Topic: Bone, growth plate and mineral metabolism

# LONG-TERM TERIPARATIDE (rhPTH 1-34) TREATMENT IN CHILDREN WITH SYNDROMIC HYPOPARATHYROIDISM

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## Background

Hypoparathyroidism is characterized by 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 represents the conventional therapy. Subcutaneous recombinant human parathormone [rhPTH (1-34)] has been proposed for hypoparathyroidism treatment, even to avoid side effects of vitamin D and calcium.

## Objective

To evaluate rhPTH (1-34) long term safety and efficacy in pediatric patients with genetically proven syndromic hypoparathyroidism.

## Patients and methods

The study is a 9.2-year self-controlled trial on six pediatric patients (four males, two females, age 9.4±5.2 years) with syndromic hypoparathyroidism: three subjects with autoimmune polyendocrinopathy candidiasis ectodermal dysplasia (APECED) syndrome (one of those with intestinal malabsorption), two with DiGeorge syndrome and one with hypoparathyroidism-deafness-renal dysplasia (HDR) syndrome.
Hypocalcemic clinical signs and biochemical parameters (blood calcium, phosphate, alkaline phosphatase and urinary calcium-to-creatinine ratio) were compared during conventional treatment and on rhPTH (1-34) (teriparatide, 12.5 µg twice a day).

Clinical features at diagnosis.

| Subject (gender) | Age | Diagnosis | Molecular genetics | Symptoms | Kidney US Morphology | Other features |
|---|---|---|---|---|---|---|
| P 1 (M) | 2 days | DiGeorge syndrome | Chromosome 22q11 microdeletion | Neonatal hypocalcemic crisis | Bilateral hyperechogenicity, right kidney hypodysplasia | Retina coloboma, hypoacusia, cryptorchidism, mental retardation, sacral hemivertebra, short stature |
| P 2 (M) | 2 days | DiGeorge syndrome | Chromosome 22q11 microdeletion | Tetany | Bilateral hyperechogenicity, | Truncus arteriosus, angioma |
| P 3 (F) | 1.7 y | APECED syndrome | AIRE gene [260 T>C] and [967-979 del] mutation | Tetany | Normal | Oral candidiasis, ungual dystrophy, autoimmune hepatitis |
| P 4 (M) | 6.4 y | APECED syndrome | AIRE gene [260 T>C] and [967-979 del] mutation | Asymptomatic | Normal | Ungual dystrophy, oral candidiasis, |
| P 5 (M) | 14.1 y | HDR syndrome | GATA3 gene mutation | Tetany | Right kidney agenesis | Vesicoureteral reflux, bilateral ptosis, bilateral hypoacusia, myopia, horizontal nystagmus, symmetric pseudopapilledema |
| P 6 (F) | 5.3 y | APECED syndrome | AIRE gene [260 T>C] and [967-979 del] mutation | Unconsciousness, hypotonia | Normal | Lymphopenia, oral candidiasis, |

M, Male; F, female; y, year

## Results

The rhPTH (1-34) treatment allowed a marked reduction, althought not always a complete suspension, of calcium supplementation and a slight reduction of calcitriol therapy. During rhPTH (1-34), mean blood calcium and alkaline phosphatase were not significantly modified, whereas significant reduction of the urinary calcium-to-creatinine ratio (0.55±0.32 vs. 0.16±0.09, p=0.02) and blood phosphate (2.01 ± 0.23 vs. 1.69 ± 0.21, p=0.03) was obtained. The number of tetanic episodes was reduced in four patients during teriparatide treatment. Renal ultrasound findings worsened in 3 patients (with nephrocalcinosis in 2 subjects) and was unmodified in the other 3. No adverse effects were detected during the observation time.

Data on last evaluation during conventional treatment

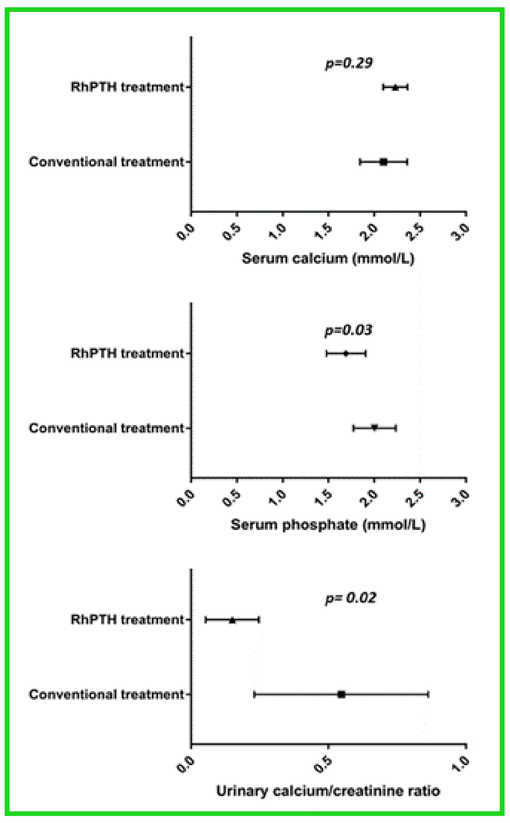
| Subject (gender) | Age | Follow up (y) | Blood Calcium [a], mmol/L | Blood Phosphorus [b], mmol/L | Ca-u/Cr-u [c], mg/mg | Alkaline Phosphatase [d] | Tetanic episodes (n) | Kidney US morphology |
|---|---|---|---|---|---|---|---|---|
| P 1 (M) | 10.7 y | 10.7 y | 2.23 | 2.13 | 0.35 | 110 | 6 | Bilateral hyperechogenicity, right kidney hypodysplasia |
| P 2 (M) | 8.9 y | 8.9 y | 2.00 | 2.16 | 0.75 | 137 | 4 | Bilateral hyperechogenicity, |
| P 3 (F) | 3.4 y | 1.8 y | 1.90 | 2.29 | 1.02 | 185 | 4 | Normal |
| P 4 (M) | 8.3 y | 1.8 y | 1.75 | 1.84 | 0.11 | 196 | 0 | Normal |
| P 5 (M) | 18.6 y | 4.3 y | 2.36 | 1.67 | 0.48 | 65 | 3 | right kidney agenesis, left kidney with two cicts |
| P 6 (F) | 6.4 | 1.0 y | 2.37 | 1.94 | 0.57 | 233 | 0 | Normal |

[a] Normal range, 2.3–2.8 mmol/L. [b] Normal range, 1.6–2.4 mmol/L, age 0–3 months; 1.5–2 mmol/L, age 3 months–5 years; 1.2–1.9 mmol/L, age 6–12 years; 0.8–1.5 mmol/L, age 12–18 years. [c] Normal values <0.2. [d] Normal range 120–350 IU/L; M, Male; F, female; y, years

Mean values during teriparatide treatment

| Subject (gender) | Age | Follow up (y) | Blood calcium, mmol/L | Blood phosphate, mmol/L | Alkaline phosphatase | Ca-u/Cr-u, mg/mg | Tetanic episodes (n) | Other features |
|---|---|---|---|---|---|---|---|---|
| P 1 (M) | 20.0 y | 9.3 y | 2.21 | 1.67 | 123 | 0.05 | 2 | No new findings |
| P 2 (M) | 18.2 y | 9.3 y | 2.35 | 1.82 | 196 | 0.24 | 1 | Hypothyroidism, Evans syndrome, seizure, obesity, asthma, hypertension |
| P 3 (F) | 12.8 y | 9.4 y | 2.43 | 1.53 | 201 | 0.25 | 4 | Puberty delay, vitiligo, alopecia, keratitis, preclinical autoimmune insulitis, intestinal malabsorption with deficit of enterochromaffin cells |
| P 4 (M) | 17.6 y | 9.3 y | 2.18 | 2.03 | 218 | 0.17 | 2 | Adrenal insufficiency, alopecia, preclinical autoimmune insulitis, Osgood-Schlatter disease |
| P 5 (M) | 27.8 y | 9.2 y | 2.09 | 1.43 | 75 | 0.05 | 0 | Anxiety–depressive disorder, Barrett's esophagus, sacro-coccygeal fistula, gouty arthritis |
| P 6 (F) | 15.1 y | 8.7 y | 2.13 | 1.67 | 239 | 0.22 | 0 | Adrenal insufficiency, |

M, Male; F, female; y, years




## Conclusions

In the presented children with syndromic hypoparathyroidism, substitutive treatment with rhPTH (1-34) allowed to maintain adequate blood calcium and phosphorus levels, to normalize urinary calcium excretion, to reduce the tetanic episodes. In patients with low compliance or with intestinal malabsorption, its utilization should be considered, even to reduce vitamin D and calcium treatment side effects.

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