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Responses to Treatment With Teriparatide in Patients With Atypical Femur Fractures Previously Treated With Bisphosphonates

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ABSTRACT

If oversuppression of bone turnover explained the association between bisphosphonate use and atypical subtrochanteric femur fractures (AFF), this could be reversed with anabolic treatment such as teriparatide. We conducted a prospective, open-label study in patients previously treated with bisphosphonates who sustained AFF, examining the response to 24-month treatment with teriparatide on bone mineral density (BMD), trabecular bone score (TBS), bone turnover markers (BTM), and fracture healing as well as quantitative histomorphometry. We studied 14 patients. Baseline BMD, BTM, and TBS varied widely. On initial bone biopsies, 12 of 14 patients showed tetracycline labels, but mineralizing surface/bone surface was below published normal values in all but 2. Lumbar spine BMD increased significantly at month 24 (6.1% ± 4.3%, $p < 0.05$ versus baseline), whereas total hip BMD and TBS did not change significantly. Changes in BTM occurred as reported previously for patients without AFF treated with teriparatide after prior bisphosphonate treatment. At month 24, fractures were healed in 6 patients, showed partial healing in 3, were unchanged in 2, and showed nonunion in 1. In a patient with two fractures, the fracture that occurred before teriparatide treatment was reported as healed, but the fracture that occurred while on treatment showed only partial healing. Bisphosphonate-treated patients who sustain AFF show heterogeneity of bone turnover. Treatment with teriparatide resulted in increases in BTM and lumbar spine BMD, as has been reported for patients without AFF. There was no significant effect of teriparatide on hip BMD, mineralizing surface to bone surface (MS/BS), or TBS and no consistent effect on fracture healing. In the context of a patient who has experienced an AFF after receiving bisphosphonate treatment, therapy with teriparatide for 24 months would be expected to increase BMD and BTM (and probably reduce the risk of fractures resulting from osteoporosis) but should not be relied on to aid in healing of the AFF. © 2017 American Society for Bone and Mineral Research.

KEY WORDS: BONE HISTOMORPHOMETRY; BIOCHEMICAL MARKERS OF BONE TURNOVER; INJURY/FRACTURE HEALING; ANABOLICS; ANTIRESORPTIVES

Introduction

Most femur fractures occur in the proximal region or "hip"; fractures in the subtrochanteric region represent approximately 10% all femur fractures.[1] The term "atypical" subtrochanteric femur fracture (AFF) was coined to describe a specific type of fracture,[2,3] which represents about 0.5% of all femur fractures. Features of AFF include the subtrochanteric location and 4 of 5 major features (minimal or no trauma; transverse or short oblique configuration; little or no comminution; incomplete fractures show a lateral stress reaction, whereas complete fractures may show a medial spike).[4,5] An increasing number of AFFs have been reported in epidemiological studies since the approval of bisphosphonates for treatment of postmenopausal osteoporosis in 1995, raising the question of a causal association;[6–14] however, AFF may also occur independent of bisphosphonate exposure.[4,5]

Bisphosphonates reduce bone turnover, increase bone strength, and reduce fracture risk.[15–17] In addition to their presence in cancellous bone, small amounts of bisphosphonates distribute to cortical bone where AFF begin.[18] Although oversuppression of bone turnover has been proposed as a mechanism by which bisphosphonates might cause AFF, no "shut-off" of bone turnover has been shown in animal models or in clinical trials even with long-term bisphosphonate therapy.[19–23]

We previously reported quantitative bone histomorphometry in 15 patients treated with bisphosphonates who sustained AFF.

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Eight of 15 subjects had no tetracycline labels on iliac crest biopsies;[24] however, the other 7 had tetracycline labels, with the ratio of mineralizing surface to bone surface (MS/BS; a reflection of osteoblast activity) measurable but below the expected rate for healthy premenopausal women.[25] After treatment with teriparatide, there was an increase in bone formation markers, MS/BS, as well as increase in most other dynamic bone turnover quantitative parameters.

Our previous study was retrospective and further limited by the lack of systematic measurements of bone turnover markers (BTM), radiological assessments beyond plain radiographs, and the absence of longitudinal data other than paired quantitative histomorphometry. Furthermore, all 15 participants in our initial report already had complete fractures with orthopedic correction (intramedullary rods).

We describe here results from a prospective study of subjects specifically recruited by advertisements/referrals and who met prespecified inclusion and exclusion criteria. All participants had documented AFF that met ASBMR criteria[5] and had longitudinal and systematic measurements of BMD, BTM, sequential radiological assessment of both femurs by X-ray and computerized tomography (CT), trabecular bone score (TBS),[26] and paired quantitative histomorphometric assessment of iliac crest bone biopsies.

Materials and Methods

Subjects were recruited by advertising in regional press. All had documented AFF within 12 months of screening and before the fracture had been treated with either oral or iv bisphosphonate. Patients were excluded if they had been treated with any prescription osteoporosis therapy other than bisphosphonates.

The study was approved by the Exempla institutional review board, Denver, CO, and all subjects signed informed consent. Bilateral radiographs of the proximal femurs and femoral shaft were obtained and examined by one of the authors (PDM) who assessed the femurs for changes in fracture lines, cortical thickening, or periosteal reactions. After baseline evaluations, all participants received teriparatide (Forteo, Eli Lilly and Company, Indianapolis, IN, USA) 20 mcg/d subcutaneously for the duration of the study and 1000 mg of calcium and a minimum of 800 IU vitamin D3 daily.

At baseline, month 12, and month 24, BMD was measured with Hologic (Waltham, MA, USA) dual-energy X-ray absorptiometry (DXA) at the lumbar spine and total hip; TBS was performed using TBS software (MediMaps, Lausanne, Switzerland) and computerized tomography (CT) of the femoral shaft was performed for assessment of fracture healing using a GE16 Slice Light Speed CT scanner (Madison, WI, USA), with scans read by a staff radiologist at Advanced Medical Imaging in Denver, CO.

Serum, plasma, or whole blood was analyzed at baseline for complete blood count, comprehensive metabolic panel, as well as parathyroid hormone and ionized calcium. BTM were measured on morning, fasting samples at baseline and months 6, 12, 18, and 24: bone-specific alkaline phosphatase activity (BAP), N-terminal propeptide of type 1 collagen (P1NP), C-telopeptide (CTX), and osteocalcin (OC). 25-hydroxyvitamin D was measured only at baseline. After double tetracycline labeling, iliac crest biopsies were performed (baseline from one side, month 12 from the other side) and quantitative histomorphometric measurements made as previously described.[24]

Results

Baseline demographics are shown in Table 1. Of the 14 patients, 5 had incomplete fractures (2 bilateral [cases 1 and 2], 3 unilateral [cases 3, 4, and 5]), 6 with complete unilateral fractures (cases 6, 7, 8, 9, 10, and 11), 1 who had bilateral complete fractures (case 12), and 2 who presented with complete unilateral fractures but sustained a contralateral fracture while receiving teriparatide treatment (cases 13 and 14). All of the complete fractures required surgical repair. Of the patients with incomplete fractures, one underwent surgical repair before enrollment (case 5), but the remaining 4 did not require surgery.

Measurements of 25-hydroxyvitamin D were made only at baseline. All subjects had values >20 ng/mL. Ten had values >30 ng/mL. Four were between 20 and 30ng/mL. Vitamin D status did not seem to be related to unilateral or bilateral fractures or to healing.

All were white females, average age 68.3 years (range 52 to 83). Mean *T*-scores were –1.0 at the lumbar spine and –1.1 at the total hip; only 2 subjects had WHO-defined osteoporosis (*T*-score –2.5 or lower) at the spine, femoral neck, or total hip, but 8 had prior fractures likely owing to osteoporosis. Mean duration of bisphosphonate therapy was 8.8 years (range 36 to 174 months [14.5 years]). The bisphosphonates used were alendronate alone ($n = 7$, cases 1, 2, 3, 5, 10, 11, and 14), ibandronate only ($n = 2$, cases 8 and 9), zoledronic acid only ($n = 1$, case 4), alendronate followed by ibandronate ($n = 2$, cases 6 and 13), and alendronate followed by risedronate ($n = 2$, cases 7 and 12). The type of bisphosphonate did not seem to correlate with fracture type (unilateral or bilateral) or healing status.

Baseline BMD, TBS, and BTM varied widely. Before initiation of teriparatide, bone-specific alkaline phosphatase was below the lower limit of the reference range for 5 patients (cases 1, 3, 8, 13, and 14), which included the 2 patients who had a subsequent AFF after starting treatment with teriparatide (cases 13 and 14). With the exception of a low C-telopeptide at baseline in case 3 (who also had a low BAP), osteocalcin and C-telopeptide were within the reference ranges at baseline.

At the initiation of teriparatide treatment, L_1 to L_4 spine BMD was available for all 14 subjects. Baseline spine BMD was 0.933 ± 0.143 g/cm^2 (mean $\pm$ SD, consistent with a *T*-score of –1.0), lowest was 0.731 g/cm^2, and highest was 1.188 g/cm^2 (individual spine BMD data not shown). At month 12, there was a nonsignificant increase of $3.1 \pm 4.0\%$, but by month 24, there was a significant increase of $6.1 \pm 4.3\%$ ($p < 0.05$) as shown in Fig. 1. Significant increases were found in 10 subjects between baseline and month 24 (4 increased at month 12 and were similarly increased at month 24 (cases 1, 5, 10, and 12), 4 increased at month 24 but not month 12 (cases 4, 6, 7, and 8), and 2 increased at month 12 and increased further at month 24 (cases 3 and 9). Spine BMD was stable from baseline to months 12 and 24 for 3 subjects (cases 2, 13, and 14), and 1 subject who did not have a month 12 spine measurement was not significantly different from baseline at month 12 (case 11).

At the initiation of teriparatide treatment, total hip BMD was available for 10 subjects. Baseline total hip BMD was 0.807 ± 0.117 g/cm^2 (mean $\pm$ SD, consistent with a *T*-score of –1.1), lowest was 0.640 g/cm^2, and highest was 0.978 g/cm^2 (individual hip BMD data not shown). Total hip BMD at month 12 ($-0.1 \pm 2.1\%$) and month 24 ($+0.4 \pm 3.2\%$) were not different from baseline, as shown in Fig. 1. Total hip BMD did not change significantly in 7 subjects at either month 12 or

Table 1. Baseline Demographics and Selected Responses to Teriparatide Treatment

	Incomplete fractures (2 bilateral, 3 unilateral)					Complete fractures, unilateral							Unilateral at entry contralateral fx during TPTD treatment	
Case no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age (years)	69	52	74	78	73	57	71	69	83	64	62	60	74	70
Prior fracture	Tibial stress fracture	None	None	Multiple vert fx	Right femur	None	Vert (L_3) tibial plateau	Left wrist ×2, knee	Vert (T_9, L_2), wrist	None	None	Left femur	None	Left femur
Lowest *T*-score	−2.4 FN	−1.3 L_1–L_4	−0.7 FN	−1.8 FN	−1.8 L_1–L_4	−0.8 L_1–L_4	−3.2 FN	−2.1 FN	−2.9 L_1–L_4	−1.2 FN	−1.7 FN	−1.6 L_1–L_4	−0.8 FN	−2.2 FN
25-OH D (ng/mL)	59	49	27	51	37	25	57	46	55	46	25	53	71	21
Long-term PPI use (years)	5		3	4			11	9			2			
BP type	ALN	ALN	ALN	ZOL	ALN	ALN, IBAN	ALN, RIS	IBAN	IBAN	ALN	ALN	ALN, RIS	ALN, IBAN	ALN
BP duration before fx (mos)	162	84	90	174	96	120	36	64	45	120	120	124	120	120
Time off BP before TPTD (days)	134	364	61	312	43	77	56	118	98	250	312	361	77	41
Time from fx to start of TPTD Rx (days)	160	360	52	66	122	67	97	60	138	131	282	410	75	60
Cause of AFF	Spont	Fall	Spont	Spont	Fall	Spont	Fall	Spont	Fall	Spont	Fall	Spont	Spont	Spont
Unilateral (L or R) or bilateral (B)	B simult	B simult	L	R	L	R	L	L	R	R	L	B, ∼1 year apart	R[a]	L[a]
Complete or incomplete	I	I	I	I	I	C	C	C	C	C	C	C	C	C
Fx status at month 12	L PH R no change	No change	PH	PH	PH	Nonunion	PH	PH	PH	PH	PH	Healed	R healed	Both healed
Fx status at month 24	Both healed	No change	PH	PH	ORIF healed	Nonunion	Healed	PH	Healed	PH	—	Healed	R healed L PH	R and L healed
Baseline BTM below LLN	BAP 8.2	0	CTX 97 BAP 9.4	0	0	0	0	BAP 7.8	0	0	0	0	BAP 9.9	BAP 7.2
MS/BS at baseline	2.59	6.73	0.95	1.82	2.43	b	4.72	0.91	5.15	2.84	2.00	2.44	b	1.04
MS/BS at month 12	3.40	7.36	5.22	c	1.21	1.09	7.67	4.01	2.55	3.81	c	4.11	4.81	2.74

[a]Two subjects who presented with unilateral fractures sustained a fracture on the contralateral side after starting teriparatide (11-02 at day 254, 12-06 at day 9). Both had a lateral stress reaction with beaking on baseline imaging on the femurs that later fractured.

[b]Two subjects (cases 6 and 13) had no tetracycline labels on baseline biopsies so MS/BS could not be calculated.

[c]Two subjects (cases 4 and11) did not have bone biopsies at Month 12.

Vert = vertebral, ALN = alendronate, RIS = risedronate, IBAN = ibandronate, ZOL = zoledronic acid, TPTD = teriparatide, Spont = spontaneous, Simult = simultaneous, PH = partial healing, ORIF = open reduction, internal fixation (surgery).

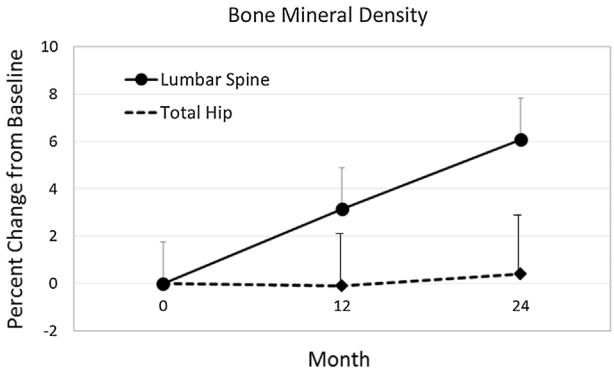

Fig. 1. Response to teriparatide treatment on bone mineral density (BMD) in the lumbar spine and total hip.

month 24 compared with baseline (cases 1, 2, 3, 4, 6, 8, and 10); in 1 patient (case 7), total hip BMD increased at month 12 and was similarly increased at month 24, in 1 patient (case 9), total hip BMD did not change significantly from baseline to month 12 but was higher at month 24, and 1 patient (case 11) did not have a month 24 measurement but did not change significantly from baseline to month 12. At month 24, mean total hip BMD was $0.813 \pm 0.115\ g/cm^2$, not significantly different from pretreatment baseline.

At the initiation of teriparatide treatment, TBS measurements were available for all subjects. Baseline TBS was 1.300 ± 0.100 (mean $\pm$ SD), lowest was 1.084, and highest was 1.412 (individual TBS data not shown). Least significant change for TBS, calculated in a different cohort, was 0.064. At months 12 and 24, mean TBS was not significantly different from baseline, but individual responses varied. With teriparatide treatment, 9 subjects had similar TBS values at baseline and month 24 (7 with no difference at month 12 or month 24 [cases 1, 2, 4, 5, 8, 10, and 13]), 2 who were lower at month 12 but back to baseline at month 24 (cases 9 and 12), 3 were higher than baseline at month 24 (2 were higher at both month 12 and month 24 (cases 3 and 14), 1 was not changed at month 12 but higher at month 24 (case 7), 1 decreased at month 12 and was similarly lower than baseline at month 24 (case 6), and 1 subject had TBS at month 12 (increased from baseline) but not at month 24 (case 11). At month 24, mean TBS was 1.324 ± 0.088, not significantly different from pretreatment baseline.

Bone turnover markers, shown in Fig. 2, followed the expected course in patients previously treated with bisphosphonates and then changed to teriparatide.[27]

By CT, after 24 months of teriparatide treatment, healing was found in 6 subjects (cases 1, 5, 7, 9, 12, and 14), including 1 patient with bilateral incomplete fractures that healed without the need for surgery (case 1). For the other 3 patients who had incomplete fractures, the fracture previously operated on had healed, but the other 3 showed either no change (cases 2 and 3) or slight healing (case 4). One patient with a unilateral complete fracture (case 6) showed nonunion at 24 months. One patient (case 13) showed healing of a complete fracture that occurred before starting teriparatide treatment but incomplete union of a contralateral fracture that occurred on day 254 of treatment. Case 11 dropped out because of side effects before month 24 but had partial healing of her fracture at month 12.

Baseline biopsies were available on 14 patients; all had normal osteoid surface percent and osteoid width. Values for MS/BS are shown in Table 2. Two patients did not have a biopsy at month 12 (case 4 developed medical problems that made doing the biopsy unwise and case 11 withdrew because of side effects from teriparatide). The reference range for MS/BS for young women is 4.73% to 14.63% ($9.68 \pm 4.95\%$). Two patients (cases 6 and 13) had no double tetracycline labels at baseline (MS/BS cannot be calculated without double labels), and neither healed their fractures with teriparatide treatment.

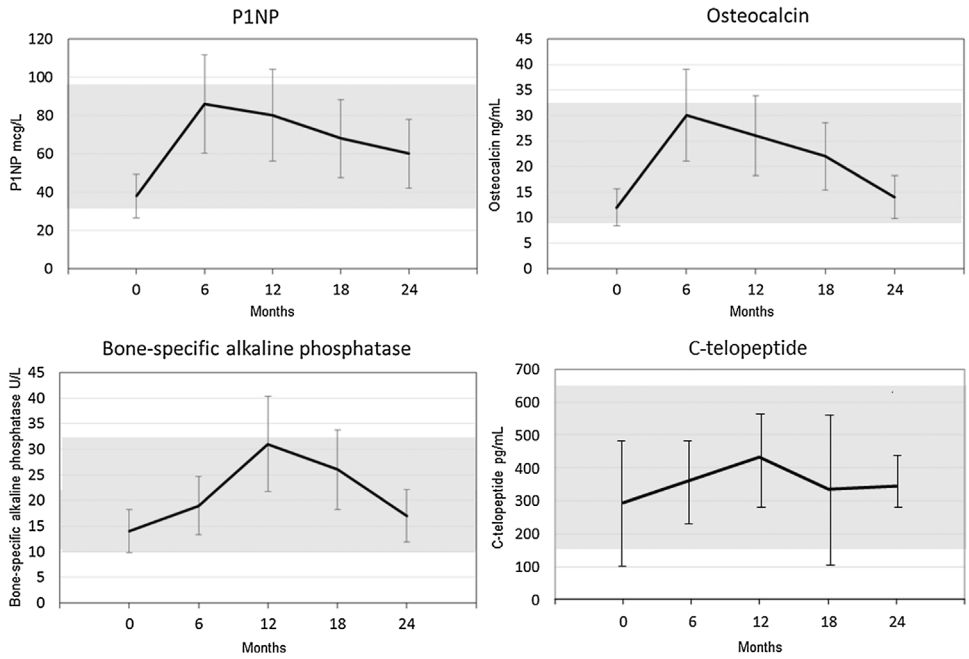

Fig. 2. Bone turnover marker (BTM) response to teriparatide treatment. Shaded areas represent reference ranges for health young women.

Table 2. Mineralizing Surface to Bone Surface (MS/BS) at Baseline and Month 12 (Units Are Percent)

	Subject	Baseline	Month 12
Patients with unilateral fractures	1	2.59	3.34
	2	6.73	7.36
	3	0.95	5.13
	4	1.82	[b]
	5	2.43	1.21
Patients with unilateral complete fractures	6	[a]	1.09
	7	4.72	7.67
	8	0.91	4.01
	9	5.15	2.55
	10	2.84	3.81
	11	2.00	[b]
	12	2.44	4.11
Patients with unilateral complete fractures at baseline who sustained a contralateral fracture during teriparatide treatment	13	[a]	4.81
	14	1.04	2.74
Counting those with no baseline value as zero and those with no month 12 biopsies as zero	Mean ± SD	2.33 ± 1.96	3.22 ± 2.39
Counting those with no baseline values as zero and excluding 4 and 11 with no month 12 biopsies	Mean ± SD	2.40 ± 2.12	3.76 ± 2.07
Excluding those with no baseline values (6 and 13) and those with no month 12 biopsies	Mean ± SD	3.60 ± 1.96	4.90 ± 2.04

[a]Patients 2 and 4 had no double labels at baseline but did have double labels at month 12.
[b]Patients 14 and 19 did not have biopsies at month 12.

Three of the subjects (cases 2, 5, and 9) had normal MS/BS values at baseline (cases 2 and 5 had incomplete fractures that did not heal; case 9 had a complete fracture that healed), but the remaining 7 patients with measurable MS/BS were low, ranging from 0.91% to 4.72%. Mean MS/BS at baseline was 2.33 + 1.96% counting the 2 patients without labels as zero and 2.40 ± 2.12% for the 12 patients with numeric baseline MS/BS values. For the 10 patients with baseline labels and a month 12 biopsy, baseline MS/BS was 3.60 ± 1.96% and month 12 was 4.90 ± 2.04%. Only 2 of the patients (cases 5 and 9) had a decrease in MS/BS from baseline to month 12. Two patients who were low at baseline had normal values at month 12 (cases 3 and 7). The two patients whose baseline biopsies did not contain tetracycline labels (cases 6 and 13) both had labels at month 12; case 6 was a nonunion at month 24 and case 13 healed the AFF that was present on entry but showed only partial healing of the fracture that occurred while on teriparatide treatment.

Discussion

Included in this prospective open-label study of patients previously treated with bisphosphonates who sustained AFF and then were treated with teriparatide were 14 women, some with incomplete fractures and some with bilateral fractures. There was heterogeneity at baseline for all parameters measured—BMD, BTM, TBS, MS/BS—as well as heterogeneity in responses to teriparatide treatment. As best we could tell, none of the likely factors that might influence response (age, BMD, baseline BMD, BTM or MS/BS, complete versus incomplete fracture, type or duration of prior bisphosphonate therapy) were predictive of any pattern of response.

Bone formation by histomorphometry in these patients with AFF was lower than published normal controls, consistent with previous reports; however, all but 2 our patients had histomorphometric evidence of turnover and MS/BS was normal at baseline in 2 patients. Overall there was a significant increase in all BTMs and lumbar spine BMD but no changes in BMD at the total hip. These observations are consistent with previous reports of patients without AFF who were changed from bisphosphonate treatment to teriparatide and confirm that the anabolic effect of teriparatide is found in patients after AFF.[27]

For the group, osteoblast-derived bone formation markers increased with teriparatide. We previously reported that an increase in PINP of >10 mcg/L with teriparatide administration is associated with either an increase in BMD and/or improvement in bone microstructure;[26,28] in this study, mean P1NP increased from 48 ± 29 mcg/L to 106 ± 33 mcg/L at month 6 and remained at least >10 mcg/L over baseline at month 24 (60 ± 22 mcg/L). We did not see a change in TBS after teriparatide treatment,

which is different from findings in a study in nonbisphosphonate-exposed subjects receiving teriparatide, where the TBS increased an average of 4.3% over time.[29,30]

For the group, the baseline MS/BS values were heterogeneous. The mean baseline MS/BS was lower than published normal controls for MS/BS ($2.33 \pm 1.96\%$ versus $9.68 \pm 5.95\%$). The MS/BS at baseline was similar to the MS/BS found in previous clinical trials for bisphosphonate-treated subjects who did not have AFF.[20,31,32] Two of our subjects had no tetracycline labels at baseline (as was found in 8 of 15 patients in our earlier report of bisphosphonate-associated AFF.[24] Nevertheless, they did develop tetracycline labels with teriparatide administration.

Two changes were made for patients in this study: discontinuation of their bisphosphonate and addition of teriparatide. The gap between study entry and bone biopsy before teriparatide administration was an average of 8 weeks. It could be argued that changes in MS/BS or BTM were related to bisphosphonate discontinuation rather than teriparatide administration. However, these patients had previously been on long-term bisphosphonates where the unique pharmacology argues in favor that the improvement in bone formation parameters were because of the anabolic nature of teriparatide rather than bisphosphonate discontinuation.

Fracture healing assessment is qualitative, not quantitative, and the number of subjects with incomplete, non-operated AFF was small ($n = 4$). Fracture healing may be irrelevant after surgical correction. In our 4 patients with incomplete fracture who did not require surgical intervention, after 24 months of teriparatide, 1 healed, 1 showed partial healing, and 2 showed no healing. To definitively assess the effect of teriparatide (or other intervention) would require a control group with no intervention (other than stopping bisphosphonates). Because teriparatide does not appear to be associated with an increased risk of AFF and is thought by some to be associated with improved healing of fractures,[33] including AFF,[34,35] it is often prescribed to patients after AFF who are at high risk of fractures at other sites. Thus, finding sufficient subjects with incomplete AFF and implementing a trial to compare teriparatide treatment with nonintervention would be difficult.

Our current report offers some important insights: Bone formation by histomorphometry in these patients with AFF is lower than published normal controls, consistent with previous reports; however, all but 2 of our patients had histomorphometric evidence of turnover and MS/BS was normal at baseline in 2 patients. BMD and BTM responded to teriparatide treatment as would be expected—the AFF in these patients did not seem to influence the response.

There are at least 2 reasons to consider teriparatide treatment in patients with AFF: for fracture healing and to reduce the risk of future fractures resulting from osteoporosis. Our data support the anabolic effects of teriparatide in this context, with improvement in anabolic bone turnover markers and lumbar spine BMD. However, we did not find a consistent effect of teriparatide on healing of the AFF.

Disclosures

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