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Teriparatide Increases Bone Mineral Density in a Man With Osteoporosis Pseudoglioma

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ABSTRACT

Osteoporosis Pseudoglioma (OPPG) is characterized by severe juvenile-onset osteoporosis and ocular abnormalities. It is caused by one of several inactivating mutations in *LRP5*, a gene importantly involved in bone formation. The objective of this study was to evaluate the efficacy of teriparatide in a young man with OPPG. The subject of this case report is a 19-year-old man with congenital blindness and low trauma fractures because of OPPG. A 2-year course of teriparatide, 20 μg/day, was initiated after a 6-year course of intravenous pamidronate infusions, the latter 3 years of which had minimal effects on bone mineral density (BMD). Measurements in serum were made of C-terminal telopeptide of type I collagen (CTX), N-terminal propeptide of type I collagen (P1NP), total and ionized calcium, phosphate, uric acid, complete blood count, and renal and liver function tests. Urinary calcium/creatinine ratio was determined. BMD was measured by DXA yearly. BMD increased by 9.7% in lumbar spine and 10.2% in right femur hip. CTX rose early, peaking in month 3, followed by an increase in P1NP, peaking in month 9. Both indices returned to baseline by month 24. The increase in CTX followed by P1NP is an unusual time course when teriparatide is used to treat osteoporosis but may be typical of low bone turnover states. There were no adverse events. In a patient with OPPG, teriparatide markedly increased BMD in the lumbar spine and femur hip. © 2011 American Society for Bone and Mineral Research.

KEY WORDS: PTH (1–34); BONE TURNOVER MARKERS; BONE MINERAL DENSITY; LRP5 MUTATION

Introduction

Osteoporosis pseudoglioma syndrome (OPPG) is characterized by severe juvenile-onset osteoporosis and ocular abnormalities, because of one of several inactivating mutations in the *low-density lipoprotein receptor-related protein 5 (LRP5)*, a gene involved in the bone formation.[1,2] These patients demonstrate a failure to reach adequate peak bone mass.[3] Nevertheless, resorption and formation bone turnover markers are usually normal in OPPG.[4] Histomorphometric findings show substantial reductions in trabecular and cortical thickness.[2,5] The animal counterpart of this syndrome, *Lrp5* knock-out mice, demonstrates reduced bone formation, with reduced osteoblasts and reduced bone mass.[5]

Bisphosphonates are most commonly used to treat the abnormal bone metabolism in this disease.[4,6] However, loss of efficacy has been described.[4] A more logic-driven therapy would seem to be osteoanabolic therapy because the principal defect in this syndrome is reduced bone formation. In *Lrp5*−/− mice, teriparatide has been shown to increase bone mass, suggesting that teriparatide's anabolic action does not require the presence of *Lrp5*.[7]

Clinical Vignette

A 12-year-old boy was seen in the bone metabolism unit of Endocrinology at the Sao Paulo Federal University (São Paulo, Brazil) because of multiple fractures. He was eutrophic (53 kg of body weight and 157 cm of stature). The lumbar spine *Z*-score was −3.99, which corresponded to a bone mineral density (BMD) of 0.512 g/cm^2. He had congenital blindness but normal neuropsychomotor development. At age 7, he presented with his first fracture, in the L4 vertebra, and at age 11, he fractured the left and right tibia within a month. Two months later, he fractured the right femur. A younger brother also had OPPG with congenital blindness and fracture. The parents were consanguineous and healthy. No other family members were blind or had sustained fractures in childhood. OPPG was suggested

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based on the clinical features, consanguinity of the parents and a brother with similar phenotype. Molecular analysis in our patient showed the presence of a novel homozygotic missense mutation in the *LRP5* gene.[8]

Cyclic intravenous pamidronate (60 mg) was administered for 6 years (every 3 months in the first year, every 4 months in the second and third year, and annually thereafter). He initially responded with an increase in BMD over the first 3 years from 0.512 g/cm^2 to 0.596 g/cm^2 in the lumbar spine.[6] However, further gains in the lumbar spine over the next 3 years of pamidronate therapy were minimal, increasing only to 0.604 g/cm^2. He did not sustain further fractures on pamidronate. Based on the results of a study showing that the anabolic action of PTH is preserved in *Lrp5* knock-out mice, the patient was treated with teriparatide, 1 year after pamidronate was stopped.

Subject and Methods

This protocol was approved by the Ethics Committee of São Paulo Federal University (CEP 1506/08), and written consent was obtained from the patient and his parents. The patient was 19 years and 11 months and had welding-complete epiphyseal growth (detected by X-ray for bone age). Teriparatide (Forteo©, Eli Lilly, Indianapolis, IN, USA) was administered, 1 year after pamidronate was discontinued, in a dose of 20 μg subcutaneously daily for 24 months. Calcium (500 mg) and vitamin D3 (1.000 international units) was included in the daily regimen. Oral alendronate (70 mg/weekly) was prescribed immediately after stopping teriparatide.

Blood samples were obtained for the following tests: C-terminal telopeptide of type I collagen (CTX), N-terminal propeptide of type I collagen (P1NP), total and ionized calcium, phosphate, uric acid, hemogram, renal and liver functions, testosterone, and 25-hydroxyvitamin D3 (25OHD3); in the urine, calcium/creatinine ratios were measured. Samples were obtained at baseline, 3, 6, 12, 18, and 24 months after starting teriparatide. Urinary calcium was measured using the calcium and creatinine ratio in a spot urine sample after fasting because the patient's blindness precluded a full 24-hour collection. BMD was measured at baseline and annually with the same instrument (Hologic QDR 4500A Hologic Inc, Waltham, MA, USA) at the lumbar spine (L1–L4) and whole body. Right total hip was measured only at 6 and 30 months because of a software problem. The distal 1/3 distal radius site was not measured. Radiographs of the lumbar and thoracic spine were obtained before and after treatment. Commercial electrochemiluminescence kits (Elecsys1010, Roche 214 Diagnostics, EUA, Indianapolis, IN, USA) were used to quantify the 25-hydroxyvitamin D3, intact PTH, and the bone turnover markers CTX and P1NP in serum. Ionized calcium was measured by an ion-specific electrode (AVL 218 9180 Electrolyte analyzer, AVL Scientific Corporation, EUA, Roswell, GA, USA). Testosterone was measured by immunochemiluminescence technology (Beckman-Coulter, Fullerton, CA, USA). Serotonin was measured by an ELISA Kit, Fitzgerald (Concord, MA, USA). Bone biopsy was not performed because the patient and his family did not agree to it.

Results

Over the 2-year treatment period, height and weight remained stable and the medication was well tolerated. The patient did not experience clinically relevant adverse effects, abnormal laboratory indices, clinical, or morphometric fractures. A minimal uric acid elevation (7.9 mg/dL; NL: 2.5–7.0 mg/dL) was transient at 6 months. BMD increased markedly in the lumbar spine (+9.7%) (Fig. 1) and in the right total hip (+10.2%) during the 2-year treatment period. Whole-body BMD did not change. The CTX level rose quickly, reaching a peak by month 3 (+163% compared with baseline), and then returned slowly to the baseline level by month 24 (Fig. 2). The P1NP level rose much more slowly, beginning to rise in month 6 and reaching a peak in month 9. The increase over baseline was +97%. Thereafter, P1NP levels declined to baseline by 24 months (Fig. 2). We indicate changes from baseline only because reference ranges of these bone turnover markers have not been established for young men. Intact PTH (24.0 pg/mL; NL: 8–55), 25-hydroxyvitamin D3 (61 ng/mL; NL: 30–100 ng/mL), and testosterone levels (4.53 ng/mL; NL: 1.75–7.81) were all normal. Intact PTH measurements remained normal during the treatment. The patient's serotonin level was 72.8 ng/mL, more than two times higher compared with normal controls median (29.4 ng/mL, from 14.0 to 47.9 ng/mL). This measurement was performed 1 month after the discontinuation of the teriparatide.

Discussion

To our knowledge, this is the first report in which teriparatide was administered to an adult with OPPG. The gain in lumbar spine bone mass after 2 years was similar to the major densitometric gains experienced in the pivotal clinical trial that led to the

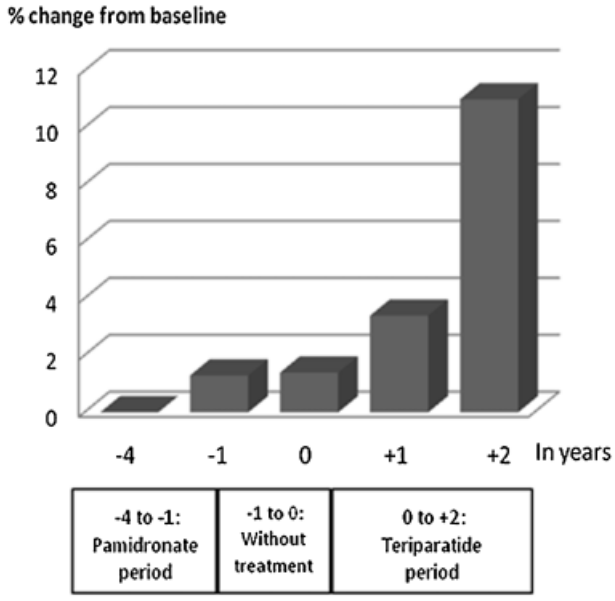

Fig. 1. Percentage change in lumbar spine bone mineral density after teriparatide. The 0 time point represents the onset of teriparatide therapy. From $T=-4$ to $T=-1$, the patient received pamidronate followed by no therapy ($T=-1$ to $T=0$).

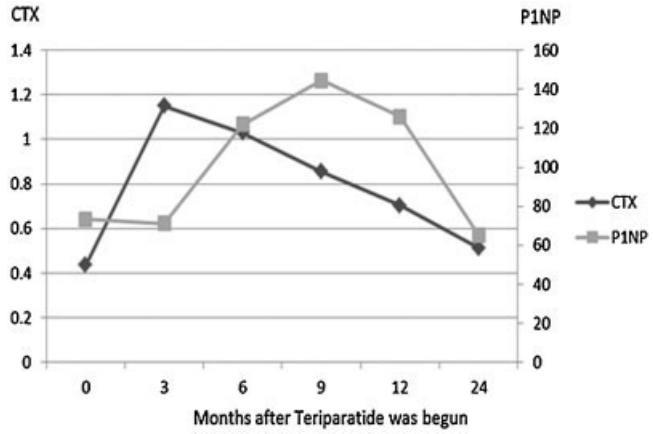

Fig. 2. Serum CTX and P1NP levels (both in ng/mL) during treatment with teriparatide.

approval of the drug[9] and more than seven times greater than the gains over the last 3 years of intravenous pamidronate therapy. The gain in BMD because of teriparatide was greater in year 2 than in year 1.

We waited until the patient's linear growth stopped before administering teriparatide in view of concerns about using this agent when epiphyses are open and bone is still accruing.[10] However, teriparatide has been used successfully in young adults.[11,12] With specific regard to OPPG, there is one report of a peripubertal adolescent patient with OPPG who was treated with teriparatide.[4] There was no gain in BMD after 15 months. The difference between that patient and the one reported here may relate to the different dosing regimen, because in that other article, the use of teriparatide was intermittent and for a shorter period of time. Alternatively, his pubertal status could have negatively impacted on the responsiveness to teriparatide. Finally, the nature of the mutation in the peripubertal male [a nonsense homozygote mutation on LRP5 (W425X)] was probably associated with more severe disease than found in our patient, might also have been a factor.

We observed an interesting time course of change in bone turnover markers, which is different from what has traditionally been found when teriparatide is used in men or postmenopausal women with osteoporosis. Usually, there is a rapid increase in bone formation markers followed by a later increase in bone resorption markers.[13] In this patient, the opposite pattern was observed, namely, an increase in CTX before the increase in P1NP. These results could be explained by the osteoblast deficiency state in OPPG[3] and in the *Lrp5*−/− knockout mouse, the animal counterpart, in which there is a reduced number of osteoblasts.[5] If the initial actions of teriparatide depend upon the presence of osteoblasts on the remodeling surface, as has been described,[14] then in OPPG this need may not be met, and thus the relatively delayed increase in the bone formation marker. In patients with hypoparathyroidism, which is also associated with low bone formation, bone turnover markers respond with the same sequence of change as found in this patient.[15,16] It is unlikely that the previous use of pamidronate could explain this different pattern of bone marker responsiveness. When bisphosphonates are used 6 or more months before teriparatide, responsiveness is unimpeded.[17,18] For pamidronate, in particular, bone turnover markers return to baseline by 1 year after discontinuation of the bisphosphonate.[19,20] Because this patient began teriparatide 1 year after stopping pamidronate infusions, it seems highly unlikely that the previous use of the bisphosphonate could be responsible for the pattern found after teriparatide.

Both CTX and P1NP returned to baseline values after the treatment. The return of bone turnover markers to baseline is expected with teriparatide treatment.[21,22] The nature of this tachyphylaxis is not understood.[23]

The salutary effect of teriparatide in the OPPG syndrome raises mechanistic questions because of the relationship between LRP5, PTH, and the anabolic β-catenin signaling pathway. The identification of LRP5 expression in several tissues including osteoblasts suggested a possible defect in the canonical Wnt/β-catenin pathway as the pathophysiologic basis of OPPG. The hypothesis implicating LRP5 in the Wnt/β-catenin pathway is supported by genetic studies of mice.[2] Sclerostin, an inhibitory molecule, is regulated by PTH.[24] The ability of teriparatide to be anabolic in the setting of LRP5 deficiency can be explained by the position of sclerostin in this signaling pathway, namely, distal to LRP5 regulation. In this formulation, teriparatide is bypassing the genetic block in OPPG.

It is possible, on the other hand, that LRP5 is not directly associated with Wnt/β-Catenin signalling. Yadav et al.[5] demonstrated in an animal model that the regulation of bone mass by *Lrp5* occurs via the modulation of serotonin production in duodenum enterochromaffin cells. Consistent with this hypothesis, they have demonstrated markedly elevated levels of serotonin in the serum of subjects with OPPG. Serotonin from the gastrointestinal tract inhibits bone formation. In our patient, also, the serotonin level was almost three times higher than normal controls.[25]

This study provides new therapeutic insight into the treatment of OPPG with teriparatide and gives support to the rationale for using an osteoanabolic agent in this syndrome.

Disclosures

Marise Lazaretti-Castro is a consultant for Sanofi-Aventis and Novartis and participates as a principal investigator in clinical research trials supported by Merck, Sharp & Dohme, Eli Lilly, and Pfizer. John Bilezikian is a consultant for Novartis, Eli Lilly, Merck, Amgen, Glaxosmithkline, and NPS pharmaceuticals. All other authors state that they have no conflicts of interest.

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