Recurrent Vertebral Compression Fracture while on Bisphosphonate Therapy – What is the Next Best Step in Management?

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Abstract: Bisphosphonates are widely used in the treatment of osteoporosis. They are highly effective in both increasing bone mass and preventing fractures in patients with osteoporosis. However, while osteoporosis treatment lowers the risk of fracture, almost half of the elderly suffer new fractures in their lifetime and many experience recurrent fractures during bisphosphonate therapy. Assessing the effectiveness of bisphosphonate therapy is problematic. Bone mineral density and markers of bone turnover are often used, but the true measure of effectiveness is prevention of new fractures. In this case report, we describe a severely osteoporotic patient who suffered a recurrent vertebral compression fracture during bisphosphonate therapy. In this case, bone turnover markers were markedly suppressed most likely as a result of bisphosphonate therapy or a combination of steroid and bisphosphonate therapy. As a result of the fracture, oral alendronate (a bisphosphonate) therapy was discontinued. We discuss the importance of understanding why some patients incur fractures while on bisphosphonate therapy and creating individualized treatment plans in these cases based on each patient's physiology. Bisphosphonate therapy may suppress bone turnover, promote micro-fracture accumulation and facilitate development of recurrent fractures, particularly in patients taking glucocorticoids. Therefore, physicians should investigate the bone turnover rate for patients suffering a fracture while taking bisphosphonates, especially after a patient experiences recurrent fracture or is taking other medications known to adversely affect bone turnover. Furthermore, investigation of bone turnover prior to initiation of osteoporosis therapy, specifically after a recurrent fracture during bisphosphonate therapy, may provide additional, important information concerning the effectiveness of treatment options.

Keywords: Vertebral fractures, bisphosphonates, osteoporosis, bone turnover markers.

INTRODUCTION

Increased use of bisphosphonates (BP) in the United States has coincided with 30% decline in the rate of hip fracture in older adults [1]. BPs are highly effective in increasing bone mass and preventing fractures in patients with osteoporosis including cases induced by glucocorticoid therapy [2,3]. Appropriate BP therapy is also associated with the prevention of fracture associated functional decline, reduced hospitalizations, disability, the need for long term care and mortality [4,5]. While BP therapy significantly lowers the risk of fracture, almost half of elderly people experience a second fracture in their lifetime and many report recurrent fractures during BP therapy [6,7]. In some cases, long term BP therapy has led to severely suppressed bone turnover (SSBT) and cortical bone fractures, called atypical fractures [8]. It is not clear if these patients respond similarly, or favorably, to BP treatment [9,10]. In the FIT trial, Bauer and coauthors suggested that BPs were most effective in patients with elevated bone turnover prior to treatment [11]. Despite this data, the bone turnover rate is not routinely measured in patients before or during BP therapy for the treatment of osteoporosis, and there are no formal treatment recommendations based on a patient's bone turnover rate.

It is important to understand the underlying cause of fracture in patients who suffer a new fracture while on BP therapy. While some data suggests the fracture healing process might be adversely affected by BP therapy [12], the clinical data is limited and some studies have seen no clinically relevant difference in bone healing with BP administration [13,14]. In general, the recurrence rate of vertebral fractures is high (11-52%) and often occurs during BP therapy [7]. Due to inconclusive evidence, there is ongoing debate on what the role for BP use is after a recurrent vertebral fracture [7]. Of note, the studies that report conflicting results on

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E-ISSN: 2313-0954/15

the risk of recurrent vertebral fractures during BP therapy did not use bone turnover markers (BTMs) to monitor the bone turnover rate and thus are limited in understanding the relationship between BP therapy, suppressed bone turnover rate, and the risk of recurrent vertebral fractures [7]. In this case report, we discuss the importance of ordering bone turnover markers and the rationale for discontinuing BP therapy in a patient who sustained recurrent vertebral compression fracture on BP therapy.

CASE PRESENTATION

A 68 year old Asian woman was admitted to the hospital with history of sudden onset severe back pain while lying in her bed. Her past medical history was significant for hypertension, depression, bilateral knee osteoarthritis, multiple falls at home, urinary retention, multiple hospitalizations due to COPD exacerbation in the past year, as well as fractures of the left 2nd, 3rd, and 4th metatarsals after fall from standing height when walking to the restroom and T11, 12 and L1 and L4 vertebral compression fractures on a separate occasion (about 6 months ago). Her family history was negative for osteoporosis or maternal hip fracture. Social history was remarkable for 27 pack-year history of smoking until she quit smoking 6 months ago. She denied alcohol or recreational drug use. Medication history revealed the patient was taking calcium supplement, oral vitamin D supplement, oral and inhaled steroids and a proton pump inhibitor. Magnetic resonance imaging (MRI) on this admission (Figure **1**) showed increased vertebral height loss in L1 (80% central vertebral body height loss) compared to 4 months ago as well as a new compression fracture at L3 (30% ventral vertebral body height loss). Neurosurgery recommended against surgical intervention due to poor bone quality and treated the patient conservatively with a thoracolumbosacral orthosis (TLSO brace). The patient was given calcitonin nasal spray for pain and supplemental hydrocodone/acetaminophen as needed. Physical therapy was initiated with caution to restrict spine flexion to less than 30 degrees.

Bone mineral density (BMD) scan one year prior to the current admission confirmed osteoporosis (-2.8 T-score for both the left femoral neck and lumbar spine). After the BMD scan, the patient took alendronate for approximately 12 months before her primary care physician (PCP) discontinued it 3 months prior to the current hospitalization. The first month of treatment consisted of a daily dose of 10 mg orally, then a weekly dose of 70 mg orally followed. The reason for discontinuation is unknown.

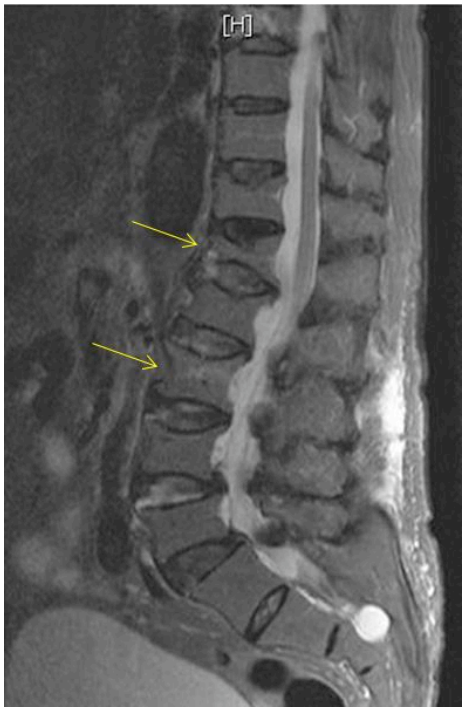

Figure 1: Midsaggital section of lumbar spine MRI.

A midsaggital section of the patient's MRI from the current admission showing increased vertebral height loss compared to 4 months ago. Arrows identify L1 and L3 each with 80% and 30% vertebral height loss, respectively.

While in the hospital, the patient was seen by the geriatrician on our fracture liaison team, who has expertise in osteoporosis and metabolic bone diseases. The geriatrician ordered a metabolic bone panel and BTMs including, osteocalcin (OC), bone-specific alkaline phosphatase (BAP), and fasting C-Telopeptide (CTX). Due to the risk of recurrence of vertebral fractures while taking alendronate and the patient's history of prior BP therapy and recurrent vertebral fracture during BP therapy, the geriatrician recommended against further BP therapy. Despite this recommendation, BP therapy was initiated by the hospitalist. It was subsequently stopped by the fracture liaison team. Of note, all serum sent for BTMs were sent prior to re-starting alendronate except fasting CTX. Delay of fasting CTX was due to difficulty in achieving a fasting, early morning sample (appropriate protocol), and as a result serum CTX was sent 12 days after hospital admission. Relevant laboratory results (Table **1**) demonstrate suppressed BTMs with an OC level below the normal range, and BAP and sCTX at the low end of the premenopausal normal range.

Table 1: Metabolic Assay Results and the Reference Range

	Results	Reference Range
25hydroxy vitamin D	38 ng/mL	>30
calcium	8.0 mg/dL	8.5-10.5
albumin	2.9 g/dL	3.5-5.0
PTH	37.9 pg/mL	11.1-79.5
magnesium	2.3 mg/dL	1.8-2.4
phosphorus	3.0 mg/dL	2.5-4.5
Serum creatinine	0.9 mg/dL	0.8 – 1.4
osteocalcin	5 ng/mL	8-32
BAP	10.2 mcg/L	5.6-29
Serum c-telopeptide (CTX)	223 pg/mL	40-465
Serum creatinine	0.9 mg/dL	0.5-1.4 mg/dL

DISCUSSION

This case report highlights the lack of consensus concerning bisphosphonate therapy after fracture. Our fracture liaison team feels that BPs should not have been prescribed after this patient presented with the fracture for three reasons. One, BPs may be detrimental for fracture healing acutely. Two, this patient suffered two vertebral compression fractures while on previous BP therapy, which may indicate a failure of BP therapy in her case. And three, although this patient had several risk factors for elevated bone turnover (recent menopause, recent fracture), she was found to low BTMs, which suggests further treatment with BP was not the best choice for reducing future fracture risk in her case.

The data related to the effects of bisphosphonates on fracture healing is inconclusive, but may depend on whether bone healing is direct in nature [12] or through callus formation and remodeling [15]. Alendronate treatment for one year did not alter fracture healing at the distal radius in a small group of postmenopausal osteoporotic women [16]. Conversely, a large case-controlled study demonstrated significant increase in the risk of humeral nonunion with BP treatment post fracture [17]. The results may also be dependent on the location of the fracture. In the HORIZON trial, there was no evidence of delayed healing regardless of the timing of zoledronic acid administration after fracture [13]. Bone healing can be significantly impacted by BP therapy in patients with suppressed bone turnover [18]. BP therapy should be discontinued in patients with atypical fractures and SSBT in order to prevent delayed or non-union of the fracture [8]. Glucocorticoid therapy is associated with atypical fractures and SSBT [8] and some authors question the use of BP in patients receiving prolonged glucocorticoid treatment [19]. Regardless of the association with glucocorticoid therapy, no human or animal studies have demonstrated that withholding BP in the immediate post-fracture period is detrimental, and for this reason we believe that the conservative approach of withholding BP therapy in the immediate post-fracture period is the best option.

Recently published guidelines suggest that osteoporosis treatment failure can be inferred if two or more fractures have occurred during treatment, if serial measurements of BTMs are not suppressed by anti-resorptive therapy, or if BMD continues to decrease despite therapy [9]. These guidelines assume that BTMs are known prior to therapy initiation, and that successful therapy would involve suppression of previously elevated bone turnover. We further suggest that if bone turnover is not elevated prior to initiation of BP therapy, as might be the case for a patient on long-term glucocorticoid therapy, there is little reason to suppose that BP therapy will be successful in suppressing them further. However, in this case we do not have information about pre-BP therapy BTM values, and this is commonly the case in osteoporosis patients. The gold standard for determining bone turnover rates is through a bone biopsy and histomorphometry. Although assessment of serum BTM has disadvantages such as high variability [20], these markers provide a glimpse into the bone turnover without requiring an invasive test. Even without information concerning the patient's status prior to treatment, serum BTMs after the fracture can provide important information to guide the future treatment for this patient.

There are few studies that can guide us with certainty whether or not to continue BP treatment in patients with low BTMs. In 2006, data from the FIT trial calculated the risk of fracture after initiation of BP therapy as a function of pre-treatment bone turnover rates [11]. Bone turnover was assessed using the biochemical markers BAP, serum CTX, and serum intact N-terminal propeptide of type 1 collagen (PINP). In this study, significant reduction in fracture risk was reported in patients with high initial BTMs. The data for

patients with low turnover demonstrated either no change in fracture risk, or even a slight, but not significant, elevation in fracture risk. While we cannot conclude that BP treatment is harmful in patients with low bone turnover, there is no evidence to suggest that bisphosphonates would be beneficial in reducing future fracture risk in patients with already low bone turnover who also suffered recurrent fracture during BP therapy. In these cases it may be prudent to consider other modalities of treatment such as denosumab or teriparatide as appropriate [21,22].

In conclusion, we submit a case that highlights the controversy of BP therapy in patients presenting with recurrent vertebral fracture. It is for these refractory, and difficult to treat situations that a sound, evidence based treatment algorithm is needed. Discontinuation of BP therapy and initiation of another treatment for osteoporosis seems to be the best next step for this patient. Our patient showed improvement in pain and calcitonin was stopped after 4 weeks. The patient was given information on possible treatment with anabolic agents (e.g., Teriparatide) that may promote bone formation and reverse suppressed bone turnover and was advised to follow up in our osteoporosis clinic after discharge.

DISCLOSURE

No funding sources or related presentations.

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Received on 12-01-2015 Accepted on 20-01-2015 Published on 27-05-2015

DOI: http://dx.doi.org/10.12974/2313-0954.2015.02.01.5