Bisphosphonate-Induced Osteonecrosis of the Jaws, Bone Markers, and a Hypothesized Candidate Gene

Steven Lehrer, MD, André Montazem, MD, DMD,†*
Lakshmi Ramanathan, PhD,‡
Melissa Pessin-Minsley, MD, PhD,§ John Pfail, DDS,‖
Richard G. Stock, MD,¶ and Rita Kogan, BS#

Purpose: To determine whether any abnormality in serum bone markers is related to bisphosphonate-induced osteonecrosis of the jaw.

Materials and Methods: We obtained serum bone markers and other relevant endocrine assays on 7 patients with osteonecrosis of the jaws (ONJ). The assays were C-telopeptide, N-telopeptide, bone specific alkaline phosphatase, osteocalcin, intact parathyroid hormone, T3, T4, TSH, and vitamin D 25 hydroxy. Diagnostic criteria for ONJ were those formulated by the American Association of Oral and Maxillofacial Surgeons.

Results: Five of our patients were women. Two had metastatic breast cancer and had been treated with zoledronic acid; 1 had also received pamidronate. Three others had osteoporosis and had been treated with daily alendronate. One man had metastatic prostate cancer treated with zoledronic acid. Another man had Gaucher's disease treated with zoledronic acid. All patients had been withdrawn from bisphosphonate for at least 6 months. None was taking or had taken corticosteroids. None of the lesions had shown any significant healing and all were still causing the patients considerable distress, yet the bone markers were within the normal range as measured in our laboratory, except for intact parathyroid hormone, which was slightly elevated in 1 case of metastatic breast cancer (177 pg/mL).

Conclusions: We hypothesize that matrix metalloproteinase 2 (MMP2) is a candidate gene for bisphosphonate-induced ONJ for 3 reasons: *1*) MMP2 is associated with bone abnormalities which could be related to ONJ. *2*) Bisphosphonates are associated with atrial fibrillation, and MMP2 is the only gene known to be associated with both bone abnormalities and atrial fibrillation. *3*) A network of disorders and disease genes linked by known disorder-gene associations indicates that cardiovascular disease and bone disease are closely related, suggesting that a single drug such as bisphosphonate, acting on a single gene, MMP2, could have both bone and cardiovascular side effects different from the osteoclast inhibition that is characteristic of bisphosphonate.

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Osteonecrosis of the jaws (ONJ) affects the mandible about twice as often as the maxilla, and has emerged as a complication of bisphosphonate treatment.[1] The estimated ONJ incidence among patients receiving zoledronic acid is 10% and the mean time to the onset of osteonecrosis 18 months.[2] The ONJ risk may increase for patients taking corticosteroids.[3,4]

Treatment for ONJ consists primarily of antibiotics for localized infection and analgesics for pain. Teriparatide (parathyroid hormone) injections may be of benefit.[5]

We previously reported that serum bone markers are within normal limits in ONJ patients.[6] We have increased our sample size, included in our new results

Received from Mount Sinai School of Medicine, New York, NY.
*Associate Professor, Department of Radiation Oncology.
†Associate Professor, Department of Dentistry.
‡Assistant Professor, Department of Pathology.
§Associate Professor, Department of Pathology.
‖Associate Professor, Department of Dentistry.
¶Professor and Chairman, Department of Radiation Oncology.
#Senior Laboratory Supervisor, Department of Pathology.
Address correspondence and reprint request to Dr Lehrer: Radiation Oncology, Box 1236, Mount Sinai Medical Center, 1 Gustave L. Levy Place, New York, NY 10029; e-mail: stevenlehrer@hotmail.com

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Table 1. BONE MARKERS AND OTHER RELEVANT ENDOCRINE ASSAYS FOR 7 ONJ PATIENTS IN THIS STUDY (MEAN ± SD)

		Normal
Calcitonin		
<2	pg/ml	0-5
TSH		
1.51 ± 0.90	μIU/mL	0.35-5.5
T4		
7.56 ± 1.79	mcg/dl	4.5-10.9
T3		
100.43 ± 31.66	ng%	79-149
N-Telopeptide		
16.79 ± 6.49	Pmol/L	8.2-34
C-Telopeptide		
459.26 ± 323.37	pg/mL	32-580
Vitamin D 25 Hydroxy		
29.93 ± 20.23	ng/ml	9.5-52
Alk Phos Bone Specific		
9.77 ± 3.59	μg/l	0-21.3
Osteocalcin		
9.96 ± 10.19	ng/ml	9.4-47.4
Intact Parathyroid Hormone		
96.00 ± 69.40	pg/ml	16-87

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below, and hypothesize a gene that may be involved, matrix metalloproteinase 2.

Methods and Results

After Mount Sinai Institutional Review Board approval of our proposed study, we obtained bone markers and other relevant endocrine assays on 7 patients with ONJ. The markers and assays are those generally recommended for evaluation of osteopenia.[7] Diagnostic criteria for ONJ were those formulated by the American Association of Oral and Maxillofacial Surgeons.[8] Five of our patients were women. Two had metastatic breast cancer and had been treated with zoledronic acid; one had also received pamidronate. Three others had osteoporosis and had been treated with daily alendronate. One man had metastatic prostate cancer treated with zoledronic acid. Another man had Gaucher's disease treated with zoledronic acid. Assay results are shown in Table 1. All patients had been withdrawn from bisphosphonate for at least 6 months. None was taking or had taken corticosteroids. None of the lesions had shown any significant healing and all were still causing the patients considerable distress. However, the bone markers were within the normal range as measured in our laboratory, except for intact parathyroid hormone, which was slightly elevated in 1 case of metastatic breast cancer (177 pg/mL).

Discussion

Marx et al[4] have proposed the following mechanism for ONJ: because the jaws have a greater blood supply than other bones, and a high bone turnover rate related both to their daily activity and the presence of teeth (which mandates daily bone remodeling around the periodontal ligament), bisphosphonates are highly concentrated in the jaws. Coupled with chronic invasive dental diseases and treatments and the thin mucosa over bone, this anatomic concentration of bisphosphonates might cause osteonecrosis to be manifested exclusively in the jaws; that is, the exposed bone in the jaws is the direct result of the action of bisphosphonates on the daily remodeling and replenishment of bone. A weakness in this mechanism is that it does not explain why bisphosphonates have a predilection for causing ONJ, while corticosteroids by themselves predispose to osteonecrosis of the femoral head but not ONJ.[9,10]

Migliorati et al[1] have posited that there might be genetic differences that produce a unique response to bisphosphonates in susceptible individuals, and that genetic polymorphisms could account for an increased risk of bisphosphonate-associated ONJ. We wish to suggest a candidate gene: matrix metalloproteinase 2 (MMP2).

Proteins of the matrix metalloproteinase (MMP) family are involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling, as well as in disease processes, such as arthritis and metastasis. MMP2 mutations have been associated with Winchester syndrome (dwarfism resulting from disturbances of the skeletal-articular system),[11] Torg syndrome (multicentric osteolysis),[12] and nodulosis-arthropathy-osteolysis syndrome (NAO syndrome).[13]

MMP2 is a candidate gene for bisphosphonate-induced ONJ for 3 reasons:

1) MMP2 is associated with bone abnormalities, described above, which could be related to ONJ.
2) Zoledronic acid[14] and alendronate[15,16] have been linked to atrial fibrillation, although the link to zoledronic acid has been questioned.[17] MMP2 is the only gene known to be associated with bone abnormalities and atrial fibrillation.[18,19]
3) A network of disorders and disease genes linked by known disorder-gene associations indicates that cardiovascular disease and bone disease are related,[20] suggesting that a single drug such as bisphosphonate, acting on a single gene, MMP2, could have both bone and cardiovascular side

effects different from the osteoclast inhibition that is characteristic of bisphosphonate.

Therefore, it would be worthwhile to do further studies of (MMP2) in bisphosphonate–induced ONJ patients and patients on bisphosphonate without ONJ to determine whether (MMP2) polymorphisms or (MMP2) expression might play a role in bisphosphonate–induced ONJ.

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