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Oral bisphosphonates-associated osteonecrosis in rheumatoid arthritis

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Abstract

Adverse effects associated with the use of bisphosphonates are infrequent and consist of pyrexia, renal function impairment, and hypocalcemia. Bisphosphonates-associated osteonecrosis of the jaws is an uncommon but potentially serious complication of intravenous bisphosphonate therapy in cancer patients. The degree of risk for osteonecrosis in patients taking oral bisphosphonates, such as alendronate, is uncertain and warrants careful monitoring. Oral bisphosphonates-associated osteonecrosis can occur in patients with rheumatoid arthritis. We report a case of mandibular osteonecrosis in a patient who received alendronate for 3.8 years. The pathology improved after bisphosphonate therapy discontinuation and sequestrectomy. To our knowledge there are only three cases published in the literature relating bisphosphonates-associated osteonecrosis of the jaws in patients with rheumatoid arthritis. All the cases published, including our case, have reported association between methotrexate, prednisone and alendronate sodium (Fosamax®) therapy. Corticosteroid therapy and dental surgery could increase the risk of developing bisphosphonates-associated osteonecrosis of the jaws in these patients.

Keywords: *Rheumatoid arthritis, osteonecrosis, bisphosphonates, alendronate.*

Case Report

In May 2006 a 73-year-old man with known rheumatoid arthritis treated with methotrexate (15 mg per week orally) and prednisone (5 mg daily orally) during 5 years was referred because of a 1-months history of pain in the left anterior mandibular region and hypoesthesia of the left inferior alveolar nerve. The patient reported left mandibular canine extraction in another centre two months before. Therapy with alendronate sodium (Fosamax® 70 mg orally once every week) was started 3.8 years before. Intraoral examination revealed a non-healing extraction site with exposed alveolar bone (<1 cm). The surrounding soft tissue was erythematous. The panoramic radiography and computerized tomography imaging showed a generalised lytic pattern of bony destruction with superimposed sclerosis of the left mandibular ramus (Fig.1A). The radiographic impression was osteomyelitis of the mandible. An incisional biopsy of the bone was performed. Histopathological examination revealed a necrotic osteitis associated with a mixed infiltrate of lymphocytes and granulocytes with medullary fibrosis and numerous Actinomyces colonies. Bis-

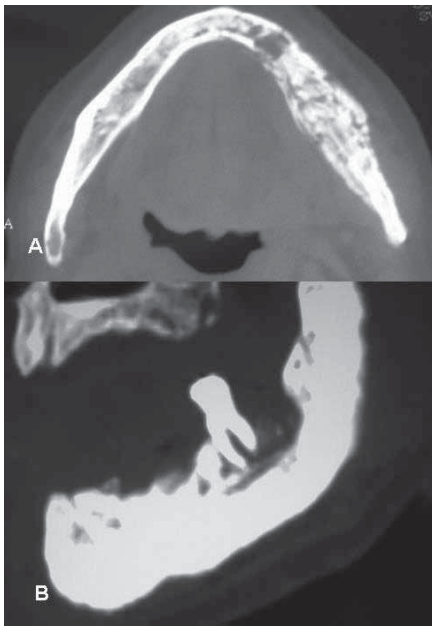

Fig. 1A. Computerized Tomography imaging showing a lytic pattern of bony destruction with sclerosis of the left mandibular ramus.

B. Multiplanar reconstruction of the mandible showing a bone sequestrum in left mandibular molar region.

phosphonates osteonecrosis jaw (BONJ) diagnosis was made, showing stage 2 following Ruggiero et al. classification (6). Conservative treatment was begun. First, we chose simultaneous oral antibiotic therapy (amoxicillin 4 gr/day, clavulanate 250 mg/day and fluconazole 100 mg/day), with chlorhexidine mouthwash. After 4 weeks, an examination revealed a complete closure of the fenestration. Mouth-washes with chlorexidine were maintained. Bisphosphonate therapy was not discontinued. Four months after, the patient presented pain and swelling in the left mandibular angle and trismus. Intraoral examination revealed a 1.5 cm. lingual posterior bone exposure. Multiplanar reconstruction of the jaws showed a bone sequestrum in left mandibular molar region (Fig.1B). Then, sequestrectomy and molar extraction were performed under local anesthesia. Bisphosphonate therapy was interrupted. After 1 year follow-up period the patient is still asymptomatic.

Discussion

Adverse effects associated with the use of bisphosphonates are infrequent and consist of pyrexia, renal function impairment, and hypocalcemia. Osteonecrosis of the jaws is a recently described adverse side effect of bisphosphonate therapy. Patients with multiple myeloma (MM) and metastatic carcinoma to the skeleton who are receiving intravenous, nitrogen-containing bisphosphonates are at greatest risk for osteonecrosis of the jaws; these patients represent 90% to 94% of published cases (7,8). The degree of risk for osteonecrosis in patients taking oral bisphosphonates, such as alendronate, is uncertain and warrants careful monitoring (9). Among several million patients who have received oral treatment for osteoporosis, fewer than 80 cases of osteonecrosis of the jaw have been reported to date (7,8). Moreover, with more than 60.000 patient-years of exposure to nitrogen-containing bisphosphonates in clinical trials of treatment for osteoporosis (involving follow-up for as long as 10 years in some patients), osteonecrosis of the jaw was not reported among the adverse events. On the one hand, given that not all reported cases have been confirmed to be osteonecrosis of the jaw, and on the other hand, that there may be underreporting, 1 in 100.000 patient-years is a reasonable estimate of the incidence of osteonecrosis of the jaw in patients receiving oral nitrogen-containing bisphosphonates (10). However, Mavrokokki et al. (11) referred that the frequency of BONJ in osteoporotic Australian patients, mainly on weekly oral alendronate was 1 in 2.260 to 8.470 (0.01% to 0.04%) patients. If extractions were carried out, the calculated frequency was 1 in 296 to 1.130 cases (0.09% to 0.34%). The total dose of oral alendronate at the onset of BONJ was 9.060 mgrs (+7.269). In general, these patients seem to have less severe manifestations of necrosis and respond more readily to treatment.

To our knowledge, there are only three cases published in the literature relating BONJ in patients with rheumatoid arthritis (8). All these cases reported association between methotrexate, prednisone and alendronate sodium (Fosamax®) therapy. The mean duration from first use of bisphosphonate to the first recognition of exposed bone in these cases was 4.3 years (8). This period was significant higher in those patients treated only with oral bisphosphonates (5.8 years) (8).

High sensitivity and specificity as a bone resorption marker is provided by a newly developed assay for degradation fragments of the C-terminal telopeptide of type I collagen that contain the b-isomerized octapeptide EKAHDb-GGR (b-CTx) (12,13). Serum measurement of b-CTx may provide a new commercially viable and relevant serum assay to guideline as to when oral surgical procedures can be accomplished with low risk in those patients receiving oral bisphosphonates (8). However, the use of bone markers as prognostic tools during therapy has remained academic, pending robust information from large clinical trials (14).

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