Do bisphosphonate-related atypical femoral fractures and osteonecrosis of the jaw affect the same group of patients? A pilot study

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Abstract

Bisphosphonates (BPs) are commonly used drugs in clinical practice. In this pilot study, we investigated whether bisphosphonate-related atypical femoral fractures (AFF) and osteonecrosis of the jaw (ONJ) occur simultaneously in the same group of patients. Six ONJ patients were examined by an orthopedic surgeon and 5 AFF patients were examined by a dentist to look for manifestations of simultaneous occurrence of AFF in ONJ patients and vice versa. The required radiological investigations and previous medical and dental records were available. No simultaneous occurrence of AFF and ONJ was found in the examined patients. In this pilot study with limited sample size, no manifestations of simultaneous occurrence of AFF and ONJ were found. This could be an indication that these complications have different pathophysiologies and affect different subgroups of patients on long-term BP treatment.

Introduction

Bisphosphonates (BPs) are the first-line armamentarium of osteoporosis treatment and thousands of patients have been on long-term therapy. BPs are also commonly used as an adjuvant therapy in patients with skeletal metastases, for instance from multiple myeloma, breast or prostate cancer. There are two main types of BPs: nitrogen containing and non-nitrogen containing. The former type, e.g., zoledronate, is more potent and administered as intravenous (i.v.) infusion, while the latter type, e.g. alendronate, is given orally. The net effect of both types is the inhibition of bone resorption by osteoclast cell apoptosis. Emerging complications of BP long-term therapy include atypical femoral fractures (AFF) and osteonecrosis of the jaw (ONJ).1 Fortunately, these complications are still rare but seem to be increasing owing to the large number of patients treated.2 Typically, AFF presents as a fragility fracture of the subtrochanteric or diaphyseal parts of the femur while ONJ presents as a healing disorder with necrosis and/or infection of the jaw bone after dental procedures, e.g. tooth extraction. The concomitant occurrence of these two complications has been reported in very few cases in the literature.3,4

In this pilot study, we investigated whether AFF and ONJ affect the same group of patients.

Materials and Methods

Between January 2008 and January 2012, 5 female AFF and 6 ONJ (5 females and 1 male) patients were treated at the Department of Orthopaedic Surgery and Department of Maxillofacial Surgery of our hospital, respectively. Patients’ characteristics are listed in Table 1. All AFF patients were treated with oral bisphosphonates because of a DEXA-verified osteoporosis, while in the ONJ group, 3 patients were treated with oral bisphosphonates because of a DEXA-verified osteoporosis, and 3 other patients with intravenous bisphosphonates for bone metastases secondary to breast cancer (n=2) and prostate cancer (n=1). In 2 patients with AFF, the fracture involved the femoral diaphysis just below the stem of a well-fixed hip prosthesis after a trivial trauma (fall in the same level). In the first patient, the prosthesis had been implanted eight years before the trauma while in the second patient the prosthesis had been implanted six years before the trauma. Both patients were slightly underweight [body mass index (BMI) 19 and 21].

Between March and June 2012, an orthopedic surgeon examined the ONJ patients when a complete orthopedic clinical examination was undertaken to exclude any manifestations of AFF changes. Plain radiographs (AP and lateral views) of the pelvis and femoral bones were taken. During the same period, a dentist...
examined the AFF patients with clinical and radiological examinations [plain radiographs with or without Cone Bean computed tomography (CT scan)] to exclude the presence of any sign of symptoms of ONJ. The previous available medical and dental records of the two groups were reviewed.

**Results**

The review of medical records, clinical and radiological examinations of the ONJ patients revealed no manifestations of AFF and the review of dental records, clinical and radiological examinations of the AFF patients revealed no manifestations of ONJ. The AFF patients had no laboratory features of infection [C-reactive protein (CRP) <30 mg/L, and white blood cell count (WBC) <10x10^9/L] apart from one patient with slightly elevated parameters due to an active lower urinary tract infection. In the ONJ group, all patients had normal CRP and WBC counts.

**Discussion and Conclusions**

Long-term therapy with BPs can give rise to severe inhibition not only for osteoclastic activity but also for osteoblastic activity. A severe suppression of bone turnover (SSBT) takes place. At the same time, mineralization of the osteoid tissue continues resulting in increased brittleness of bone. This acellular brittle bone fails to remodel; nor does it repair accumulated microfractures, a process that is required for normal bone metabolism. Another part of bone metabolism that is affected by BP therapy is the formation of new blood vessels and the significant reduction in circulating vascular endothelial growth factor (VEGF) levels. In AFF, fractures at the subtrochanteric or diaphyseal region of the femur occur after minimal or no trauma. Some patients record prodromal pain at the upper thigh while others sustain bilateral fractures. Radiologically, the affected area shows thickening of the lateral femoral cortex and transverse fracture line (Figure 1). In patients with hip arthroplasty, the fracture is usually located below the tip of the stem or cement mantle (Figure 2). On the other hand, patients with ONJ demonstrate mucosal healing disorder, necrosis with or without infection of the jaw bone (mandible, maxilla or both) for more than eight weeks after dental procedures such as tooth extraction (Figure 3), although spontaneous ONJ is also described. It is still unclear whether necrosis of the jaw bone occurs first to be followed by mucosal dehiscence and infection or whether infection initiates the whole process. ONJ has also been described in patients treated with denosumab. In his thorough review, Compston illustrated that the pathophysiological changes underlying ONJ differed from those underlying AFF. On the other hand, in their letter, Subramanian et al. advocated a common setting where combined osteoporotic bone changes and antiresorptive effects of BP attenuate bone remodeling to physiological stimuli. Despite the increasing number of AFF and ONJ reported in the literature, simultaneous occurrence of these two complications has only been reported in a very few number of patients, mainly after parenteral BPs for oncological diagnoses. Furthermore, no studies that actively investigated this occurrence have been published. In this pilot study, we found no such combination. Patients with ONJ developed their necrosis after a shorter period of BP therapy compared to patients with AFF (2.5 vs 7.5 years). This concurs with other reports that related ONJ to the cumulative effect of high-dose BPs in their intravenous form while AFF was related to the long duration of therapy with low-dose BPs leading to gradual fatigue failure. The main limitation of this pilot study is the small sample size. This is because patients with AFF and ONJ are not commonly seen patients in clinical practice or in a county hospital; the reported number represents the actual incidence of these complications. Another limitation is that ONJ can occur in AFF patients later on if they undergo dental procedures. However, our main study purpose was to actively look for any manifestations for concomitant AFF and ONJ changes. Further investigations are needed to approve or rule out any possible correlation between AFF and ONJ. This would help health care providers to plan adequate management of these patients in both medical and dental settings.

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