Despite the reassuring data emerging from the long-term use of rhPTH1-34 in children, a continuous surveillance for bone neoplasms is mandatory in treated patient cohorts. In particular, additional long-term studies in children with developing skeletons are necessary. Further studies are also required regarding the effects of prolonged rhPTH therapy on hypercalciuria, nephrocalcinosis, nephrolithiasis, renal impairment, ectopic calcifications, BMD, bone quality and quality of life. In addition, further research on gradation of rhPTH doses according to weight and therapeutic response, and delivery systems that can mimic physiological PTH levels and calcium-phosphate homeostasis is needed.