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

Silvina R. Mastaglia1, 2, Gabriel Aguilar3, Beatriz Oliveri1, 2

Abstract

Bisphosphonates (BPs) are the most widely used drugs to treat osteoporosis. However, recent reports associated to long-term BPs 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] (TPTD) 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 BPs 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 (reference values (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.) TPTD (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. TPTD 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

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 (2-4). Such fractures develop in skeletal sites predominantly in the cortical bone, most frequently in the diaphysis and subtrochanteric region of the femur (5). It is estimated that 26% of the cases of atypical fractures associated with long-term use of BPs show delayed healing or nonunion (5).

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 (6).

Teriparatide [PTH 1-34] (TPTD) 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. Aspdenber et al. (7) studied the effect of 20 and 40 µg doses of TPTD 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 TPTD in treating delayed union of atypical fractures associated with long-term BPs use.
The aim of the present communication is to describe the clinical course of a patient on long-term alendronate therapy and presenting 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, osteoarthrosis 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.) TPTD (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. a-d. Radiological healing of the right femur fracture post-teriparatide (TPTD) 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 TPTD 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 (TPTD) treatment

<table>
<thead>
<tr>
<th></th>
<th>Pre-TPTD (Baseline) g/cm²</th>
<th>T-score</th>
<th>Post-TPTD (3rd Month) g/cm²</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>0.928</td>
<td>-2.3</td>
<td>0.939</td>
<td>-2.2</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.963</td>
<td>-0.1</td>
<td>0.926</td>
<td>-0.5</td>
</tr>
<tr>
<td>Total Femur</td>
<td>0.808</td>
<td>-1.6</td>
<td>0.832</td>
<td>-1.4</td>
</tr>
</tbody>
</table>

Least significant change (LSC): lumbar spine: 3.0%; femoral neck: 4.2% and total femur: 3.4%.

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

Table 2. Bone and mineral metabolism laboratory results

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

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

The aim of the present communication is to describe the clinical course of a patient on long-term alendronate therapy and presenting with delayed union of a diaphyseal fracture of the right femur, which rapidly resolved with TPD therapy.

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Figure 1 shows the radiographic course of the fracture prior to and after TPTD 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-TPTD treatment, respectively. No adverse effects associated with TPTD 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 BPs use, which resolved after the administration of 20 µg/day of s.c. TPTD for 3 months. Visekruna et al. (8) and Gomberg et al. (9) 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. TPTD. Interestingly, unlike the above cases, the BPs-associated atypical fracture in our patient consolidated 3 months after the administration of 20 µg/day s.c. TPTD. This suggests that TPTD 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 BPs-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 endochondral 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 (10).

Sloan et al. (11) experimentally showed that TPTD 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 TPTD on osteoclasts and osteoblasts. TPTD affects osteoclast maturation and function, whereas it stimulates osteoblast proliferation, activity, and lifespan. The ultimate effect of TPTD on stress fractures is that it accelerates bone remodeling induced by microcrack formation. Another potential intervening factor is long-term BPs administration, which decreases osteocyte apoptosis. It has been posited that osteocyte apoptosis initiates bone remodeling after a stress fracture (12, 13). 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 TPTD therapy, as has been observed during osteoporosis treatment. This result may be due to the effect of BPs therapy. Prior treatment with BPs would prevent the TPTD-induced increases in bone remodeling parameters observed in treatment-naïve patients (14). This observation may be related to the availability of target cells for the anabolic action of TPTD, 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 (15).

Although the present results do not allow drawing definitive conclusions, they suggest that TPTD 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 µg/day of s.c. TPTD in achieving the healing of diaphyseal femoral fractures associated with long-term BPs use. Until then, TPTD should be used with caution.

Mastaglia et al. Delayed healing and teriparatide

Ethics Committee Approval: N/A.
Informed Consent: Written informed consent was obtained from patient who participated in this case.
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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.
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