JOURNAL OF BONE AND MINERAL RESEARCH
Volume 21, Number 10, 2006
Published online on July 17, 2006; doi: 10.1359/JBMR.060712

Editorial

Osteonecrosis of the Jaw: More Research Needed

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I was gratified to be able to answer promptly and I did. I said I didn't know.

—*Life on the Mississippi;* Mark Twain

In the past 2 years, an increasing number of reports have appeared in the medical literature that suggest that the use of bisphosphonates, especially intravenous bisphosphonates, is associated with osteonecrosis of the jaw (ONJ). The majority of these reports are in patients with multiple myeloma, breast cancer, or other malignancies. In connection with these malignancies, the patients were receiving or did receive intravenous nitrogen-containing bisphosphonates in much higher doses than those used for osteoporosis and Paget's disease. However, a much smaller number of cases of ONJ have been associated with oral bisphosphonates used at lower doses to treat osteoporosis and Paget's disease. The leadership of ASBMR recognizes that these reports have raised great concern among patients and health care professionals. Therefore, we responded to these concerns with this editorial, in which we summarize the current evidence for an association between ONJ and bisphosphonates in doses used for osteoporosis and Paget's disease.

Dr Drezner receives research support from Eli Lilly & Co., Merck, and Roche. Dr Eisman receives research support and/or provides consulting to Amgen, deCode, Eli Lilly & Co., GE-Lunar, Merck, Sharpe & Dohme, Novartis, Organon, Pfizer, Roche-GSK, Sanofi-Avenits, and Servier. Dr Goldring receives research support from Boehringer Ingelheim and holds consultancies with Amgen, Genzyme, and Omeros. He also serves on the Board of Directors for Telik, the Osteoarthritis Advisory Board for Genzyme, and the Abbott Scholars Advisory Board for Abbott. Dr Shane receives research support from Novartis. Dr Silverman receives research support from Aventis, Eli Lilly & Co., Novartis, Roche, and Wyeth. He serves as a consultant to Merck, Procter & Gamble, Roche, and Wyeth. He also serves on the Speakers' Bureau for Eli Lilly & Co., Merck, and Procter & Gamble. Drs Christakos and Dr Pendrys state that they have no conflicts of interest.

DESCRIPTION

There is no universally accepted definition of ONJ. However, clinically it typically appears as an area of exposed alveolar bone that can occur in the mandible or the maxilla.[1] It may or may not be painful and may or may not be associated with infection or local trauma.[1] This area of exposed alveolar bone has most often developed after a recent tooth extraction[2] or oral contusion/abrasion. However, there are also cases in which there is no history of a preceding intraoral event. The contribution of infection to the development of ONJ is unclear, although ONJ may develop after dental surgery for infection. Lack of a generally agreed on case definition for ONJ has greatly hampered study of its incidence and etiology.

EPIDEMIOLOGY

ONJ in association with bisphosphonate therapy was first reported in 2003, primarily among patients with cancer, such as multiple myeloma or breast cancer, who were receiving high doses of intravenous bisphosphonates, often at frequent intervals.[3] In many of these patients, ONJ seemed to occur after recent dental pathology, trauma, or oral surgery. Many also had a medication history that included chemotherapy and corticosteroids. As of May 2006, the published literature includes a much smaller number of cases in patients receiving oral bisphosphonates: ~30 cases in patients receiving oral bisphosphonates for osteoporosis and 5 cases in patients receiving oral bisphosphonates for Paget's disease.[3–14] These represent ~5% of the total number of the ONJ patients reported worldwide. In patients receiving intravenous bisphosphonates for malignancy, the median time to appearance of ONJ is ~25 months. Unfortunately, the majority of the reports in patients with osteoporosis and Paget's disease provide no information on dose and duration of bisphosphonate therapy, general health history of the patients, or potentially relevant medication history. Also noteworthy, there have been no cases of ONJ

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reported in any of the randomized clinical trials designed to test the efficacy of oral alendronate, risedronate, and ibandronate or intravenous ibandronate and zoledronic acid in the treatment of either osteoporosis or Paget's disease (Merck, Procter & Gamble, Roche, and Novartis, personal communication, 2006). This amounts to >60,000 patient-years of exposure, although most of these clinical trials were relatively brief, of 2- or 3-year duration, and did not include dental issues in their adverse event reporting. The Council on Scientific Affairs of the American Dental Association, referring to pharmaceutical sources, reported that 170 ONJ cases associated with alendronate therapy and 20 cases with risedronate therapy have been seen. To our knowledge, these cases have not been adjudicated, nor was an agreed on definition used to make the diagnosis.

Recently, a case of osteonecrosis of the external auditory canal was reported subsequent to removal of an exostosis in a patient with multiple myeloma who had received intravenous pamidronate and zoledronic acid therapy.[15] If verified, this case of osteonecrosis would be the first to be reported outside of the oral cavity.

ASBMR TASK FORCE ON ONJ

Given all these uncertainties, ASBMR believes that there would be great value in convening a forum that would bring together physicians, oral surgeons, dentists, and scientists with expertise in key areas to address this emerging and urgent clinical problem. Therefore, to further basic and clinical research in this area, ASBMR is convening a multidisciplinary, international task force. Scientific leadership will be invited to participate from organizations with a key, but unbiased, interest in this question and its impact on the public health, such as the NIH (including the National Institute of Dental and Craniofacial Research, National Institute for Arthritis, Musculoskeletal and Skin Diseases, National Cancer Institute), ASBMR (and other interested societies), and the dental and oncology communities to work in close cooperation with academic scientists and other professional organizations. We believe that such a task force will facilitate an exchange of information that is critical to the development of the best research efforts to address this issue and guide the research agenda.

The charges to the task force will be as follows:

To make a recommendation for a provisional case definition, so that subsequent studies report on the same condition.

To review carefully the current available information, with the goal of assessing what is actually known about ONJ.

To identify what is not known and to identify the key questions that the scientific community should address, both in the short and long term.

To recommend the development of noninvasive diagnostic and imaging techniques with which to better characterize and diagnose the disorder.

To offer a research agenda that will elucidate incidence, pathophysiology, and etiology of ONJ.

To suggest recommendations for clinical management when the diagnosis of ONJ has been made.

CLINICAL RECOMMENDATIONS

Existing data suggest that the risk of developing ONJ is very low in patients taking oral bisphosphonates for osteoporosis and even lower among patients taking oral bisphosphonates for Paget's disease. Intravenous bisphosphonate therapy for the management of these diseases has only recently been introduced. To date, there have been no findings to suggest a difference in the risk for ONJ associated with this route of administration and at the doses approved for osteoporosis compared with oral bisphosphonate therapy for the management of osteoporosis. Thus, there is no information available. This low risk must be balanced against the established benefits of bisphosphonate treatment for osteoporosis and Paget's disease.

At present, there are insufficient data available to construct evidence-based guidelines for the prevention and therapy of ONJ in patients taking oral bisphosphonates for treatment of osteoporosis or Paget's disease. Although the risk of ONJ is very low, we believe it reasonable for health care professionals and patients to consider some suggested recommendations for the interim management of such patients, until the recommendations of the ASBMR Task Force on Osteonecrosis of the Jaw become available. We recognize that the implementation of these recommendations will depend on the local availability of resources for dental care. We also recognize that country-specific national recommendations may exist or be developed for patients receiving oral bisphosphonates. When such recommendations exist, health care professionals should adhere to their national recommendations.[16]

1. If possible, patients about to begin oral bisphosphonate therapy for osteoporosis or Paget's disease should have a dental examination before or soon after initiating therapy. If oral surgery or other invasive dental procedures are necessary, it may be advisable to complete them before or soon after beginning bisphosphonates, as long as the patient's skeletal condition permits a delay in initiation of therapy.
2. Patients taking oral bisphosphonates for the treatment of osteoporosis and Paget's disease should be informed about the low risk of developing ONJ associated with oral surgery and other invasive dental procedures.
3. Patients taking oral bisphosphonates for treatment of osteoporosis and Paget's disease should have the same dental care (such as good dental hygiene and cleaning, routine fillings and root canal procedures) recommended for the general population. There is no need to stop bisphosphonate therapy or to take special precautions.
4. Patients receiving oral bisphosphonates for treatment of osteoporosis and Paget's disease should inform their dentist that they are taking these medications and, if possible, their physician if they require oral surgery or invasive dental procedures, such as extractions or dental implants.
5. Dental surgery should be limited to that required for good dental health and undertaken only when more conservative nonsurgical therapies are either not appropriate or ineffective.

6. Patients with a suspected ONJ lesion should be referred to a dentist or an oral surgeon for evaluation and treatment.
7. Some health care professionals recommend stopping bisphosphonates for several weeks before and after dentoalveolar surgery. Given the very long half-life of bisphosphonates in bone, it is unlikely that this practice would have an adverse impact on the therapy of osteoporosis or Paget's disease. However, it is also unclear whether stopping bisphosphonate use for several weeks before and after dentoalveolar surgery would have any effect to reduce the low risk of developing ONJ.

The Council on Scientific Affairs of the American Dental Association (ADA) has advanced more detailed recommendations on dental care for patients who require treatment with bisphosphonates for osteoporosis or Paget's disease.[17] These recommendations are available on the ADA web site (http://www.ada.org/prof/resources/topics/topics_osteonecrosis_recommendations.pdf).

SUMMARY

Further research is needed to better understand the incidence and pathophysiology of ONJ, to rigorously study the association with intravenous and oral bisphosphonates and to identify specific patient risk factor sets when these drugs are used in the doses recommended for treatment of osteoporosis and Paget's disease. The goal of the ASBMR Task Force for Osteonecrosis of the Jaw is to facilitate the work of scientists, physicians, dentists, and oral surgeons and to help establish the best recommendations for patients with osteoporosis and Paget's disease, for whom bisphosphonates are an important therapeutic option.

ENDORSEMENTS

This editorial has received the endorsements of the following organizations: The American Association of Clinical Endocrinologists, The American College of Rheumatology, *Bone,* The Canadian Society of Endocrinology and Metabolism, Endocrine Society, The European Calcified Tissue Society, The International Bone and Mineral Society, The International Society of Clinical Densitometry, The National Osteoporosis Foundation, Osteoporosis Canada, *Osteoporosis International,* and The Paget Foundation.

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