

Teriparatide for the rapid resolution of delayed healing of atypical fractures associated with long-term bisphosphonate use

Silvina R. Mastaglia^{1, 2}, Gabriel Aguilar³, Beatriz Oliveri^{1, 2}

Abstract

Bisphosphonates (BPs) are the most widely used drugs to treat osteoporosis. However, recent reports associated to long-term BP use with atypical low-impact fractures and prodromal pain. It is estimated that 26% of the cases of atypical fractures associated with the long-term use of BPs show delayed healing or nonunion. Teriparatide [PTH1-34] (TPD) is an anabolic drug shown to be effective in stimulating bone formation. The aim was to describe the course of a right diaphyseal femoral fracture sustained by a patient on long-term BP treatment. A 57-year-old postmenopausal Caucasian female presented with delayed healing of a right femoral diaphyseal fracture 10 months after the fracture, despite having received orthopedic treatment. The fracture was preceded by progressive, severe, and bilateral thigh pain. Her medical history included osteopenia that was treated with alendronate over 7 years. On presentation at our clinic, the patient ambulated with the aid of a walking cane. The diagnosis was an atypical right femoral fracture associated with long-term alendronate use. The levels of the following parameters were measured: mineral metabolism laboratory intact parathormone, 40 ng/mL (rv: 10–65 ng/mL); 25-hydroxyvitamin D, 40 ng/mL (rv: >30 ng/mL); serum Crosslaps, 318 ng/mL (rv: 80–590 ng/mL); and bone-specific alkaline phosphatase, 76UI/L (rv: 31–95UI/L). Magnetic resonance imaging of the left femur was performed, which revealed a diaphyseal stress fracture. She was prescribed 20 µg/day of subcutaneous (s.c.) TPD (PTH1-34, Forteo; Eli Lilly Co., Indianapolis, IN, United States). A computed tomography scan performed 3 months later showed that the fracture had healed; the patient was able to resume her usual activities. Twenty micrograms per day of s.c. TPD accelerated the healing of the atypical fracture associated with long-term alendronate therapy, allowing a fast recovery of ambulation and quality of life.

Keywords: Bisphosphonate, stress fracture, non-healing fracture, teriparatide



1 Laboratorio de Enfermedades Metabólicas Óseas, Instituto de Inmunología, Genética y Metabolismo (INIGEM), Hospital de Clínicas, CONICET-UBA, Buenos Aires, Argentina

2 Researcher of the National Council for Scientific and Technical Research (CONICET), Aires, Argentina

3 Centro de Diagnóstico Dr. Enrique Rossi, Buenos Aires, Argentina

Address for Correspondence:
Silvina Mastaglia, Laboratorio de Enfermedades Metabólicas Óseas, Instituto de Inmunología, Genética y Metabolismo (INIGEM), Hospital de Clínicas, CONICET-UBA, Buenos Aires, Argentina

E-mail: silvinamastaglia@hotmail.com

Submitted: 03.02.2015

Accepted: 07.05.2015

Available Online Date: xxxxxxxxxx

Copyright 2015 © Medical Research and Education Association

Introduction

Osteoporosis is a metabolic bone disease characterized by low bone mass and impaired microarchitecture, which result in greater bone fragility and increased fracture risk (1). Bisphosphonates (BPs) are widely used to treat osteoporosis because of their efficacy in reducing osteoporotic fractures and increasing bone mineral density (BMD). However, recent reports have associated the long-term use of BPs with atypical low-impact fractures and prodromal pain. Such fractures develop in skeletal sites predominantly in the cortical bone, most frequently in the diaphysis and subtrochanteric region of the femur (2). It is estimated that 26% of the cases of atypical fractures associated with long-term use of BPs show delayed healing or nonunion (2).

Fracture consolidation is a complex process involving the reconstitution of skeletal integrity after trauma. Fracture healing time depends on type of fracture, age, presence of chronic disease, and/or use of medication, and it can take several months before skeletal integrity is restored. Delayed healing is a condition where healing time is longer than expected for that particular type of fracture. According to the Food and Drug Administration, nonunion is a fracture that is more than nine months old and that has not shown radiographic signs of progression toward healing for three consecutive months (3).

Teriparatide [PTH 1-34] (TPD) is an approved anabolic drug for treating osteoporosis with a proven efficacy in stimulating bone formation in addition to promoting growth factor production for fracture healing. Aspenber et al. (4) studied the effect of 20 and 40 µg doses of TPD for 8 weeks on distal radial fracture healing (Colles' fractures) in postmenopausal women. The 20 µg dose proved to be more effective in reducing the average healing time than the 40 µg dose. There is scant information on the possible efficacy of TPD in treating delayed union of atypical fractures associated with long-term BP use.

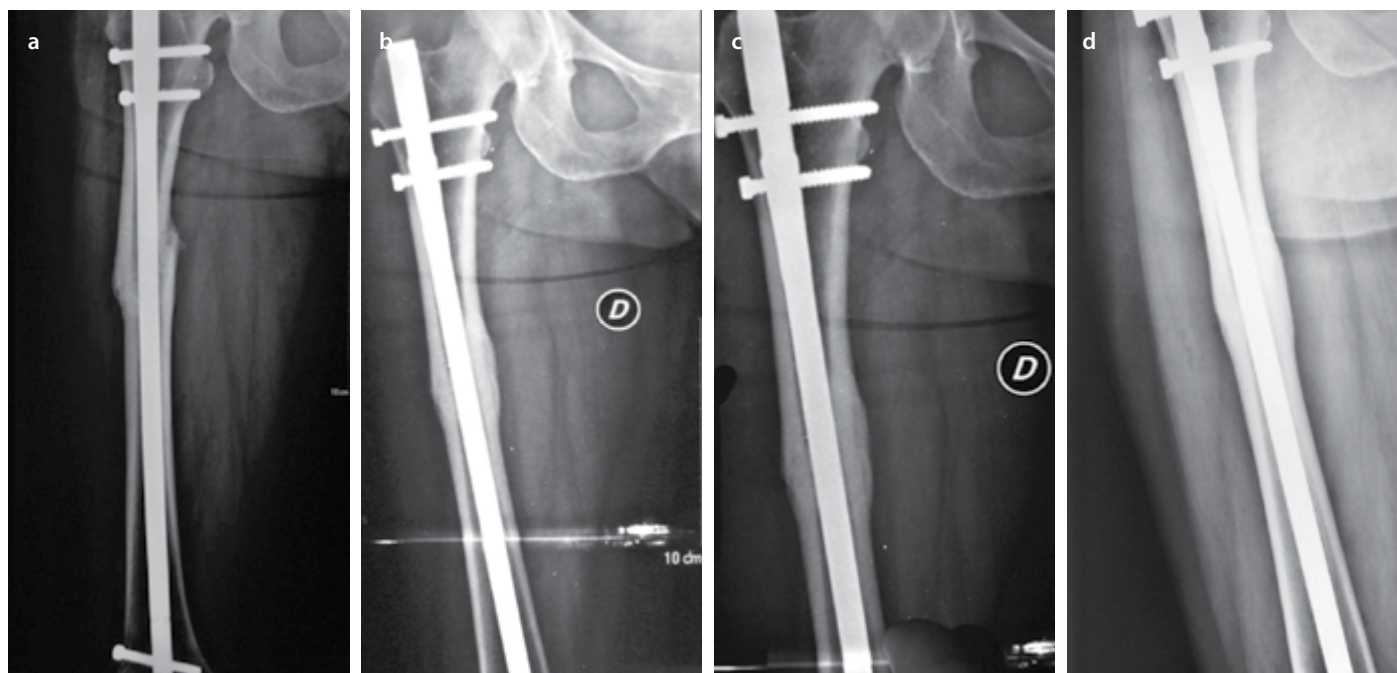


Figure 1. a-d. Radiological healing of the right femur fracture post-teriparatide (TPD) treatment. Radiological healing of a mid-diaphyseal fracture in the right femur showing signs of intramedullary osteosynthesis

The first radiograph (a) shows an exuberant callus and persistence of a transverse fracture line. The second (b) and third (c) radiograph show the radiological healing evolution after 1 and 3 months of TPD treatment. Post-treatment radiograph (d) shows callus remodeling and no fracture line, indicative of fracture healing

Table 1. Bone mineral density (DXA; Lunar Prodigy) pre-and post-teriparatide (TPD) treatment
Lumbar spine: 3.0%

	Pre-TPD (Baseline) g/cm ²	T-score	Post-TPD (3 rd Month) g/cm ²	T-score
Lumbar spine	0.928	-2.3	0.939	-2.2
Femoral neck	0.963	-0.1	0.926	-0.5
Total Femur	0.808	-1.6	0.832	-1.4

Femoral neck: 4.2% and total femur: 3.4%

DXA: dual energy X-ray absorptiometry; TPD: teriparatide

Table 2. Bone and mineral metabolism laboratory results

	Pre-TPD (Baseline)	Post-TPD (3rd Month)
sCa (8.9–10.4 mg%)	8.8	8.9
sP (2.6–4.4 mg%)	3.2	3.0
25OHD (>30 ng/mL)	40.0	48.2
sCTX (80–590 ng/mL)	318	348
BSAP (31–95 IU/L)	76.0	52.8
iPTH (6–65 pg/mL)	44.0	64.0
uCa (80–250 mg/24 h)	189	131

sCa: serum calcium; sP: serum phosphate; 25OHD: 25-hydroxyvitamin D; sCTX: serum Crosslaps; BSAP: bone-specific alkaline phosphatase; iPTH: intact parathormone; uCa: urinary calcium; TPD: teriparatide

The aim of the present communication is to describe the clinical course of a patient on long-term alendronate therapy and present-

ing with delayed union of a diaphyseal fracture of the right femur, which rapidly resolved with TPD therapy.

Case Presentation

A 57-year-old post-menopausal Caucasian woman presented for consultation because of a lack of healing of a diaphyseal fracture of the right femur 10 months after the fracture, despite having received orthopedic treatment (placement of an intramedullary screw). The fracture was preceded by progressive, severe, and bilateral thigh pain for 1 year. The patient had a relevant history of vulvar cancer at the age of 44 years, osteoarthritis treated with glucosamine and chondroitin sulfate, and osteopenia treated with alendronate for 7 years. She had no family history of fractures, smoking, excess alcohol consumption, or diabetes, and she was not taking glucocorticoids, proton pump inhibitors, or any other antiresorptive drug.

On presentation at our clinic, she ambulated with the aid of a walking cane. Tests performed at our laboratory included the evaluation of bone mineral metabolism, BMD, and nuclear magnetic resonance imaging (MRI) of the contralateral femur to confirm the presence of a diaphyseal fracture of the left femur, which was suspected on the initial simple radiograph taken at the time of the fracture. MRI showed a diaphyseal stress fracture of the left femur. Treatment with 20 µg/day of subcutaneous (s.c.) TPD (Forteo; Eli Lilly Co., Indianapolis, IN, United States) was initiated after the patient gave informed consent. After 1 month of treatment, the patient reported a significant decrease in pain, and no longer needed a walking aid. Figure 1 shows the radiographic course of the fracture prior to and after TPD therapy. Three months after the onset of treatment, multislice computed tomography (CT) showed that the fracture had healed, and the patient was able to resume her usual activities (Figure 2). Table 1 and 2 show densitometric and mineral metabolism values obtained pre- and post-TPD treatment, respectively. No adverse effects associated with TPD were observed, showing that the patient tolerated the drug well.

Discussion

We herein presented a case of delayed union of a diaphyseal fracture associated with long-term BP use, which resolved after the administration of 20 µg/day of s.c. TPD for 3 months. Visekru-



Figure 2. Coronal reconstruction computed tomography (CT) scan of both femurs (third month post-teriparatide treatment). Note the presence of metallic osteosynthesis artifacts in the right femur.

The image shows the course of the mid-diaphyseal fracture of the right femur, involving bone remodeling, fracture repair callus formation, and fracture healing. Healing of stress fracture associated with insufficiency resulting in cortical thickening can be observed in the mid-diaphysis of the left femur

na et al. (5) and Gomberg et al. (6) reported two cases of women with delayed union of bilateral diaphyseal femoral fracture associated with long-term use of alendronate (≥ 10 years), who achieved fracture consolidation after 1-year treatment with 20 μg s.c. TPD. Interestingly, unlike the above cases, the BP-associated atypical fracture in our patient consolidated 3 months after the administration of 20 $\mu\text{g}/\text{day}$ s.c. TPD. This suggests that TPD therapy was a more crucial factor of fracture consolidation than time since fracture. It must be pointed out that other factors may have contributed to the shorter fracture healing time of the patient presented here, such as younger age and shorter duration of alendronate therapy, both of which affect the bone remodeling rate.

A typical femoral fractures are stress fractures associated with BP-induced suppression of bone remodeling. In addition to suppressing bone remodeling, BPs prevent microcrack repair, thereby increasing microfracture burden and reducing crack removal.

The fracture healing process is completely different in the case of a traumatic or fragility fracture and a stress fracture. In the former case, callus formation initiates the formation of a cartilage callus, which later undergoes endochon-

dral ossification, resulting in union and mineralization. It is only after the stabilization stage that bone remodeling begins reconstructing the structure of the lamellar bone. In the case of stress fractures, the process is initiated only through the bone remodeling process so that the damaged area is first resorbed and then repaired with the newly formed bone (7).

Sloan et al. (8) experimentally showed that TPD significantly increases the area of intracortical resorption and the percentage of crack length repair compared with those of controls. The observed increase in bone remodeling activation during stress fracture repair is due to the effect of TPD on osteoclasts and osteoblasts. TPD affects osteoclast maturation and function, whereas it stimulates osteoblast proliferation, activity, and lifespan. The ultimate effect of TPD on stress fractures is that it accelerates bone remodeling induced by microcrack formation. Another potential intervening factor is long-term BP administration, which decreases osteocyte apoptosis. **It has been posited that osteocyte apoptosis initiates bone remodeling after a stress fracture.** The suppression of osteocyte apoptosis suppresses osteoclast activation. Nevertheless, further studies are necessary to establish whether osteocyte apoptosis leads to a delay in stress fracture healing.

In agreement with other cases reported in literature, none of the bone remodeling parameters show excessive suppression of bone turnover, though it must be pointed out that the markers were evaluated after the fracture occurred. We did not observe an increase in bone remodeling parameters during TPD therapy, as has been observed during osteoporosis treatment. This result may be due to the effect of BP therapy. Prior treatment with BPs would prevent the TPD-induced increases in bone remodeling parameters observed in treatment-naïve patients (9). This observation may be related to the availability of target cells for the anabolic action of TPD, which promotes bone formation. It has also been reported that activation frequency and mineralizing surfaces decrease by approximately 90% after 2–3 years of alendronate treatment (10).

Although the present results do not allow drawing definitive conclusions, they suggest that TPD therapy was effective in the consolidation of a stress fracture after three months. Further clinical studies are necessary to determine the safety and effectiveness of 20 $\mu\text{g}/\text{day}$ of s.c. TPD in achieving the healing of diaphyseal femoral fractures associated with long-term BP use. Until then, TPD should be used with caution.

Ethics Committee Approval: N/A.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.M.; Design - S.M.; Supervision - S.M.; Materials - S.M.; Data Collection and/or Processing - S.M.; Analysis and/or Interpretation - S.M., G.A.; Literature Review - S.M.; Writer - S.M.; Critical Review - B.O.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The author declared that this study has received no financial support.

References

1. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med* 1993; 94: 646-50.
2. Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2010; 25: 2267-94.
3. Ellegaard M, Jorgensen NR, Schwarz P. Parathyroid Hormone and Bone Healing. *Calcif Tissue Int* 2010; 87: 1-13.
4. Aspenberg P, Genant HK, Johansson T, Nino AJ, See K, Krohn K, et al. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. *J Bone Miner Res* 2010; 25: 404-14.
5. Visekruna M, Wilson D, McKiernan FE. Severely suppressed bone turnover and atypical skeletal fragility. *J Clin Endocrinol Metab* 2008; 93: 2948-52.
6. Gomberg SJ, Wustrack RL, Napoli N, Arnaud CD, Black DM. Teriparatide, vitamin D, and calcium healed bilateral subtrochanteric stress fractures in a postmenopausal woman with a 13-year history of continuous alendronate therapy. *J Clin Endocrinol Metab* 2011; 96: 1627-32.
7. Li J, Mori S, Kaji Y, Mashiba T, Kawanishi J, Norimatsu H. Effect of bisphosphonate (incadronate) on fracture healing of long bones in rats. *J Bone Miner Res* 1999; 14: 969-79.
8. Sloan AV, Martin JR, Li S, Li J. Parathyroid hormone and bisphosphonate have opposite effects on stress fracture repair. *Bone* 2010; 47: 235-40.
9. Ettinger B, San Martín J, Crans G, Pavo I. Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. *J Bone Miner Res* 2004; 19: 745-51.
10. Chavassieux PM, Arlot ME, Reda C, Wei L, Yates AJ, Meunier PJ. Histomorphometric assessment of the long-term effects of alendronate on bone quality and remodeling in patients with osteoporosis. *J Clin Invest* 1997; 100: 1475-80.