JOURNAL OF BONE AND MINERAL RESEARCH
Volume 22, Number 10, 2007
Published online on July 19, 2007; doi: 10.1359/JBMR.0707ONJ

Editorial

Bisphosphonate-Associated Osteonecrosis of the Jaw: Report of a Task Force of the American Society for Bone and Mineral Research

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ABSTRACT: ONJ has been increasingly suspected to be a potential complication of bisphosphonate therapy in recent years. Thus, the ASBMR leadership appointed a multidisciplinary task force to address key questions related to case definition, epidemiology, risk factors, diagnostic imaging, clinical management, and future areas for research related to the disorder. This report summarizes the findings and recommendations of the task force.

Introduction: The increasing recognition that use of bisphosphonates may be associated with osteonecrosis of the jaw (ONJ) led the leadership of the American Society for Bone and Mineral Research (ASBMR) to appoint a task force to address a number of key questions related to this disorder.
Materials and Methods: A multidisciplinary expert group reviewed all pertinent published data on bisphosphonate-associated ONJ. Food and Drug Administration drug adverse event reports were also reviewed.
Results and Conclusions: A case definition was developed so that subsequent studies could report on the same condition. The task force defined ONJ as the presence of exposed bone in the maxillofacial region that did not heal within 8 wk after identification by a health care provider. Based on review of both published and unpublished data, the risk of ONJ associated with oral bisphosphonate therapy for osteoporosis seems to be low, estimated between 1 in 10,000 and <1 in 100,000 patient-treatment years. However, the task force recognized that information on incidence of ONJ is rapidly evolving and that the true incidence may be higher. The risk of ONJ in patients with cancer treated with high doses of intravenous bisphosphonates is clearly higher, in the range of 1–10 per 100 patients (depending on duration of therapy). In the future, improved diagnostic imaging modalities, such as optical coherence tomography or MRI combined with contrast agents and the manipulation of image planes, may identify patients at preclinical or early stages of the disease. Management is largely supportive. A research agenda aimed at filling the considerable gaps in knowledge regarding this disorder was also outlined.
J Bone Miner Res 2007;22:1479–1491. Published online on July 19, 2007; doi: 10.1359/JBMR.0707ONJ

Key words: osteoporosis, bone, oral cavity, pain, metastases

INTRODUCTION

The increasing recognition that use of bisphosphonates may be associated with osteonecrosis of the jaw (ONJ) led the leadership of the American Society for Bone and Mineral Research (ASBMR) to appoint a task force to address a number of key questions related to this disorder.[1] Specifically, the task force was asked to:

1. Make a recommendation for a provisional case definition, so that subsequent studies report on the same condition.
2. Review existing reports of ONJ and other relevant data to assess what is known and what is unknown about ONJ.
3. Recommend the development of noninvasive diagnostic and imaging techniques with which to better characterize and diagnose the disorder.
4. Suggest recommendations for clinical management before initiating and during bisphosphonate therapy as well as when the diagnosis of ONJ has been made.
5. Identify the key questions that the scientific community should address, both in the short and long term, and

Drs Koka, McGowan, Mohla, Ruggiero, and Shum state that they have no conflicts of interest. The conflicts for Drs Khosla, Shane, Burr, Cauley, Dempster, Ebeling, Felsenberg, Gagel, Guise, McCauley, McKee, Pendrys, Raisz, Shafer, Silverman, Van Poznak, Watts, and Woo are detailed within the manuscript.

ASBMR Task Force on Bisphosphonate-Associated ONJ.

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

This report summarizes the findings and recommendations of the task force.

MATERIALS AND METHODS

Expert committee

The expert committee consisted of an international, multidisciplinary group of 24 individuals with expertise in clinical and basic bone biology, epidemiology, radiology, oncology, dentistry, periodontal disease, and oral surgery, as well as representatives from the United States NIH and the Canadian Institutes of Health Research. The individuals on the task force also served as representatives for a number of national and international organizations with a stake in this issue, including the ASBMR, American Association of Clinical Endocrinologists, American Academy of Oral Medicine, American Academy of Oral and Maxillofacial Pathology, American Association of Oral and Maxillofacial Surgeons, American College of Rheumatology, American Society for Clinical Oncology, Endocrine Society, International Bone and Mineral Society, International Society for Clinical Densitometry, National Osteoporosis Foundation, Orthopaedic Research Society, and Paget Foundation.

Review of the literature/data acquisition

A list of pertinent publications was compiled by the task force. This reference list was developed using Medline/PubMed searches, review of the proceedings of national academic society meetings, word of mouth, Google searches, and by accessing the references cited in all identified publications. Cases of bisphosphonate-associated ONJ reported in patients with osteoporosis and Paget's disease were considered separately from those reported in patients with malignancy.

a. Cases of bisphosphonate-associated ONJ in patients with osteoporosis or Paget's disease. Published literature pertaining to cases of ONJ reported in association with osteoporosis and Paget's disease of bone was reviewed. A literature search and list of publications likely to be relevant was made and each publication was reviewed. The numbers of subjects in each study, the type of bisphosphonate(s) used, the duration of bisphosphonate exposure, the site of the oral lesion(s), the clinical presentation, the type of any intraoral predisposing event, and any other information relevant to the study was included when available. Identification of case duplication between studies was sought by cross-referencing studies whenever possible.

b. Cases of bisphosphonate-associated ONJ in patients with malignancy. Data extracted from the literature review were evaluated for the type of publications (case report, commentary, clinical trial, etc). The clinical data presented in the publication were extracted and when available, included the definition of bisphosphonate-associated ONJ used to identify cases, clinical patient data including indication for bisphosphonate use, cancer diagnosis and cancer treatment, oral health history, and bisphosphonate use including drug, dosage, duration, as well as the management and outcome of bisphosphonate-associated ONJ cases.

c. Input from the pharmaceutical industry. Two members of the task force (SK and ES) conducted teleconference sessions with representatives of companies currently marketing bisphosphonates in the United States (Merck, Procter and Gamble, Roche, Novartis) and representatives from Amgen, which is developing an alternative, potent anticatabolic agent. These sessions were informational and permitted experts from the industry to provide their input for consideration by the task force.

Table 1. Additional Signs and Symptoms That May or May Not Be Present in Confirmed or Suspected Cases of Bisphosphonate-Associated ONJ

Pain
Swelling
Paresthesia
Suppuration
Soft tissue ulceration
Intra- or extraoral sinus tracks
Loosening of teeth
Radiographic variability (ranging from no radiographic alterations to varying radiolucencies or radiopacities)

RESULTS AND DISCUSSION

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

A ***confirmed*** case of bisphosphonate-associated ONJ was defined as an area of exposed bone in the maxillofacial region that did not heal within 8 wk after identification by a health care provider, in a patient who was receiving or had been exposed to a bisphosphonate and had not had radiation therapy to the craniofacial region. The 8-wk duration is consistent with a time frame where most trauma, extractions, and oral surgical procedures would have resulted in soft tissue closure, and exposed bone would no longer be present. In the event that the lesion was spontaneous or history was lacking regarding its duration, the 8-wk duration would start at the time that exposed bone was first documented by a health care provider.

A ***suspected*** case of bisphosphonate-associated ONJ was defined as an area of exposed bone in the maxillofacial region that had been identified by a health care provider and had been present for <8 wk in a patient who was receiving or had been exposed to a bisphosphonate and had not had radiation therapy to the craniofacial region. Suspected cases of bisphosphonate-associated ONJ should receive follow-up evaluation to determine whether they ultimately meet the definition of a confirmed case.

Additional signs and symptoms may or may not be present in confirmed or suspected cases of bisphosphonate-associated ONJ (Table 1). However, the task force considered that these signs and symptoms are neither individually nor collectively sufficient for a diagnosis of bisphosphonate-associated ONJ, in the absence of exposed bone as defined

Table 2. Differential Diagnosis of Bisphosphonate-Associated ONJ

Periodontal disease
Gingivitis
Mucositis
Infectious osteomyelitis
Sinusitis
Periapical pathology caused by a carious infection
Temporomandibular joint disease
Osteoradionecrosis
Neuralgia-inducing cavitational osteonecrosis (NICO)
Bone tumors or metastases

Table 3. Conditions That May Present With Exposed Bone in the Absence of a History of Bisphosphonate Use

Trauma
Odontogenic infections leading to osteomyelitis
Herpes zoster infection associated osteonecrosis
Benign sequestration of the lingual plate
HIV-associated necrotizing ulcerative periodontitis

Table 4. Hierarchy of Evidence Quality for Classification of Future Studies Reporting ONJ

A. Patient
1. Age
2. Sex
B. Diagnosis of lesion
1. Presence/absence/duration of exposed bone (documented by a clinician)
2. Presence/absence of history of therapeutic radiation
3. General anatomic location (i.e., oral cavity, auditory canal)
C. Local (site) clinical history
1. Specific prior event (extraction, surgical procedure, etc.)
2. Time from event to first notation by clinician of lesion
3. Specific location of lesion(s) (e.g., mandible)
D. Bisphosphonate exposure history
1. Specific drug(s)
2. Specific dose history
3. Duration of therapy to first notation by clinician of lesion
E. Indication for bisphosphonate therapy
1. Disease (osteoporosis, myeloma, etc.)
2. Time from disease diagnosis to first notation by clinician of lesion
F. Comorbidity history
1. Specific comorbid diagnoses (include examples)
2. Duration of comorbid conditions to first notation by clinician of lesion
G. Co-medication history
1. Identity of co-medications (include examples)
2. Co-medication dosages and duration of therapy to first notation by clinician of lesion

Best evidence, information complete for all seven categories; good evidence, information complete for categories A–D, plus E1, F1, and G1; acceptable evidence, information complete for categories A–D but E1, F1, and G1 not all complete; marginal evidence: information complete for B1, C1, and D1; insufficient evidence, information unavailable for B1, C1, and D1, regardless of other information provided.

Additional information: reports should also seek to provide the following information: patient race/ethnicity; presence or absence of pain, inflammation, sinus tracks, swelling, infection, paresthesia, or other unusual or outstanding presentations; more specific anatomic location if available (e.g., posterior mandible, anterior maxilla); results of any imaging, cultures, or biopsy if performed.

above. However, these symptoms and signs could also herald early disease, and over time, may become associated with exposure of bone. As diagnostic techniques improve (see Section 3), clinical symptoms and signs may be identified that prove to be predictive of the development of ONJ.

The differential diagnosis of bisphosphonate-associated ONJ should specifically exclude other common intraoral conditions including periodontal disease, gingivitis or mucositis, infectious osteomyelitis, temporomandibular joint disease, sinusitis, periapical pathology caused by a carious infection, osteoradionecrosis, neuralgia-inducing cavitational osteonecrosis (NICO), and bone tumors or metastases (Table 2; Appendix 1 contains a glossary of dental terms for the nondental practitioner). However, in the absence of exposed bone as defined above, these conditions should not be considered as cases of bisphosphonate-associated ONJ. In addition, bisphosphonate-associated ONJ does not include other conditions that may present with exposed bone but without a history of bisphosphonate use (Table 3), such as trauma, odontogenic infections leading to osteomyelitis, herpes zoster infection–associated osteonecrosis, benign sequestration of the lingual plate, or HIV-associated necrotizing ulcerative periodontitis.

2. Review carefully existing reports of ONJ and other relevant data to assess what is known and what is unknown about ONJ.

The task force recognized at the outset that the incidence of ONJ in the general population not exposed to bisphosphonates is unknown. However, the disorder has come to medical attention principally in the setting of bisphosphonate use. Although this association is consistent with a role for bisphosphonates, bisphosphonates have not been proven to be causal. The task force also recognized that quality of the evidence reported in a substantial proportion of case descriptions of patients with ONJ was poor and that many reports were missing important historical or clinical information. The task force recommended that a hierarchy of evidence quality should be established for all future studies reporting cases of ONJ. The overall hierarchy of evidence quality for a case would be based on the quality of seven areas, as indicated in Table 4. Because the incidence of ONJ is very different in patients receiving oral bisphosphonates for osteoporosis or Paget's disease compared with patients receiving high doses of intravenous bisphosphonates for management of malignancy, the literature was examined separately for these two groups of patients. The task force recognized that information on incidence of ONJ is rapidly evolving, that continued surveillance will undoubtedly result in identification and publication of more cases, and that estimates of the frequency of ONJ may change for patients receiving bisphosphonates for both malignant and nonmalignant disease.

TABLE 5. LITERATURE REVIEW OF BISPHOSPHONATE-ASSOCIATED ONJ REPORTS IN PATIENTS WITH OSTEOPOROSIS OR PAGET'S DISEASE

Study	*N*	*Age (yr)*	*M/F*	*Disease*	*Bisphosphonate*	*Oral site*
Ruggerio et al.[11]	7	59–82	1M/6F	O (7)	A (6)	Mand (6)
					A + Z (1)	Max (1)
Cheng et al.[40]	8	39–84	4M/4F	O (3)	A (5), P (2),	Mand (3)
				P (5)	A + P (1)	Max (5)
Marx et al.[23]	3			O (3)	A (3)	
Marunick et al.[41]	2	59, 64	2F	O (2)	A (2)	Mand (2)
Migliorati et al.[21]	1	61	1F	O (1)	A (1)	Max (1)
Purcell et al.[42]	1	67	1F	O (1)	A (1)	Max (1)
Farrugia et al.[43]	5	63–83	1M/4F	O (4)	A (5)	Mand (3)
				P (1)		Max (2)
Chang et al.[44]	11			O (11)	A (11)	
Mavrokokki et al.[4]	32*			O (26)	A (25), P (2), R (2),	Mand (23)
				P (6)	A + R (2), A + P (1)	Max (9)
Starck et al.[45]	1	75	1F	O (1)	E	Mand (1)
Hoefert et al.[46]	3			O (3)		
Najm et al.[47]	3	45–84	1M/2F	O (3)	A (2)	Mand (2)
					P + Z (1)	Max (1)
Carter et al.[48]	3			P (3)	A (1), P (2)	Max (3)
Pozzi et al.[49]	1			O (1)		
Total (excluding overlapping cases)	64			O (57)		
				P (7)		

O, osteoporosis; P, Paget's disease; A, alendronate; Z, zoledronic acid; P, pamidronate; R, risedronate; E, etidronate; Mand, mandible; Max, maxilla.
* Includes overlap cases reported in other series.

Osteoporosis and Paget's disease: The literature review of bisphosphonate-associated ONJ reports in patients with osteoporosis or Paget's disease is shown in Table 5. The total number of reported cases was 64 after overlapping case reports had been excluded. There were 57 cases that occurred in association with treatment for osteoporosis and 7 cases that occurred in association with treatment of Paget's disease. Of the latter, three were treated with intravenous pamidronate, one with the combination of intravenous pamidronate followed by oral alendronate, and three with oral alendronate. Where it could be ascertained, the dose of bisphosphonate was felt to be unusually high in four of the seven patients.

Of the 57 ONJ cases associated with bisphosphonate therapy for osteoporosis, only 4 were men, but sex was not identified in several cases. Most had been treated with alendronate, two received risedronate, one received a combination of alendronate and risedronate, and two received intravenous pamidronate and/or zoledronic acid. When the site of osteonecrosis was identified, about two thirds of cases occurred in the mandible and most of the remainder occurred in the maxilla, whereas four cases occurred at both sites.

Exposed bone was the most commonly reported clinical presentation. However, it was not invariable. Some reports included the presence of ulcerated mucosa or abscess and fistula formation, but these were less common. Pain was a common finding but was not reported in all cases. A minority of cases had biopsies of the affected jaw, and all biopsies showed necrosis of bone. The duration of bisphosphonate therapy was frequently not included; however, it is noteworthy that the minimum duration of alendronate therapy was 2 yr. Similarly, the duration of the clinical presentation, particularly the duration of exposed bone, was frequently not described.

The task force recommends that there should be a minimal reporting requirement to the respective companies and the Food and Drug Administration (FDA) for future cases of ONJ based on the clinical definition noted above. The task force also recommends that an external agency follow-up and validate FDA drug adverse event report data in detail, both to confirm all reported cases and to accumulate further accurate information on the condition.

The incidence of ONJ in patients receiving bisphosphonates for osteoporosis is not known. Both U.S. pharmaceutical industry (Merck) estimates of the worldwide, cumulative reporting rate of osteonecrosis of the jaw of <1 in 100,000 patient-treatment years, regardless of causality, and the prevalence of <1 in 250,000 in a recent German study are consistent.[2,3] However, data from Australia[2,4] suggest that the incidence could be up to 10-fold higher. In part, these different estimates may be related to underreporting, different durations of exposure in countries that have adopted bisphosphonates more recently, and/or differing definitions of the disease. The task force fully recognizes that the true incidence of ONJ in patients with osteoporosis may be higher than noted in these estimates because of these potential confounders.

Malignancy: Patients with malignant bone disease are at risk for skeletal-related events, including pathological fracture, metastases requiring surgery or radiation therapy to bone, and spinal cord compromise. They may experience fragility fractures either because of comorbid conditions or because of toxicities of their cancer therapy. Bisphosphonates have been shown to decrease the risk of skeletal complications by approximately one third.[5] In addition, bisphosphonates are clinically important for the treatment of hypercalcemia of malignancy and can reduce cancer induced bone pain. The two bisphosphonates approved by

the FDA for use in patients with cancer involving bone are pamidronate and zoledronic acid. Clodronate and ibandronate have been licensed for use in malignant bone disease in other countries. Because of the high frequency of skeletal involvement in advanced cancers, bisphosphonates are routinely prescribed in the practice of medical oncology.[6]

When treating patients with skeletal lesions from cancer, current oncology practice in the United States typically uses either pamidronate, 90 mg, infused over at least 2 h every 3–4 wk, or zoledronic acid, 4 mg, infused over at least 15 min every 3–4 wk.[7–9] With the FDA approval of zoledronic acid in 2001, this agent has gained popularity in clinical practice because of its efficacy in reducing skeletal-related events and the shorter infusion time. The American Society of Clinical Oncology (ASCO) has established guidelines for the use of bisphosphonates in patients with metastatic breast cancer and multiple myeloma.[7,8] The ASCO guidelines suggest that once the bisphosphonate is initiated, it should be continued until there is substantial decline in the patient's clinical condition.[7,8] Because of the lifelong risk of skeletal-related events in patients with metastatic bone disease, the clinical practice in the palliative setting has been to continue bisphosphonate therapy indefinitely.

Bisphosphonate-associated ONJ in patients with malignancy has come to the attention of the medical and dental communities primarily through case reporting, and the number of reported cases has been increasing over the past 3 yr. Most patients in case reports published to date have cancer that involves bone and have been treated with high-potency, nitrogen-containing intravenous bisphosphonates. All bisphosphonates have been associated with cases of ONJ; however, this must be tempered with the acknowledgment of the lack of a consensus definition for ONJ and the unknown incidence of ONJ in the general population. The published literature reviewed by the task force identified <1000 cases. This is consistent with the estimate of 654 cases presented during the Oncology Drug Advisory Committee meeting in March 2005.[10] Although case reporting is a classic means of communicating information on rare conditions, there are limitations to case reports. Presumably, prospective data on bisphosphonate-associated ONJ are limited because of the short amount of time since the condition has come to widespread attention and the low frequency of events.

The recent flurry of case reports began in 2003 in the form of abstracts presented at academic meetings. Ruggiero et al.[11] published the first peer-reviewed report of bisphosphonate-associated ONJ. In this publication, a chart review was performed of patients who presented with a diagnosis of osteonecrosis or osteomyelitis of the jaw and who did not have a history of radiation therapy to the jaw or of neoplasm directly involving the jaw. From February 2001 through June 2003, a total of 63 patients were identified, and their charts were reviewed. Relevant findings included the use of a bisphosphonate (intravenous or oral) in all affected individuals. Therapy included debridement, with some patients requiring a surgical procedure; two patients were treated with hyperbaric oxygen (30 1-h dives) without significant benefit. The clinical observation was made that discontinuing the bisphosphonate did not seem to alter the outcome of bisphosphonate-associated ONJ.

The estimated incidence of bisphosphonate-associated ONJ in patients with malignancy seems to range between 1% and 10%.[4,12–15] The bisphosphonate used and the duration of exposure, which often is correlated with cumulative dose, has been related to risk of bisphosphonate-associated ONJ. Thus, whereas the mean time to onset of bisphosphonate-associated ONJ in individuals receiving zoledronic acid was 18 mo, it was 39–72 mo in patients receiving pamidronate.[13,16] Using insurance claims data, investigators identified an association between patient with cancer receiving intravenous bisphosphonate therapy and oral surgery. Compared with never users, the odds ratio of surgery for intravenous bisphosphonate users was 4.24 ($p < 0.05$).[17] In a prospective clinical trial performed in Greece of 252 patients with a variety of cancers who had received at least 6 mo of bisphosphonate therapy, the risk of developing bisphosphonate-associated ONJ increased with longer exposure to bisphosphonate therapy and was associated with the bisphosphonate used. For the whole population, the cumulative hazard ranged from >1% at 12 mo to 11% at 4 yr. However, for those who received zoledronic acid alone, the hazard was 1% within the first year but rose to 21% at 3 yr.[18]

Patients with cancer involving the skeleton may be exposed to other medications that compromise oral health, including chemotherapy, glucocorticoids, and antibiotics that may alter the microenvironment of the mouth. Although there are no specific known oral changes associated with the bisphosphonates, those individuals with cancer receiving pamidronate and/or zoledronic acid seem to be the population at greatest risk for bisphosphonate-associated ONJ. The true incidence of bisphosphonate-associated ONJ is unknown, given the difficulty in obtaining accurate assessment of the denominator and the limitations of voluntary case reporting.

Although our present understanding of the risk factors associated with and the pathogenesis of bisphosphonate-associated ONJ is limited, the clinical and patient community has developed an awareness of the condition through the use of guidelines, position papers, and statements generated by the oral and medical academic community, as well as the bone-related national or disease-specific agencies. There are established guidelines for oral health care before initiating chemotherapy.[19,20] Table 6 summarizes risk factors currently felt to predispose to bisphosphonate-associated ONJ[14,21–24]; however, the task force recognized that the evidence on risk factors predisposing to ONJ was weak.

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

The use of various imaging modalities for diagnosing bisphosphonate-associated ONJ depends on the definition of bisphosphonate-associated ONJ and the natural history of the disease process. For established pathology, there is little need for diagnostic imaging techniques because the pres-

Table 6. Risk Factors for Bisphosphonate-Associated ONJ

Intravenous bisphosphonates
Cancer and anti-cancer therapy
Dental extraction, oral bone manipulating surgery, poor fitting dental appliances, intraoral trauma
Duration of exposure to bisphosphonate treatment
Glucocorticoids
Co-morbid conditions (i.e., malignancy)
Alcohol and/or tobacco abuse
Pre-existing dental or periodontal disease

ence of exposed bone and associated symptoms such as pain, swelling, paresthesia, suppuration, and soft tissue ulceration can be detected without them. However, early identification of bisphosphonate-associated ONJ, although more challenging, is potentially important for patient care and prevention of disease.

Some imaging modalities, such as MRI, have been used successfully for diagnosing radiation-induced osteoradionecrosis or avascular necrosis of the hip (AVN). Although the pathogenesis of bisphosphonate-associated ONJ may differ from these conditions, the techniques described below may prove to be helpful in the future, when the pathogenesis of bisphosphonate-associated ONJ is better understood and defined.

Modalities that image bone structure: Panoramic radiography: Panoramic radiographs are routinely used in clinical dentistry and are widely available. They are inexpensive, provide a good overview of the entire jaw, and provide a good first line of documentation of the status of the jaw. Radiography can adequately distinguish between osteonecrosis and metastatic lesions, when radiopaque sequestra are present, but is less useful if the lesion is osteolytic.[27] Radiography is particularly useful when there is a combination of osteolysis and osteosclerosis,[27] but a significant (30–50%) loss of bone mineral is required before detection is optimal,[25,26] and it is unlikely that this ever occurs in bisphosphonate-associated ONJ before the lesion becomes clinically apparent. Radiography also requires a high radiation dose and results in a 2D image with significant overprojections that could potentially obscure important anatomical or pathological details. The image quality is poor, and it is difficult to demarcate the margins between necrotic and healthy bone. Early lesions frequently can be missed. Nevertheless, despite these limitations, the general consensus suggests conventional radiographs should be taken as a first line of routine radiological investigation.[27]

CT: CT provides an improvement over conventional radiography in that it allows 3D reconstruction, has the potential to detect both cancellous and cortical bone involvement, and can identify the presence of both osteosclerotic and osteolytic regions (the latter may be areas of bacterial infection) in patients with advanced bisphosphonate-associated ONJ.[27] However, CT did not contribute additional information to conventional radiography in an asymptomatic subject with osteonecrosis.[27] The use of this technique for detecting early changes of bisphosphonate-associated ONJ is currently unknown, in part because the early manifestations of ONJ, particularly in terms of mineralization and vascularity, are not well understood. Because CT can detect differences between cortical and trabecular bone, it may be useful for differential diagnosis when ONJ is suspected.[27]

Cone beam CT: Cone beam CT (CBCT) is a relatively new technique that imparts lower radiation to oral tissues (<1/15 that of a spiral CT), but has higher spatial resolution than conventional CT and provides better image quality, particularly for cancellous bone.[28,29] Although it may be limited in its discrimination of soft tissue because of its low contrast resolution, it can provide detailed information about cortical thickness and integrity, marrow involvement, irregularities after tooth extraction, and cancellous BMD. However, the equipment is not widely available at present.

Modalities that image bone marrow and soft tissues: MRI: Currently, MRI may provide the method of choice for the assessment of osteonecrosis. Regardless of the site affected, the histopathologic changes of necrotic bone are comparable and are depicted similarly by MRI. The imaging appearance results from progressive cell death and host response through repair (edema). Because fat cells provide high signal intensity of normal marrow, the speculation is that marrow signal changes begin with the death of fat cells. Controversy exists, however, regarding the length of time between the death of fat cells and changes in the MR signal intensity. Additionally, the general consensus is that marrow edema is not part of the pathogenesis of bisphosphonate-associated ONJ, as it is for AVN, considerations that may limit the use of MR in the diagnosis of ONJ.[30] The region of ischemia can be recognized, however, as a nonenhanced area after the use of a contrast agent, such as gadolinium, especially in fat-suppressed T1-weighted sequences. Chronic cases, in which fibrosis and sclerosis of bone occur, can result in low signal intensity on both T1- and T2-weighted images. Nonetheless, to date, available data on MRI findings of bisphosphonate-associated ONJ are limited and suggest that this technique may be associated with a high percentage of false-positive diagnoses.[31]

Functional/physiological tests: Technetium-99 radioisotope scintigraphy: For several years, this was the best technique for diagnosing ischemic osteonecrosis. However, this technique assumes a change in vascularity within the necrotic region, which may not be part of the early pathogenesis of bisphosphonate-associated ONJ. If hypervascularity is associated with early phases of bisphosphonate-associated ONJ or if avascularity is a component of later stage bisphosphonate-associated ONJ, this could prove to be a very useful functional test that might detect subclinical lesions. This technique might also be a useful screening tool, because its sensitivity depends on the stage of the osteonecrotic lesion.[27] The primary drawbacks to Technetium-99 radioisotope scintigraphy (^{99m}Tc-MDP) are that it subjects the patient to significant radiation exposure, and it is a lengthy procedure. However, this procedure is often performed in patients with metastatic bone disease for clinical indications. The technique has low resolution, and regions of inflammation may obscure other areas that may be more avascular. In patients with cancer, it may sometimes be difficult to distinguish between inflammatory and meta-

static processes as well as between healing osteolytic lesions versus progressing osteoblastic lesions.

Positron emission tomography: Although this is also a functional/physiological test, there is general consensus that it will not be a useful technique for diagnosing bisphosphonate-associated ONJ because of poor resolution. In addition, it delivers a high radiation dose.

Modalities with potential for development: Optical coherence tomography: Based on the interference of light (partial coherence interferometry), optical coherence tomography (OCT) uses various light wavelengths in the infrared range to dictate the depth of penetration (from 1.0 to 4.0 mm)[32] and the resolution of the scanning beams (from 10 to 17 μm).[33,34] One advantage is that it does not use ionizing radiation. This technique could image small "prelesions" in the alveolar bone if they differ in mineralization. However, the depth of penetration is a serious drawback, and birefringence can cause image artifacts in some cases.

Combinational approaches: Although each imaging approach by itself has its own limitations, combinations of different techniques could provide valuable information in diagnosing bisphosphonate-associated ONJ. For example, CBCT is used in conjunction with scintigraphy for diagnosing mandibular osteomyelitis.[29] Another novel approach is to use sequential images to provide a temporal history of developing change. Although changes may not be evident at a single point in time, comparative measures may be helpful in alerting the clinician to developing changes in the jaw. Some of the imaging approaches may also be enhanced by the contribution of contrast agents. For example, ^{99m}Tc-MDP may be indicative of osteoblast activity, whereas gallium citrate can be used to image an infective focus. Likewise, gadolinium can be used to improve image contrast with MRI in areas with normal or high vascularization.

At present, the task force believes that there is little need for diagnostic imaging techniques in patients who present with overt clinical evidence of ONJ. However, the use of contrast agents combined with MRI and the manipulation of different planes of image may be the most promising approach currently available for differential diagnosis, when the diagnosis is uncertain. Additional technological development of some relatively new approaches, such as OCT or CBCT, whose capabilities have not yet been fully explored, may prove in the future to be valuable for detecting early stage disease.

4. Suggest recommendations for clinical management before initiating bisphosphonate therapy and when the diagnosis of ONJ has been made.

General recommendations:

- There should be free and complete communication between health care professionals (physicians and dentists) involved in treatment and between health care professionals and patients.[35] Physicians should encourage patients to inform their dentist that they are taking a bisphosphonate.
- All patients starting or taking bisphosphonates should be informed of the benefits of bisphosphonate treatment. They should also be informed of the risks of bisphosphonates, including the risk of ONJ, the signs and symptoms of ONJ (Table 1), and the risk factors for developing ONJ (Table 6) .[35–38]
- Patients taking bisphosphonates should be encouraged to maintain good oral hygiene and to have regular dental visits during which they can be instructed in proper dental hygiene and can receive proper dental care. They should be urged to report any oral problems to their dentist and physician.
- Education of physicians and patients about bisphosphonate-associated ONJ is vitally important in all circumstances and particularly in circumstances or locations where the resources to provide dental examinations and treatment are limited.

Recommendations for patients with osteoporosis or other nonmalignant bone disease initiating or already receiving bisphosphonate therapy:

- Patients should be informed that the risk of developing bisphosphonate-associated ONJ with routine oral therapy for osteoporosis or Paget's disease seems to be low, ranging between 1/10,000 and 1/100,000, as summarized in the previous discussion.
- Patients who express concern about ONJ should be encouraged to seek additional information from a dentist or dental specialist.
- Health care providers should encourage their patients who are starting or continuing to take bisphosphonates to practice good oral hygiene and have regular dental visits during which they can receive proper dental care.
- Because the risk of developing bisphosphonate-associated ONJ seems to be related to longer duration of bisphosphonate exposure and the risk is low, it is not necessary to recommend a dental examination before beginning oral bisphosphonate therapy or to otherwise alter routine dental management.
- For the patient who has been on long-term oral bisphosphonate therapy (empirically defined as >3 yr), the following precautions are advised.
  - Patients with periodontal disease should receive appropriate nonsurgical therapy. If surgical treatment is necessary, it should be aimed primarily at reducing or eliminating periodontal disease. Modest bone recontouring may be considered when necessary.
  - Current information indicates that taking bisphosphonates for osteoporosis is not a contraindication for dental implant placement. However, if dental implants are considered, appropriate informed consent is recommended and should be documented.
  - Endodontic treatment is preferable to extraction or periapical surgery when possible.
  - If an invasive dental procedure is anticipated, some experts suggest stopping the bisphosphonate for a period before and after the procedure. It should be noted, however, that there are no data to suggest stopping the bisphosphonate will improve dental outcomes. On the other hand, given the long retention of bisphosphonates in the skeleton, temporary

discontinuation of bisphosphonate therapy is unlikely to have an adverse effect on the patient's skeletal condition.

Intravenous bisphosphonate therapy has only been recently introduced for the management of osteoporosis. To date, there have been no findings to suggest a difference in the risk of ONJ associated with this route of administration at the doses approved for osteoporosis compared with oral bisphosphonate therapy for management of osteoporosis.

Recommendations for patients with malignancy initiating or already receiving bisphosphonate therapy:

- Patients should be informed that the estimated incidence of bisphosphonate-associated ONJ in patients with malignancy seems to range between 1% and 10%,[12–15] as summarized in the previous discussion.
- Whenever possible, patients should have a dental evaluation by a qualified dental specialist before starting intravenous bisphosphonates for bone metastases. Dental evaluations should continue throughout the course of bisphosphonate therapy at 6- to 12-mo intervals or as dictated by the clinical and dental status of the patient.
- If the patient's clinical condition permits a delay in initiating bisphosphonate therapy, invasive dental procedures should be performed and healing completed before starting treatment with a bisphosphonate.[12] Otherwise, bisphosphonate therapy should be instituted concomitantly with dental therapy with careful follow-up to ensure complete healing of the surgical site.
- Elective dentoalveolar surgical procedures (such as implant placement, tori reduction, and extraction of asymptomatic teeth) are not recommended.
- If possible, symptomatic teeth that would otherwise require extraction should receive nonsurgical endodontic or periodontal therapy and should be left in place. Only if the tooth is excessively mobile and presents an aspiration risk should it be extracted. Periapical or periodontal surgery are not recommended. If symptomatic teeth are located within an area of bone that is already exposed and necrotic, extraction should be considered because it is unlikely that it will exacerbate the established necrotic process.

Recommendations for patients with established ONJ:

- Management should be by a qualified dental specialist.[37,38]
- Pain should be managed appropriately.
- The case should be reported to the appropriate agencies, including the manufacturer(s) of the agent(s) implicated.
- Management of infection:
  - Oral antimicrobial rinses (such as 0.12% chlorhexidine digluconate) should be used.
  - Systemic antibiotic therapy may be prescribed if there is evidence of infection.[12,37–39]
  - Establishing and maintaining an "infection-free" oral environment is especially important for patients with multiple myeloma who are being considered for stem cell transplantation. However, despite aggressive antibiotic therapy, some patients will have persistent infection and exposed bone, and the risks and benefits of proceeding with the transplantation in this scenario must be considered on a case-by-case basis.
- Surgical management:
  - Surgical treatment should be conservative or delayed.[12,37,38]
  - Removal of sharp bone edges is recommended to prevent trauma to adjacent soft tissues.
  - Loose segments of bony sequestra should be removed without exposing uninvolved bone.
  - Segmental jaw resection may be required for symptomatic patients with large segments of necrotic bone or pathologic fracture.
- Bisphosphonate therapy:
  - Some experts suggest stopping intravenous bisphosphonates in cancer patients with established ONJ if the clinical situation permits. As noted earlier, however, no published data have established that stopping bisphosphonates will promote resolution of ONJ. Bisphosphonates have a long half-life in the skeleton, particularly alendronate and zoledronic acid. Although temporary discontinuation of bisphosphonates may not adversely affect the progression of established bone metastases or the development of new metastases, this is by no means a certainty. Therefore, the task force recommends that the indication for which the patient is receiving bisphosphonates should be taken into consideration, when deciding whether to discontinue bisphosphonates in patients with established ONJ. For example, if the patient has aggressive skeletal metastatic disease, one might continue bisphosphonate treatment. In contrast, if skeletal disease is mild or the patient is receiving therapy for prevention of metastases rather than for established metastases, one might consider discontinuing bisphosphonate treatment.
- Additional considerations:
  - Whereas some have advocated the use of hyperbaric oxygen, the efficacy of this approach has not been established.[37]
  - Patients with advanced ONJ and limited ability to eat may require dietary supplements or feeding by nonoral routes (e.g., tube feedings) to meet nutritional needs.

5. Identify the key questions that the scientific community should address, both in the short and long term, and offer a research agenda that will elucidate incidence, pathophysiology, and etiology of ONJ.

The task force considered areas of clinical and animal/basic research separately, and key unresolved issues in each of these areas are summarized below.

Clinical research: The task force recognized that, particularly in the case of bisphosphonate use for osteoporosis or

Paget's disease, where the incidence of ONJ is relatively low, data from prospective clinical trials addressing the issues noted below may be difficult to obtain; here, greater reliance will likely need to be placed on descriptive center/practitioner surveys and/or retrospective and prospective cohort investigations.

a. Important unknowns are the true incidences of ONJ in patients with malignancy receiving high doses of intravenous bisphosphonates, in patients with Paget's disease receiving intermediate doses of intravenous or oral bisphosphonates, and in patients with osteoporosis receiving lower doses of oral bisphosphonates. In addition, because it remains possible that it is suppression of bone resorption rather than bisphosphonate use that is the risk factor for ONJ, it is important to study whether ONJ occurs in patients treated with antiresorptive drugs other than bisphosphonates and with other diseases associated with suppressed bone resorption, such as osteopetrosis. Several different types of clinical studies could address this question, including descriptive center/practitioner surveys, retrospective and prospective cohort studies, and phase IV (postmarketing) clinical trial follow-up studies.

b. It is important to identify specific factors that place patients at risk for ONJ. Likely candidates include the following: bisphosphonate exposure history, such as the particular drug, route of administration, and cumulative dosage; age, sex, comorbid medical conditions (i.e., underlying malignancy), concomitant medications (estrogen, glucocorticoids, others); skeletal factors such as generalized low BMD or localized areas of low BMD, low bone turnover when bisphosphonates are initiated, or the degree of reduction in bone turnover induced by bisphosphonates; dental health risk factors, such as dental hygiene, trauma, periodontal disease, and xerostomia, as well as characteristics such as salivary pH and protein and oral flora.

c. Whether alternative dosing schedules, such as lower doses or less frequent administration in patients with or at risk for bone metastases, could reduce the incidence of ONJ while maintaining the benefits of bisphosphonate therapy needs to be addressed. Similarly, whether "drug holidays" could reduce the incidence of ONJ in patients with osteoporosis needs to be examined.

d. Another important area is whether monitoring of bone turnover markers to help avoid oversuppression of bone turnover could reduce the incidence of ONJ and whether salivary or dental crevicular fluid markers could be used as indicators of local bone metabolism. It is also important to assess the use of existing imaging technology to detect early changes of ONJ that could identify those patients most likely to develop a clinical lesion if oral trauma or extractions occur. Imaging could also help determine the true extent of the ONJ lesion among patients who have developed a clinical lesion. A staging and grading system needs to be developed, based on physical exam, symptoms, imaging, and other parameters that would define disease severity and could be used to guide assessment of subsequent response to therapeutic interventions.

e. The outcomes of routine dental therapy/dental implants among patients with a history of current and past oral or intravenous bisphosphonates need to be defined. In addition, we need to determine whether optimizing oral hygiene and dental care can prevent ONJ from occurring and whether bisphosphonates should be stopped before patients undergo dental surgery, and if so, for how long before and after surgery?

f. While the task force made recommendations for clinical management (see Section 4), the best management approach to the patient who develops ONJ is still unclear and needs to be better defined. The approach to this problem may need to rely initially on descriptive studies that rigorously evaluate current practice attempts to manage these lesions. The development of an appropriate animal model (see below) may be necessary and essential, particularly given the common observation that many interventions appear to worsen the condition. Such an animal model, once developed, in combination with good descriptive clinical findings, would hopefully provide the rational/ethical basis on which human randomized clinical trial investigations could occur.

Animal/basic studies:

a. The effects of bisphosphonates on mandibular and maxillary bone homeostasis and healing, specifically on bone microarchitecture, and the rate, extent, and quality of bone healing after routine trauma need to be evaluated.

b. The cellular/molecular mechanisms by which bisphosphonates may predispose to the development of ONJ remain unclear and need to be identified.

c. The relationship of osteoclastogenesis and bone resorption to angiogenesis is an important area that may help define the mechanisms by which bisphosphonates could predispose to ONJ.

d. The role of oral infection or trauma in the development of ONJ is unclear and needs to be defined.

e. The role of inflammatory/immune cells in the pathogenesis of ONJ needs to be addressed.

Specific approaches suggested to investigate these questions include the following:

- Studies that examine the bioavailability and biodistribution of bisphosphonates
- Studies of regional differences in bone metabolism and turnover in mandibular and maxillary bone relative to other skeletal sites
- Studies on regional differences in the vascularization and blood flow of mandibular and maxillary bone relative to other skeletal sites
- Evaluation of bone wound healing in the mandible and maxilla using various surgical and animal models after bisphosphonate treatment; additionally, could adding back agents to stimulate bone turnover, such as PTH, be counteractive?
- Studies of gingival–bone interactions after bisphosphonate treatment
- Development and validation of crevicular fluid and saliva biomarker assays to allow for localized sampling of ONJ-affected and adjacent regions
- If direct skeletal accumulation of bisphosphonates, rather than alterations in the rate of bone turnover, is found to be associated with ONJ, mouse models may

be particularly useful in pharmacogenetic studies because of the availability of a panel of genetically well-characterized strains.

SUMMARY

Bisphosphonate-associated ONJ is a relatively recently described entity, and the task force strongly recommends that a consistent case definition, a minimal reporting requirement, and a hierarchy of evidence be used for subsequent reporting of the disorder. The incidence of the disease seems to be relatively low in patients receiving oral bisphosphonates for osteoporosis or Paget's disease and considerably higher in patients with malignancy receiving high doses of intravenous bisphosphonates. However, more information is needed on the true incidence of bisphosphonate-associated ONJ and the other major risk factors for developing this complication. The task force recognizes that information on incidence of ONJ is rapidly evolving, that continued surveillance will undoubtedly result in identification and publication of more cases, and that estimates of the frequency of ONJ may change for patients receiving bisphosphonates for both malignant and nonmalignant disease. The task force recommends that an external agency follow-up and validate reports of ONJ, both to confirm all reported cases and to accumulate further accurate information on the condition. Improved diagnostic imaging may help identify patients at early or preclinical stages of ONJ, thereby leading to approaches to prevent the disease, because treatment is currently mainly supportive. A number of clinical and basic research questions were identified by the task force, which should help to formulate a research agenda to better understand, prevent, and treat this condition.

ACKNOWLEDGMENTS

The task force thanks the staff of the ASBMR, in particular Douglas Fesler, for help with all aspects of this effort.

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Received in original form March 15, 2007; revised form May 16, 2007; accepted July 17, 2007.

APPENDIX 1: GLOSSARY OF DENTAL TERMS FOR THE NONDENTAL PRACTITIONER

Term	*Definition*
Periodontal disease	A collective term for a range of conditions that result in inflammation of the soft and hard tissues surrounding teeth. Left untreated, these conditions may lead to tooth mobility and tooth loss consequent to progressive resorption of periodontal bone. The most common forms of periodontal disease are gingivitis and chronic periodontitis.
Gingivitis	Inflammation of the gingiva (gum tissue associated with teeth) resulting in swelling, redness, and easy bleeding. Gingivitis is the least serious form of periodontal disease, and although very common, is often painless. Improvement in oral hygiene procedures will usually reverse gingivitis.
Chronic periodontitis	Inflammation of the connective tissue and bone surrounding teeth associated with loss of connective tissue attachment to tooth root surfaces and loss of supporting bone. Often associated with recession of the gingiva and/or periodontal pocket formation. Loss of alveolar bone is not a reversible condition.
Mucositis	Inflammation of any mucous lining surface of the oral cavity.
Tooth apex or root apex	The terminal end of the root of a tooth. The term "periapical" connotes the tissues immediately surrounding the root apex.
Crown	Usually used to describe the "clinical crown" or that portion of a tooth that is exposed to the oral cavity
Endodontic therapy	A collective term to describe treatment of the dental pulp and associated dental root associated structures. Root canal therapy is a form of endodontic therapy.
Periradicular surgery	Typically a soft tissue flap is reflected to permit removal of bone to gain direct surgical access to the periapical region of a tooth.
Dentoalveolar surgery	Surgical management of tooth and associated soft tissues and other jaw bone diseases. Extraction of either exposed teeth or impacted teeth are commons forms of dentoalveolar surgery.
Torus	A slow growing protuberance of bone. Most commonly seen in the midline of the palate (torus palatinus) as well as bilaterally on the lingual aspects of the mandible. Larger tori often have thin mucosal covering.
Crevicular fluid	Gingival fluid containing plasma proteins, which is present in increasing amounts in association with gingival inflammation.

APPENDIX 2: CONFLICT/DUALITY OF INTEREST SUMMARY AND DISCLOSURES

The ASBMR is well served by the fact that many of those responsible for policy development and implementation have diverse interests and are involved in a variety of activities outside of the Society. The ASBMR protects itself and its reputation by ensuring impartial decision-making. Accordingly, the ASBMR requires that all ASBMR Officers, Councilors, Committee Chairs, Editors-in-Chief, Associate Editors, and certain other appointed representatives disclose any real or apparent conflicts of interest (including investments or positions in companies involved in the bone and mineral metabolism field), as well as any duality of interests (including affiliations, organizational interests, and/or positions held in entities relevant to the bone and mineral metabolism field and/or the American Society for Bone and Mineral Research).

Name	*Affiliation/representation*	*Conflicts*	*Commercial entity/no. of relationships*
Sundeep Khosla	Mayo Clinic College of Medicine/ ASBMR	Yes	Glaxo Smith Kline 2; Novartis 2
Elizabeth Shane	Columbia University/ASBMR	Yes	Amgen 1; Novartis 1
David Burr	Indiana University School of Medicine	Yes	Eli Lilly 1, 2; Amgen 5 (<$10,000); Procter & Gamble 1, 2; Merck; Biomet, Pfizer, J&J 5 (<$10,000 each)
Jane Cauley	University of Pittsburgh	Yes	Merck 1,3; Lilly 1,2; Pfizer 1; Novartis 1,2
David Dempster	Columbia University	Yes	Merck 1, 2, 3; Eli Lilly 2, 3; Sanofi Aventis P&G 2, 3; NPS Pharmaceuticals 2, 3; GSK-Roche 2, 3; Bone Editorial Board; Osteoporosis International Associate Editor
Peter Ebeling	University of Melbourne	Yes	Amgen 1,2; Novartis 1,2; Roche 2; Merck 2
Dieter Felsenberg	University Hospital Benjamin Franklin	Yes	Novartis 1,2; Roche 1,2; MSD 1,2; P&G 1,2; Sanofi-Aventis 1,2; Lilly 1,2; Wyeth 1; Onganon 1; Scheming 1; Nycomed 1,2; GSK 1,2; Amgen 1; Goy,Teva 1,2; Chugai 1,2; Synarc 1; Siemens 1; GE-Lunar 1; Kyphon 1
Robert Gagel	University of Texas MD Anderson	Yes	Novartis 1, 3; Merck 3; P&G 3
Theresa Guise	Univ. of Virginia/ENDO, IBMS, Paget's's Foundation	Yes	IBMS, Paget's's Foundation & ASCI 6; Amgen 1,2; Novartis 2; Merck 2; SCIOS 1,2; Fibrogen 1
Laurie McCauley	University of Michigan	Yes	Eli Lilly 1; Amgen 5
Marc McKee	McGill University	Yes	Targanta Therapeutics, Montreal, QC 1,2,; Enobia Pharma, Montreal, QC 1,2; Biosyntech Inc., Laval, QC 5 (stock options); CIHR Institute of Musculoskeletal Health and Arthritis 6 (scientific advisory board); Int'l Assoc. Dental Research Science Awards Subcommittee 6 (Committee for Distinguished Scientist Awards)
Sreenivas Koka	Mayo Clinic	No	
Joan McGowan	NIH – NIAMS	No	
Suresh Mohla	NIH – NCI	No	Society for Melanoma Research 6 (Editorial Board); J Cellular Biochemistry 6 (Editorial Board); Paget's's Conference on Skeletal Complications of Malignancy 6 (Scientific Planning Committee); Cancer Induced Bone Diseases Mol Meeting 6 (Scientific Planning Committee)
David Pendrys	University of Connecticut	Yes	Straumann 1
Larry Raisz	University of Connecticut/NOF	Yes	Novartis 2; Servier International 1; Procter & Gamble 2; Pfizer 2
Salvatore Ruggiero	Long Island Jewish Medical Center	No	
David Shafer	University of Connecticut	Yes	Novartis 2 (vice chair adjudication committee); ITI 2,3 (speaker and committee member); Straumann 1
Lillian Shum	NIH-NIDCR	No	
Stuart Silverman	ASBMR/ACR	Yes	Amgen 2; Eli Lilly 1, 2, 3; Kyphon 3; Merck 1, 2, 3; Novartis 1, 2, 3; Procter & Gamble 1, 2, 3; Roche/ GlaxoSmithKline 1, 2, 3; Wyeth 1, 2
Catherine Van Poznak	University of Michigan	Yes	Amgen 2; Beslex 2; Novartis 2; Roche 2
Nelson Watts	University of Cincinnati/ISCD, AACE	Yes	Eli Lilly 1,2; Glaxo Smith-Kline 2,Novartis 1,2; NPS 2; Procter & Gamble 1,2; Roche 2; Sanofi Aventis 1,2; Servier 2; Wyeth 2; Amgen 1,2, Editorial Board JCEM, Osteoporosis International, Journal of Clinical Densitometry, several committees for ISCD
Sook-Bin Woo	Harvard School of Dental Medicine	Yes	Novartis 1

Relationship key: 1, research grant or financial support from commercial entities; 2, consultant or member of advisory board to a commercial entity; 3, participant in a speaker's bureau; 4, employment or executive positions in pharmaceutical, medical device, or diagnostic companies; 5, stock holdings in pharmaceutical, medical device, or diagnostic companies; 6, any other situation or transaction in which you have a formal role or interest (e.g., you serve on a bone related organization's board, committee, journal; a family member contracts with ASBMR, etc.).