Editorial

Osteonecrosis of the Jaw and Rheumatoid Arthritis. Is It the Disease or the Drugs?

Bisphosphonates (BP) are a widely used class of drugs indicated for the prevention and treatment of postmenopausal and steroid-induced osteoporosis, Paget's disease of bone, hypercalcemia of malignancy, multiple myeloma, and bone metastases associated with breast, prostate, lung, and other solid tumors[1,2,3,4]. In late 2003, a letter to *The Journal of Oral and Maxillofacial Surgery* described 36 patients who developed avascular necrosis of the jaw after receiving intravenous BP[5]. Twenty-four patients were taking pamidronate (90 mg monthly) and 12 patients were receiving zoledronate (4 mg monthly). Patients were receiving BP for multiple myeloma (18), metastatic breast cancer (17), and osteoporosis (1). All patients presented with painful, necrotic bone in the mandible (80%), maxilla (14%), or both (6%). In 78% of cases, the necrosis was associated with a history of tooth extraction. The remainder of cases appeared to arise spontaneously[5]. In late 2004, Ruggiero, *et al*[6] reported on 63 cases of BP-associated osteonecrosis accrued over a 26-month period from 2 medical centers. Twenty-eight of the 63 patients had multiple myeloma, 21 patients had breast cancer, 3 patients had prostate cancer, and 1 patient each had lung cancer, uterine leiomyosarcoma, plasmacytoma, and leukemia. All patients within the oncologic group were receiving chemotherapy and/or corticosteroids. Seven patients were diagnosed with osteoporosis and had no history of treatment with chemotherapeutic agents or corticosteroids. Fifty-four of 63 patients reported a recent extraction at the necrotic site while the remaining 9 patients had apparent spontaneous bone exposure. The reported length of BP therapy in this series ranged from 6 to 48 months although the treatment time for each individual patient was not specified. In a followup report to their 2003 letter, Marx, *et al* documented an additional 119 patients with osteonecrosis of the jaw (ONJ). Similar to other case series, the majority of patients were undergoing treatment for multiple myeloma (52.1%) and metastatic breast cancer (42%)[7].

Osteonecrosis of the jaws (ONJ) is a clinical term that has been defined by a number of professional associations[8,9,10]. Although there are slight differences in the various definitions, all involve a breach in mucosa leading to exposed bone that fails to heal in 6 to 8 weeks. Further, there should be no history of head and neck radiation in the affected patients. Over the past several years, there have been numerous case reports and case series as well as several retrospective and prospective studies that suggest a strong association between BP therapy and ONJ; however, a definitive cause-and-effect relationship between the 2 has yet to be clearly established. Recently, denosumab (Dmab), a receptor activator of nuclear factor-κB ligand inhibitor was approved for similar indications to BP, and has also been strongly associated with ONJ[11]. While the occurrence rate of ONJ in oncology patients for both BP and Dmab ranges from 1.5% to 15%, patients treated with these agents for benign conditions appear to have a much lower incidence of ONJ (1/10,000–1/100,000)[9,12,13]. Further, the role that glucocorticoids, chemotherapeutic agents, and disease-modifying antirheumatic drugs (DMARD) play in the development of ONJ has not been clearly defined but appears to be significant. Many questions regarding the incidence, pathophysiology, and natural history of this condition still need to be answered.

BP are commonly used in patients with rheumatoid arthritis (RA) for treatment and/or prevention of osteoporosis (idiopathic or steroid-induced). In this issue of *The Journal,* Lescaille, *et al* report on a retrospective chart review of patients with ONJ treated over a 5-year period in a Parisian hospital setting[14]. Fifteen of 112 cases of ONJ occurred in patients treated for nonmalignant diseases. These cases were reviewed for comorbidities, as well as clinical course, treatment, and outcomes. The study found that mean time to onset of ONJ in 12 of 15 patients was 36 months, similar to the published literature. Eight patients in this cohort were diagnosed with RA and all but one were

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receiving medications in addition to BP that affect bone turnover (prednisone 5/8 patients, methotrexate 3/8 patients, DMARD 2/8 patients). The clinical, radiographic, and histological aspects of ONJ did not appear to be altered by the presence of RA. Prior to the current report by Lescaille, *et al,* a number of case reports[7,15] and a recent literature review by Conte-Neto *et al* using the US National Library of Medicine database Pubmed/Medline identified 28 ONJ cases in patients receiving oral BP who were diagnosed with RA[16]. In addition, O'Ryan and Lo[12] recently reported on a large retrospective cohort of patients receiving BP for benign conditions from 2004 to 2011 from Kaiser-Permanente, northern California, USA. In this study 30 cases of ONJ were identified, of which 4 patients had RA. While the age, sex, and BP exposure in the Kaiser-Permanente population was similar to that reported by Lescaille, *et al*, the initiation rate of ONJ secondary to a traumatic event was significantly lower than in the current study (51.7% vs 86.6%). A study from southeastern Scotland by Malden and Lopes[17] on alendronate-associated ONJ drew from a population of 900,000 patients. Drug prescriptions, monitored by a government agency, were used to identify 11 ONJ cases, of which 4 patients were reported to have RA. Patient demographics from the Scottish population were comparable to that reported by Lescaille, *et al*, with initiation of ONJ lesions by trauma somewhat lower than in the current study (64% vs 86.6%). Previous reports, with the addition of the 8 cases described here by Lescaille, *et al,* appear to indicate that RA may represent a significant risk factor for the development of ONJ when BP are used to treat benign conditions. Unfortunately, this conclusion may indeed be flawed because a review of the data from the above studies showed that in almost every report the patients with RA were taking steroids, DMARD, methotrexate, or a combination of these immunosuppressive agents. In the Lescaille series only 1/8 patients with RA was *not* taking any immunosuppressive agent; however, the authors do not indicate whether historical prescription data were available in their cohort. Data from the Kaiser-Permanente study revealed that 7/30 (23%) were taking steroids and 5/30 (17%) were taking DMARD. The Scottish study reported that 6/11 cases (55%) were treated with steroids. Further, the Conte-Neto review reported that 19/28 (39%) patients were receiving steroid therapy although 4 patients in their analysis from a study by Manfredi, *et al* were reportedly not taking immunosuppressive agents. However, upon critical review of the methodological section, it was noted that 3/4 RA patients were receiving methotrexate[18].

Glucocorticoids are well known to inhibit wound healing in both soft tissue and bone. In fact, many believe that the exposed bone that occurs in ONJ represents an inability of oral tissues (mucosa, submucosa, and bone) to respond to traumatic injury[19]. Additionally, methotrexate appears to be toxic to the oral epithelium. Several animal models of ONJ (Sonis, *et al*[20]; Abtahi, *et al*[21]) have shown that steroids in addition to BP and surgical trauma are required to induce ONJ-like lesions. In the current study by Lescaille, *et al*, as well as the above-cited literature, the number of patients with RA who were taking steroids or other immunosuppressive agents was high. As the authors have indicated in their discussion, even in a large retrospective study using significant data manipulation, it may be impossible to determine whether RA alone or in combination with steroids or DMARD is a significant risk factor for the development of ONJ. Ideally, a prospective cohort of RA patients would be required to improve the understanding of the relationship of this disorder and its therapies to ONJ. Finally, RA is a chronic, systemic disorder whose pathophysiology involves both inflammatory and autoimmune mechanisms, and the contribution of these factors to ONJ risk cannot be underestimated. The current study demonstrates the challenges of discerning all of the critical clinical factors that predispose to the development of ONJ. Additionally, there may be local oral, genetic, or biochemical factors that influence individual susceptibility. It appears that it may be extremely difficult, if not impossible, to separate RA from other risk factors for ONJ. The current study by Lescaille, *et al*, points out the critical need for further research in ONJ, an important clinical condition that significantly affects patients both with benign and malignant disease.

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REFERENCES

1. Major P. The use of zoledronic acid, a novel, highly potent bisphosphonate, for the treatment of hypercalcemia of malignancy. Oncologist 2002;7:481-91.
2. Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. Cancer J 2001;7:377-87.
3. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002;94:1458-68.
4. Van Poznak CH. The use of bisphosphonates in patients with breast cancer. Cancer Control 2002;9:480-9.
5. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 2003;61:1115-7.
6. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL.

Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 2004;62:527-34.
7. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. J Oral Maxillofac Surg 2005;63:1567-75.
8. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 2009;67 Suppl:2-12.
9. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2007;22:1479-91.
10. Kyle RA, Yee GC, Somerfield MR, Flynn PJ, Halabi S, Jagannath S, et al. American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. J Clin Oncol 2007;25:2464-72.
11. Saad F, Brown JE, Van Poznak C, Ibrahim T, Stemmer SM, Stopeck AT, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol 2012;23:1341-7.
12. O'Ryan FS, Lo JC. Bisphosphonate-related osteonecrosis of the jaw in patients with oral bisphosphonate exposure: clinical course and outcomes. J Oral Maxillofac Surg 2012;70:1844-53.
13. Felsenberg D, Hoffmeister B, Amling M, Mundlos S, Seibel MJ, Fratzl P. Kiefernekrosen nach hoch dosierter bisphosphonattherapie [Jaw necrosis after high-dose bisphosphonate therapy]. Dtsch Arstebl 2006;103:A3078.
14. Lescaille G, Coudert AE, Baaroun V, Javelot M-J, Cohen-Solal M, Berdal A, et al. Osteonecrosis of the jaw and nonmalignant disease: is there an association with rheumatoid arthritis? J Rheumatol 2013;40:781-6.
15. Park W, Kim NK, Kim MY, Rhee YM, Kim HJ. Osteonecrosis of the jaw induced by oral administration of bisphosphonates in Asian population: five cases. Osteoporos Int 2010;21:527-33.
16. Conte-Neto N, Bastos AS, Marcantonio RA, Junior EM. Epidemiological aspects of rheumatoid arthritis patients affected by oral bisphosphonate-related osteonecrosis of the jaws. Head Face Med 2012;8:5.
17. Malden N, Lopes V. An epidemiological study of alendronate-related osteonecrosis of the jaws. A case series from the south-east of Scotland with attention given to case definition and prevalence. J Bone Miner Metab 2012;30:171-82.
18. Manfredi M, Merigo E, Guidotti R, Meleti M, Vescovi P. Bisphosphonate-related osteonecrosis of the jaws: a case series of 25 patients affected by osteoporosis. Int J Oral Maxillofac Surg 2011;40:277-84.
19. Landesberg R, Woo V, Cremers S, Cozin M, Marolt D, Vunjak-Novakovic G, et al. Potential pathophysiological mechanisms in osteonecrosis of the jaw. Ann NY Acad Sci 2011;1218:62-79.
20. Sonis ST, Watkins BA, Lyng GD, Lerman MA, Anderson KC. Bony changes in the jaws of rats treated with zoledronic acid and dexamethasone before dental extractions mimic bisphosphonate-related osteonecrosis in cancer patients. Oral Oncology 2009;45:164-72.
21. Abtahi J, Agolme F, Sandberg O, Aspenberg P. Bisphosphonate-induced osteonecrosis of the jaw in a rat model arises first after the bone has become exposed. No primary necrosis in unexposed bone. J Oral Pathol Med 2012;41:494-9.

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