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Teriparatide for treatment of patients with bisphosphonate-associated atypical fracture of the femur

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Abstract

Summary—The Fracture Improvement with Teriparatide (Fix-IT) study randomized 13 women with an atypical femur fracture to immediate vs delayed teriparatide therapy; all were followed for 12 months. Results suggested a trend for superior healing and lesser bone mineral density declines in the immediate vs delayed group with no differences in adverse events.

Purpose—Little clinical data are available on the use of teriparatide for the treatment of bisphosphonate-associated atypical femur fractures (AFF). The goal of the Fix-IT study was to determine if immediate therapy with teriparatide was superior for fracture healing after an AFF compared to a 6-month delay in teriparatide therapy.

Methods—This randomized pilot clinical trial included 13 women with an AFF who were randomized to immediate teriparatide vs a delay of 6 months. All were followed for 12 months on teriparatide. The primary outcomes included individual and composite measures of radiologic bone healing (scored 1 point [no healing] to 4 points [complete healing]) at 6 and 12 months. Secondary outcomes included bone mineral density of the unfractured contralateral hip, spine, 1/3 distal radius, and adverse events.

Results—We found there was a trend for superior healing with the composite score (12.6 vs 11.2 at 6 months and 15.4 vs 13.2 at 12 months), and lesser bone mineral density declines at the 1/3 distal radius (12-month change − 1.9 vs − 6.1%) in the immediate vs the delayed group. There were no differences in adverse events. There was one implant failure in the delayed group.

Conclusions—There is a preliminary signal for greater improvements with immediate teriparatide therapy vs delayed therapy. However, because an AFF is a rare event, and only a small number of patients were included, the results must be interpreted with caution.

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Keywords

Atypical femur fracture; Bisphosphonate; Bone mineral density; Osteoporosis; Teriparatide

Introduction

Bisphosphonates are the mainstay for the treatment of osteoporosis and have been shown to improve bone mineral density and reduce fractures [1]. However, approximately a decade ago, atypical femoral shaft fractures were found to be a rare complication of bisphosphonate treatment [2–4]. In 2009, the American Society for Bone and Mineral Research (ASBMR) convened a Task Force to formally define the criteria for these subtrochanteric and diaphyseal femoral fractures [5] that was updated in 2014 [2].

A major concern about the atypical femoral fracture (AFF) has been determining the most appropriate medical management after the fracture has been surgically evaluated and/or repaired. Although several case reports and reviews have suggested shorter healing time for these fractures with use of an anabolic agent such as teriparatide [6–10], there have been no clinical trials to support this. Miyakoshi and colleagues retrospectively reviewed the medical records of 45 patients with atypical femoral fractures [11]. In a subanalysis for those treated surgically, the time to fracture healing was better in those treated with teriparatide (5.4 ± 1.5 months) compared to those not treated with teriparatide (8.6 ± 4.7 months; $p < 0.05$). However, patients were not randomized, and potential allocation bias exists.

The goal of the Fracture Improvement with Teriparatide (Fix-IT) study was to determine if “immediate” therapy with teriparatide following repair of an AFF would enhance healing and improve bone mineral density compared to “delayed” treatment initiated 6 months after the acute fracture and repair. We examined if up-front teriparatide would provide greater bone density and healing at 1 year compared to teriparatide initiated at 6 months after the acute fracture. To examine these objectives, we randomized patients presenting to the hospital with an acute AFF to receive immediate (approximately 2 weeks after the acute fracture and repair) or delayed (teriparatide after 6 months from the acute fracture) and examined radiologic bone healing indices and bone mineral density over 12 months for both groups and radiologic indices over 18 months for the delayed group.

Methods

Study design

Participants were randomized to open label immediate teriparatide (20 μg subcutaneous per day for 12 months) vs delayed (teriparatide initiated 6 months after the acute fracture and continued daily for 12 months). Following informed consent, all were screened to ensure there were no contraindications to treatment with teriparatide. All received calcium up to 1000 mg/day and vitamin D 800 IU/day. The protocol was approved by the University of Pittsburgh Institutional Review Board.

Participants

Thirteen women who were admitted to the University of Pittsburgh Medical Center Presbyterian Hospital with an acute AFF between 2013 and 2015 were included. Participants had to fulfill the ASBMR Task Force 2010 criteria for an atypical femoral shaft fracture, except we also included patients with a peri-prosthetic fracture [5].

Outcomes

Clinical baseline assessment and outcomes—Clinical assessment at baseline included age, body mass index, dietary calcium, bisphosphonate, and other osteoporosis medication use prior to fracture, type of fracture repair (plates/screws/wires or intramedullary nail), and the Duke Comorbidity Index prior to fracture [12]. We also assessed baseline serum calcium, vitamin D, parathyroid hormone, and hemoglobin. Clinical outcomes that were followed included the modified SF-36 for quality of life [13], pain assessment [13], hospitalizations, falls, use of assistive devices (cane, walker), and adverse events.

Radiologic indices—The radiologic indices of fracture healing included (1) cortical continuity on two of four cortices, (2) nonunion, (3) persistence of alignment, (4) implant failure, (5) decreased conspicuity of fracture line, and (6) increased callus formation [14]. Cortical continuity on two of four cortices refers to radiographic follow-up of fractures that routinely include a minimum of two orthogonal views of the fracture site, which allows for assessment of bone bridging the anterior, posterior, medial, and lateral cortices. Nonunion is a cessation of fracture healing prior to establishing osseous continuity between fracture fragments. Nonunion is often diagnosed clinically and radiographically. Radiographic features of nonunion include absence of bone or callus bridging the fracture site. Persistence of alignment refers to the position of the proximal and distal fracture fragments relative to each other and is described with regard to displacement, angulation, distraction, foreshortening, and rotation. Fracture alignment can influence healing, and the goal is to achieve anatomic alignment. Radiographic follow-up of fractures routinely examine for any change in fracture alignment over time. Implant failure/breakage refers to failure of the hardware used in the fracture repair. Fractures may require internal fixation with hardware such as reconstruction plates, screws, and intramedullary rods. Implanted hardware is routinely assessed on follow-up radiographs for breakage (e.g., fractured hardware) or failure (e.g., screw backing out, loosening—lucency adjacent to the hardware measuring two millimeters or more in thickness). Disruptions in the continuity of bone manifest as lucent lines or gaps between fragments. Decreased conspicuity of fracture line refers to the gradual indistinctness and disappearance of lucencies or gaps as callus bridges the fracture site during healing. Increased callus formation occurs during the reparative phase of fracture healing, where fibrous tissue, collagen, hyaline cartilage, and bone are deposited across the fracture site. As the cartilage is replaced by bone and mineralized, callus can be radiographically identified as increased density around and eventually bridging the fracture site.

Conventional x-rays of the healing femoral shaft fracture were done at baseline and approximately 6 and 12 months after the acute event for both groups, and at 18 months for the delayed group only to assess 1 year of teriparatide therapy. Occasionally, patients had CT or MR radiologic imaging that was utilized. Healing was graded on a scale of 1 to 4 with 1 = no healing (less than 25%), 2 = minimum healing (approximately 25–50%), 3 = moderate healing (approximately 50–75%), and 4 = complete healing (greater than 75%). We also included a composite measure that included the sum of (1) cortical continuity, (2) persistence of alignment, (3) decreased conspicuity of fracture line, and (4) increased callus formation ratings. The primary grading was performed by a radiologist with expertise in musculo-skeletal radiology, and then independently repeated by a second radiologist, both of whom were blinded to the study allocation.

Bone mineral density—Measured sites included the contralateral unfractured hip (total hip, femoral neck), spine (posterior-anterior), and 1/3 distal radius. Dual x-ray absorptiometry (DXA) was performed at the first orthopedic follow-up visit at approximately 2 weeks following the fracture, and at 6 and 12 months using a Discovery densitometer (Hologic Inc., Bedford, MA). The precision ranged from 1.2 to 1.9% at these skeletal sites [15].

Statistical analysis—We used appropriate descriptive statistics to summarize baseline participant characteristics. As appropriate for an initial pilot trial in a rare disease population with small sample size, we interpreted magnitudes of descriptive statistics in addition to p values. We used independent samples t, Wilcoxon signed rank, and Fisher's exact tests to obtain statistical significance of between group comparisons. We performed a sensitivity analysis after removing the participants with peri-prosthetic fractures and another using independent ratings of x-ray images from a second radiologist. Statistical analysis was performed using SAS® version 9.3 (SAS Institute, Cary, NC).

Results

Patient Characteristics

The 13 participants included women with an age of 74.2 ± 2.5 years (mean ± standard error) (Table 1). Eighty-five percent or 11 were Caucasian, one was African-American, and one was Asian-American. Six had a past history of estrogen use, and one had used raloxifene for osteoporosis. All had been on one or more oral bisphosphonates in the past, including 4 (31%) on risedronate, 3 (23%) on ibandronate, and 11 (85%) on alendronate. None had received intravenous zoledronic acid, calcitonin, denosumab, or teriparatide. There were no differences in the comorbidity index between the two groups. Four patients (three in the immediate and one in the delayed group) had a peri-prosthetic fracture occurring around the components of or implant of a previous hip repair. For the fracture repair, three patients in the immediate group and one in the delayed had plates, screws, or wires used; four patients in the immediate and five in the delayed groups had an intramedullary nail placed. The dietary calcium intake was 732 ± 102 mg/day.

The baseline T-scores were − 0.67 ± 0.48 (spine), − 1.63 ± 0.25 (total hip), − 1.82 ± 0.31 (femoral neck), and − 1.99 ± 0.39 (1/3 distal radius, Table 1). The average serum 25-hydroxy vitamin D level was 39.4 ± 3.4 ng/mL in the immediate group and 48.7 ± 6.9 ng/mL in the delayed group.

Radiographic healing indices

Of 13 patients, 12 had a complete fracture through both cortices and required surgical intervention. One had an incomplete fracture that included the lateral cortex, and the patient underwent surgical repair. When individual indices were examined, there were no material differences in the healing indices at 6 months between the immediate and delayed group (Table 2). However, composite score (cortical continuity, persistence of alignment, decreased conspicuity of fracture, and increased callus formation) was 12.6 vs 11.2 in the two groups (immediate and delayed, respectively; $p = 0.3820$). There was one implant failure/breakage at 12 months in the delayed group.

At 12 months, cortical continuity was 4.0 vs 3.6 (immediate and delayed respectively; $p = 0.1032$), and composite scores were 15.4 vs 13.2 (immediate and delayed, respectively; $p = 0.1456$). There were no further differences or improvements in the healing scores from the radiographs in the delayed group at 18 months. When the four patients with peri-prosthetic fractures were excluded in a sensitivity analysis, similar composite trends for healing were observed (13.0 vs 10.2 and 15.5 vs 12.5, respectively at 6 and 12 months). Another sensitivity analysis with the second independent radiologist readings found similar trends (12.3 vs 11.8 and 14.1 vs 13.2, respectively).

Representative radiographs of a patient in the immediate group with complete healing at 6 months and a patient in the delayed group with incomplete healing at 6 months are shown in Supplemental Fig. 1.

Bone Mineral Density

There were no significant differences in the bone mineral density of the spine, total hip, femoral neck, or 1/3 distal radius at 6 or 12 months (Table 2). There was a suggestion of less bone loss at the 1/3 distal radius at 12 months in the immediate group compared to delayed ($-1.9 \pm 1.7\%$ vs -6.1 ± 2.1; $p = 0.1605$).

Clinical Outcomes

There were no significant differences in the quality of life questionnaire, pain assessment, hospitalizations, falls, or adverse events between the two groups at 6 and 12 months. At 6 months, two patients in each group were using assistive devices during ambulation. At 12 months, only one patient in the immediate group was using an assistive device.

Discussion

In this randomized pilot clinical trial, we found that patients with an acute atypical facture of the femur, who had previously been treated with an oral bisphosphonate, appeared to have improved healing to a greater extent after surgical repair if teriparatide was started immediately after the acute fracture rather than delaying teriparatide by 6 months. Because this is a rare event, and the FDA recommends intermittent reevaluation of the need for bisphosphonate use, many patients who were previously treated with a bisphosphonate are now pursuing a bisphosphonate holiday [16–19]. Furthermore, bisphosphonate use has significantly decreased in the USA, and the number of those patients with AFF may be on the downswing [18]. These results substantiate some of the observational data that support the use of teriparatide for healing of bisphosphonate-associated AFF [6]. However, this study only aimed to determine if up-front treatment was superior to delayed treatment, and despite a suggestion of a preliminary signal, the results must be viewed with caution.

The changes in BMD were not significantly different at the spine or hip between the immediate and delayed group except for a suggestion of less loss at the 1/3 distal radius. In a recent study by Watts et al. [20] whose results were consistent with ours, 14 patients with AFF previously treated with bisphosphonates were followed on teriparatide treatment for 24 months. These patients had fractured 52–410 days prior to beginning teriparatide therapy, and five were incomplete fractures. However, they also found no significant changes in BMD at the spine or hip at 12 months despite teriparatide treatment. Because bone loss is also associated with weight bearing, and the weight bearing would be on the contralateral and unfractured hip, depending on the patient's mobility and activity, the changes may have been substantially influenced by this [21]. We have no data on the patients' daily activity or mobility at 6 and 12 months after the fracture. However, use of assistive devices for ambulation was similar in the two groups through the 12 months. In the delayed group, we only had BMD on two of the four patients available for assessment due to previous surgery in the contralateral hip. Since the 1/3 distal radius is less weight bearing, these changes in BMD may be more reflective of therapy with teriparatide.

There were several advantages to this study. Both radiologists who scored the primary outcome of bone healing were blinded to the study allocation. We were able to see preliminary signals for improvement in healing with the rating scale with the immediate treatment compared to the delayed treatment. Although previous observational studies have often been retrospective, and some have been based on database classification of an AFF, our study was designed to include AFFs that satisfied the majority of the ASBMR classification criteria. In the investigation by Watts et al., they reported that only three of 14 patients demonstrated healing at 12 months, but the definitions of healing were not provided [20]. However, at 24 months, seven of 14 had healed. In comparison, in our immediate group, the composite healing score was 15.4/16 points for the seven participants suggesting complete healing in almost all participants. We found similar trends in the sensitivity analysis excluding the patients with peri-prosthetic fractures and the results using blinded scores by the second radiologist. Moreover, we found no differences in hospitalization, falls or adverse events, quality of life, or pain scores between groups, although numbers were small. All patients received an appropriate dose of daily calcium and vitamin D for the duration of the study, and both groups received a total of 12 months of therapy with teriparatide. We were able to assess BMD measurements in 11/13 patients for the 6- and 12-month time periods for the spine and 1/3 distal radius.

However, the study also had several limitations. Although patients were randomized, the coordinator and patients were not blind to study allocation. The numbers of participants were small with only six to seven in each group due to the rareness of the disease, the willingness to self-administer a daily subcutaneous medication, the decline in use of bisphosphonates in the last 5 years, and the FDA warnings to reassess bisphosphonate use after 3 to 5 years. The differences in healing may have been due to the surgeon and surgical procedure; however, the four surgeons were distributed between the two groups. Finally, the sample sizes are very small to verify the assumptions underlying traditional significance testing, and thus, the *p* values should be viewed with caution.

In conclusion, in this randomized pilot clinical trial designed to examine immediate vs delayed treatment with teriparatide for skeletal healing of an atypical femoral fracture, we found a preliminary signal for greater improvement in healing indices with immediate treatment. The treatment was well tolerated and appears to be safe. However, because this is a rare event, and numbers were small, the results must be interpreted with caution.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline clinical and bone health characteristics

	Immediate (N=7)	Delayed (N=6)	p-value
Clinical Variables			
Age (years)	78.0 ± 3.3	69.8 ± 3.3	0.1085
Body mass index (kg/m2)	29.8 ± 3.2	26.3 ± 4.1	0.5144
Dietary calcium intake (gm/day)	859 ± 131	584 ± 147	0.1887
Duke Co-morbidity Index (0–8)	3.1 ± 0.3	3.2 ± 0.2	0.9601
25-hydroxy vitamin D (ng/mL)	39.4 ± 3.4	48.7 ± 6.9	0.2347
Parathyroid hormone (pg/mL)	93.0 ±32.8	62.8 ± 3.5	0.3949
Calcium (mg/dL)	8.3 ± 0.2	8.8 ± 0.2	0.1627
Hemoglobin (g/dL)	11.5 ± 0.6	11.4 ± 0.7	0.9148
Bone Mineral Density T-Scores (SD)			
Spine-PA	−0.77 ± 0.67	−0.52 ± 0.75	0.8095
Total Hip (contralateral)	−1.81 ± 0.28	−1.20 ± 0.47	0.2803
Femoral Neck (contralateral)	−1.89 ± 0.38	−1.67 ± 0.66	0.7672
Distal 1/3 Radius	−2.34 ± 0.38	−1.50 ± 0.78	0.3133
Patients Previously on Bisphosphonates (%)			
Alendronate$^{\Delta}$	85.7	83.3	1.0000
Risedronate$^{\Delta}$	42.9	16.7	0.5594
Ibandronate$^{\Delta}$	0.0	50.0	0.0699
Zoledronic Acid	0.0	0.0	-

Results as mean ± SEM or percent where indicated

Table 2

Radiographic and bone mineral density changes at 6 and 12 months

	6 months			12 months		
	Immediate (N=7)	Delayed (N=6)	p-value	Immediate (N=7)	Delayed (N=6)	p-value
Bone Healing Scores						
Cortical continuity on 2 of 4 cortexes (1–4)	3.1 ± 0.1	2.8 ± 0.3	0.3810	4.0 ± 0.0	3.6 ± 0.2	0.1032
Nonunion (yes)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Persistence of Alignment (1–4)	3.1 ± 0.1	3.0 ± 0.3	0.6985	4.0 ± 0.0	3.6 ± 0.2	0.1032
Implant Failure/Breakage (yes)	0 (0.0)	0 (0.0)	NA	0 (0.0)	1 (16.7)	NA
Decreased conspicuity of fracture line (1–4)	3.1 ± 0.1	2.7 ± 0.4	0.3820	3.7 ± 0.2	3.0 ± 0.5	0.2666
Increased callus formation (1–4)	3.1 ± 0.1	2.7 ± 0.4	0.3820	3.7 ± 0.2	3.0 ± 0.5	0.2666
Composite Score (1–16)	12.6 ± 0.6	11.2 ± 1.3	0.3820	15.4 ± 0.4	13.2 ± 1.2	0.1456
Bone Mineral Density Changes (%)						
Spine-PA	2.1 ± 1.5	−0.6 ± 1.3	0.2428	2.8 ± 2.0	5.4 ± 2.8	0.4633
Total Hip	−1.6 ± 1.5	−0.8 ± 0.7	0.8158	−0.3 ± 1.8	1.5 ± 2.7	0.6329
Femoral Neck	−1.8 ± 2.1	−2.7 ± 1.0	0.8275	−2.5 ± 3.0	−1.9 ± 3.6	0.9265
Distal 1/3 radius	−0.6 ± 1.9	−0.7 ± 1.1	0.9548	−1.9 ± 1.7	−6.1 ± 2.1	0.1655

Results as mean ± SEM or *N* (%)

NA not applicable