S Rayman
K Almas
E Dincer

Bisphosphonate-related jaw necrosis: A team approach management and prevention

Authors' affiliations:
Salim Rayman, Dental Hygiene, Eugenio Maria de Hostos Community College, The City University of New York, New York, NY, USA
Khalid Almas, Division of Periodontology, University of Connecticut School of Dental Medicine, Farmington, CT, USA
Elvir Dincer, Dental Hygiene, Eugenio Maria de Hostos Community College, The City University of New York, New York, NY, USA

Correspondence to:
Dr Khalid Almas
Division of Periodontology
University of Connecticut School of Dental Medicine
Farmington
CT, USA
Tel.: +1 860 679 3721
Fax: +1 860 679 1027
E-mail: khalidalmas@yahoo.com

Abstract: Osteonecrosis means the process of bone death. Bisphosphonates (BPs) are becoming recognized increasingly as having a significant impact on dental treatments. BPs are the most widely used class of anti-resorptive drugs. They prevent bone resorption through osteoclast inhibition and are considered the standard of care for the management of metastatic bone disease. BPs are used for the treatment of skeletal disorders such as osteoporosis, hypercalcaemia of malignancy, ostoelytic lesions arising from solid tumours and Paget's disease, breast cancer or prostate cancer. Jaw necrosis appears to be associated with the intravenous (i.v.) use of BPs. The aim of this review paper is to update the understanding of healthcare professionals to the osteonecrosis of jaws, mechanism of action and classification of BPs, management of the patients with BP-related osteonecrosis (BRON) of the jaws. An interdisciplinary approach has been emphasized to prevent and manage the condition. Finally, the role of dental practitioners including dental hygienists has been discussed to early diagnose the BRON and improve the quality of life of patients with the condition.

Key words: bisphosphonates; dental professionals; interdisciplinary approach; osteonecrosis of jaws; prevention

Dates:
Accepted 12 June 2008

To cite this article:
Int J Dent Hygiene **7**, 2009; 90–95
DOI: 10.1111/j.1601-5037.2008.00331.x
Rayman S, Almas K, Dincer E. Bisphosphonate-related jaw necrosis: A team approach management and prevention.

Introduction

Osteonecrosis means the process of bone death. Osteonecrosis of the jaws (ONJ) is a serious condition that has been reported by dental practitioners and physicians in cancer and osteoporosis patients on bisphosphonate (BP) therapy. The risk of ONJ in patients taking BPs is low, but its clinical implications are unavoidable. General practitioners generally do not routinely make specific efforts to identify patients who have taken BPs and

are going on BP therapy therefore it is likely that many patients are currently not identified when they attend general dental practice. The review would help to understand and update understanding of healthcare professionals about BP-related jaw necrosis.

Osteonecrosis of the jaws

Osteonecrosis of the jaws (ONJ) may be associated with a number of different predisposing systemic conditions such as haemoglobinopathies, lymphoproliferative disorders, Paget's disease, phosphorous exposure and BPs, and local conditions of sepsis (apical or periodontal), trauma (surgical or local) and radiotherapy. ONJ is often asymptomatic for some time before clinical presentation. As long as the overlying mucosa is intact and infection is not introduced into the bone, which has limited healing potential, then there may be no clinical signs or symptoms of the underlying bony pathology (1). Risk factors for the development of clinically evident osteonecrosis include dental infection, periodontal disease and invasive dental treatment. Presenting features include non-healing ulceration, pain, loosening of teeth and were present, features of infection such as swelling, erythema and a discharging sinus. However, in the early stages there may be no obvious radiological changes but later on there will be evidence of bone mottling and sequestrum formation similar to osteomyelitis (2).

Bisphosphonates: mechanism of action and classification

In the mid-1990s BPs were first introduced and prescribed as alternatives to hormone replacement therapies for osteoporosis and to treat osteolytic tumours and possibly slow tumour development. The strategy in the treatment of osteoporosis is to inhibit the resorption of trabecular bone by osteoclasts and hence preserve its density (3). In 1996, fosamax (alendronate) was the first BP drug approved for osteoporosis in post-menopausal women and later approved for the treatment of Paget's disease. Table 1 lists BPs drugs use and prescribed in the United States.

Bisphosphonates are also used in the treatment of malignant bone diseases. Cancer patients with both primary and metastatic bone lesions develop the skeletal complications of pain, pathologic fracture, spinal cord compression and hypercalcaemia for which BPs appear to help.

There are two classes of BPs which have different mechanisms of action on osteoclasts based on the presence or absence of a nitrogen side chain on the pyrophosphate group (1). Non-nitrogen containing BPs are taken up by the osteoclast and antagonize the cellular energy pathways leading to cell apoptosis (cell death) (4). Therefore, decrease bone breakdown by reducing osteoclast cell numbers. Nitrogen containing BPs has a more complex pathway of action, where they inhibit the 3-hydroxy-3-methyl-glutaryl-Coenzyme A (HMG-CoA) reductase pathway. This is an important cellular pathway that generates hydrophobic molecules for diverse tasks such as maintenance of cell membranes, production of hormones, anchoring of proteins and for *N*-glycosylation. Nitrogenous BPs binds and blocks the enzyme in the HMG-CoA reductase pathway which is essential for connecting some small proteins to the cell membrane (4). This disruption affects the osteoclastogenesis, apoptosis and cytoskeletal dynamics, resulting in loss of adherence of osteoclasts to the surface of bone (4).

Table 1. **Bisphosphonate drugs approved for use in the United States**

Generic name	Brand name	Medical uses	Administration route
Alendronate sodium	Fosamax (Merck and Co. Inc., Whitehouse Station, New Jersey, USA)	Osteoporosis in post-menopausal women Osteoporosis in men Paget's disease	Oral
Clodronate	Bonefos (Schering AG, Berlin, Germany)	Excess calcium resulting from malignant cells	Intravenous/oral
Etidronate	Didronel (Procter & Gamble Pharm, Cincinnati, Ohio, USA)	Paget's disease	Oral
Ibrandronate sodium	Boniva (Roche Lab Inc., Basel, Switzerland/ GlaxoSmithKline, London, UK)	Osteoporosis in post-menopausal women Glucocorticoid-induced osteoporosis Paget's disease	Oral
Pamidronate disodium	Aredia (Novartis Pharm)	Cancer associated with bone Moderate-to-severe Paget's disease	Intravenous
Risedronate sodium	Actonel (Procter & Gamble Pharm)	Paget's disease Osteoporosis in post-menopausal women Glucocorticoid-induced osteoporosis	Oral
Tiludronate	Skelid (Sanofi-Aventis, Paris, France)	Paget's disease	Oral
Zoledronic acid	Zometa (Novartis Pharm)	Excess calcium resulting from malignant cells Cancer associated with bone	Intravenous

Bisphosphonates seems to affect osteoclasts in terms of both numbers and function; the effects on the osteoblasts and the osteocyte are not well understood, and a number of studies are under way to better describe BPs' mode of action. In animal studies, BPs also demonstrated some anti-angiogenic properties; this may partially explain the development of osteonecrosis, in the sense that the bone has limited healing ability because of reduced vasculature (5).

Bisphosphonates-associated osteonecrosis of the jaws

Osteonecrosis of the jaw associated with the use of BPs, primarily zoledronic acid or pamidronate, was first described by Marx (6) (Figures 1–4 a and b), and as there have been a multitude of case series published (7). Marx *et al.* (3) reviewed 119 cases of BP-related bone exposure and found that 48 (40.3%) were receiving zoledronate and 32 (26%) were receiving pamidronate. Cartsos *et al.* (8) assessed medical claims data from 714 217 people to determine the prevalence of jaw pathologies among patients with osteoporosis and patients with cancer. They also looked at whether that prevalence was related to the method of BPs administration used. They found that patients with conditions requiring i.v. BPs had a much higher risk of developing adverse conditions in the jaw compared with patients taking oral BPs. The incidence of ONJ among patients with cancer varies, most retrospective studies estimate that a minimum of 5% of IV BP users develop ONJ. The majority of osteonecrosis cases are in cancer patients who have received i.v. BPs. Approximately 94% of all osteonecrosis cases are due to i.v. use and 6% are linked to oral BPs (9). A hospital retrospective chart review of 479 oncologic patients at the University of Arkansas Medical Center identified 25 patients who had received BPs for an average of 4.4 years (range, 1–8 years), mostly pamidronate, and had developed ONJ. Eleven of the 25 patients had undergone dental treatment before their development of ONJ (10).

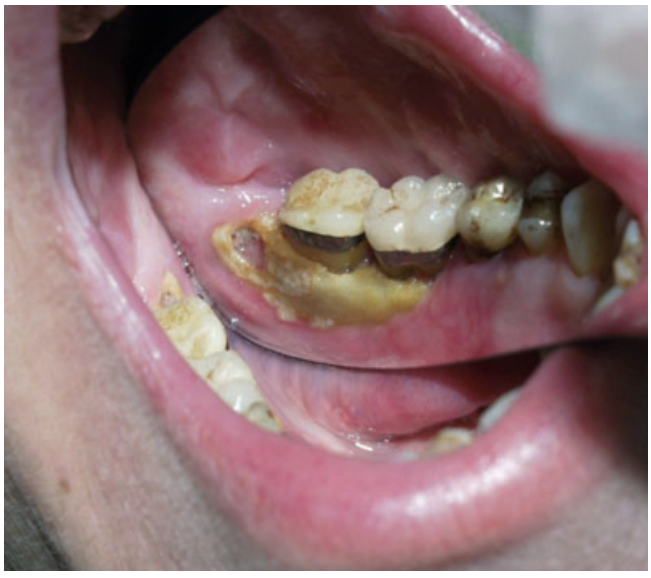

Fig. 1. Stage 1 – Characterized by exposed bone that is asymptomatic with no evidence of significant soft tissue infection.

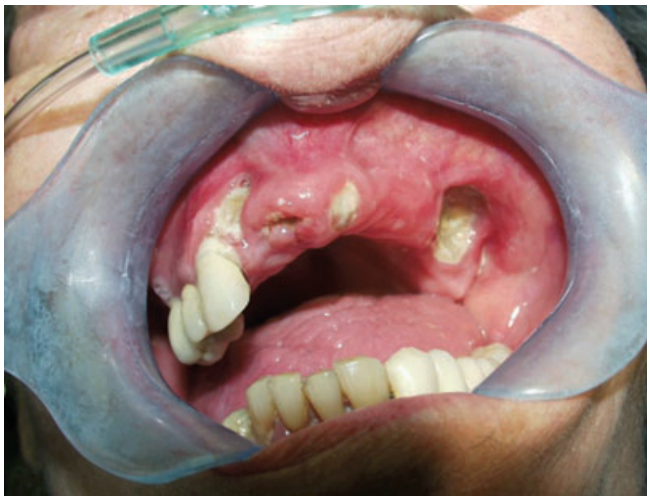

Fig. 2. Stage 2 – Exposed bone associated with pain, soft tissue and/-or bone infection.

The mandible and maxilla were the only bones involved in bone exposures. In Marx study of 119 cases, 81 (68.1%) occurred exclusively in the mandible, 33 (27.7%) exclusively in the maxilla and five (4.2%) simultaneously in the mandible and maxilla (3). Marx *et al.* (3) also noted that the most common dental comordidity was clinically and radiographically apparent periodonititis which was present in 100 (84%) of the cases.

Management of patients with bisphosphonate-related osteonecrosis

Once BP-related osteonecrosis (BRON) has been identified by the oncologist or a dental practitioner, the patient should be referred to an oral and maxillofacial surgeon. Procedures such as debridement to cover the exposed bone with flaps, or bone-contouring procedures have been counterproductive and have mostly led to worsening of symptoms, further exposed bone and greater risk for a pathologic fracture of the jaw. In BRON the entire bone is affected and therefore cannot be debrided to a viable bone margin. Hyperbaric oxygen (HBO_2), which has proven effective in the treatment of osteoradionecrosis by establishing an oxygen gradient, was

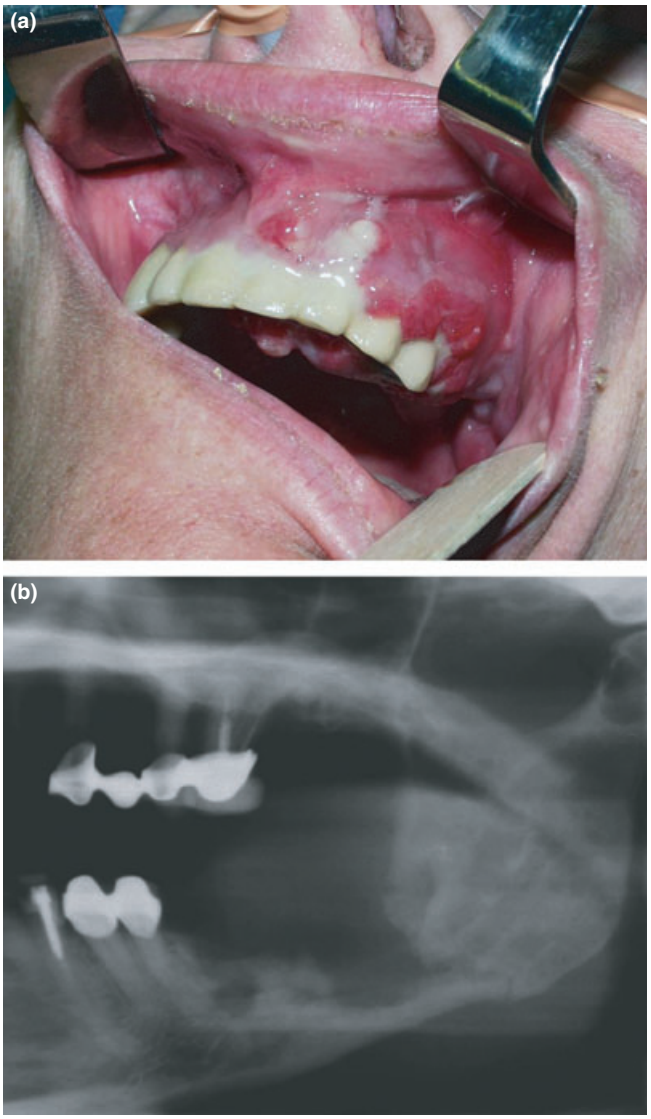

Fig. 3. (a) Stage 3 – Pathologic fracture – exposed bone associated with soft tissue infection or pain that is not manageable with antibiotics because of the large volume of necrotic bone. (b) Stage 3 – Radiograph of pathologic fracture.

investigated by Freiberger *et al.* (11) as a possible therapy for BRON. The pilot study treated 16 BRON patients with HBO_2 and found that seven patients (44%) were in remission and eight (50%) had stabilized; however, stabilization without remission was sustained in only two patients. In addition, seven patients who continued on BP treatment during HBO_2 therapy had a shorter time to failure than those who discontinued the drug. Freiberger and colleagues concluded that while adjunctive HBO_2 therapy may benefit patients with BRON, the outcome is improved with cessation of BP administration. Marx stated that HBO_2 has no benefit to the patient with BRON because of the mechanism of the two diseases of bone necrosis is entirely different. Because of the long half-life of the BPs and their great efficacy in stabilizing metastatic cancer deposits in bone, there is no absolute reason to discontinue BP therapy (3). Therefore, if surgery is counterproductive and HBO_2 and BP discontinuation are of little or no benefit, patients must and can live with some exposed bone. Necrotic exposed bone itself is not painful and can remain structurally sound to support normal jaw function. If secondary infection should arise, the condition will become painful and may lead to cellulitis and fistula formation. The current treatment for BRON includes pain control, a broad spectrum of oral antibiotics (long term and sometimes permanent), superficial debridement of sharp bony projections that produce soft tissue inflammation and pain along with 0.12% chlorohexidine mouth rinses (12).

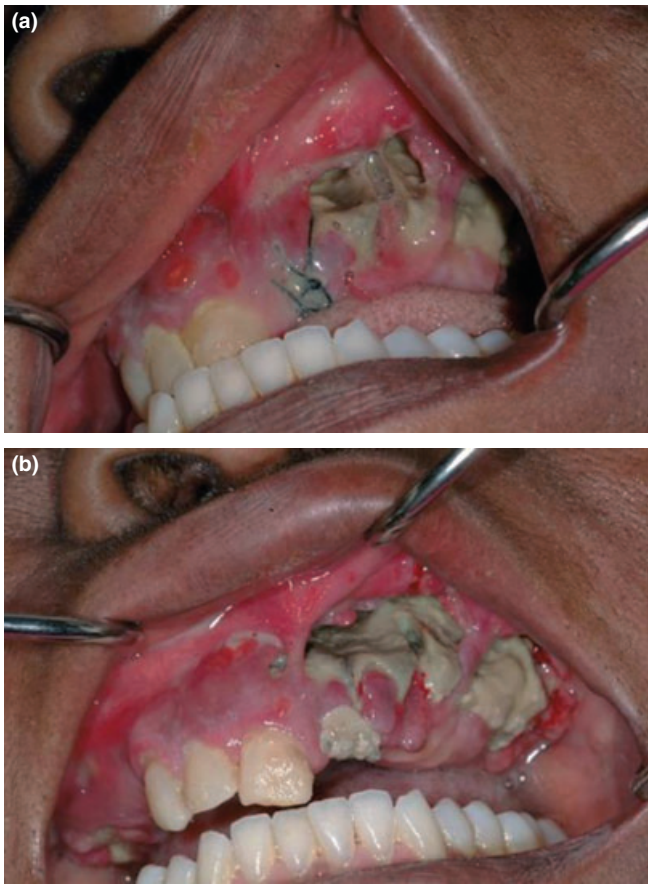

Fig. 4. (a and b) A 40-year old with female with a diagnosis of breast cancer and Zometa therapy (6 months) presents with pain, exposed and infected maxillary bone following extraction.

Prevention – an interdisciplinary approach

The true cause of BRON has not been determined, what is clearly established is its association with poor dental health. For this reason, preventive measures are of supreme impor-

Table 2. **Summary of guidelines on dental management of bisphosphonate patients**

	Before prescribing	After prescribing
Medical Practitioner Prescriber Information	Consider and inform patient of risk of BRON Advise patient to seek dental assessment and treatment	Advise regular dental maintenance visits Refer for the assessment of oral symptoms consistent with BRON
Dental Practitioner Information	Full dental examination Complete all necessary dental treatment and preventive advice	Non-surgical treatment when possible 0.12% Chlorhexidene mouthwash preoperatively and until all wounds have healed Consider prophylactic antibiotics pre- and post-operatively

tance. Until prospective studies of BRON provide information about effective treatment protocols, the best approach is prevention, with the dental practitioner and the physician working collaboratively (13). The American Dental Association (14) have produced guidelines regarding the dental management of patients prescribed BPs, which states that there is currently no evidence basis for the guidelines and they are based on the recommendations of panels of experts. A summary of the available guidelines is presented in Table 2.

The general consensus is that a patient should undergo a dental assessment any necessary treatment before BPs therapy begins. The dental practitioner should obtain medical information from the physician such as a complete review of all medical diagnosis, the diagnosis for which the patient will receive BP therapy, history of cancer treatment and of oral complications associated with that treatment, expected toxicity resulting from the current treatment regimen, complete blood counts, the type of BP that is going to be used and the administration protocol (including the expected duration of therapy) (13). This medical information will be used as a guide by the dental practitioner for developing a dental treatment plan. The primary objective of the treatment plan is to eliminate all potential sites of infection with a goal of attaining a state of good oral and dental health. A comprehensive extra- and intraoral examination should be performed along with full mouth radiographic series and a panoramic radiograph which will aid in the diagnosis of caries and periodontal disease. Periodontal health status should be obtained and therapy provided to eliminate pockets is of utmost importance. Extraction of teeth must be completed as soon as possible and restorative dentistry should be performed to eliminate caries and defective restorations. Prophylaxis and oral hygiene instructions are also paramount. The dental practitioner should inform the patient about BRON and the early signs of development of this conditions as well as the importance of oral hygiene home care and oral hygiene maintenance visits.

The role of the dentist and dental hygienist (dental practitioners)

It is imperative that the dental practitioners and other medical professionals become familiar with BRON. Treatment management involves educating the dental practitioner, pharmacist, physician, and patient about BRON and preventive measures that need to be taken to avoid these oral complications. The American Academy of Periodontology published a statement on BPs, making periodontists aware of the need to determine if patients are currently taking i.v. BPs or if any patients will be treated with these drugs (15). The Food and Drug Administration (FDA) and drug companies have published statements for dental health professionals regarding the development of BRON in patients being treated with BPs. For example, in 2004 Novartis (Basel, Switzerland) implemented changes to Zometa and Aredia product labels to include precautions on BRON. The precaution states that a dental examination and preventive dentistry should be considered prior to treatment with BPs in patients with concomitant risk factors such as poor oral hygiene, cancer, chemotherapy and corticosteroids (16).

Because of the potential catastrophic consequences of developing established BRON are such that dental practitioners must ask specifically about BPs as part of their medical history for new patients and enquire again with returning patients (17). In addition, evidence suggests that BPs are retained in a therapeutic dosage in bone for several years after the drug therapy is discontinued (18). Therefore, dental practitioners must manage patients with past history of BPs therapy in the same manner as patients on current therapy.

The dental hygienist may be the first person on the dental team to discover spontaneous necrosis of the jaws. In most offices it is the dental hygienist who takes the patient medical history, preliminary intra- and extraoral examination and radiographs prior to seeing the dentist. It is also the goal of the dental hygienist to promote periodontal health, perform prophylaxis,

and educate patients on good oral health and importance of oral hygiene maintenance visits, which are all paramount in preventing BRON and treating patients with BRON. On recall visits the dental hygienist is most likely the one to review the patients chart and perform oral hygiene maintenance. It is very important that the dental hygienist at this recall visit review the medical history thoroughly with the patient.

The dental hygienist and dentist play a pivotal role in educating the patient about the potential adverse events that can occur, once starting BPs. The dental hygienist is in the best position to advise and educate the patient on how to maintain excellent oral hygiene to reduce the risk of dental and periodontal infections as well as the importance of routine dental examinations before and during BP therapy.

Conclusion

As researchers and clinicians learn more about BRON and who is at risk, better recommendations for prevention and treatment will evolve. In the meantime, communication between dental and medical practitioners must be improved to allow patients to have the best of both dental and medical treatment. The information available regarding the risk of developing BRON is based on expert opinion and clinical experience, and patients who are receiving BP therapy must be informed of the possibility of BRON developing after routine dental treatment. The dental practitioner, physician and patient must come to a consensus before any dental treatment begins.

It is recommended that dental practitioners follow existing guidelines for a dental consultation for the prevention of oral complications of cancer therapy. Prevention measures is of paramount importance and dental practitioners including dentist and dental hygienist, physicians and oncologist must use a team approach when treating patients receiving or going to be receiving BP therapy. Dental professionals including dental hygienists should be on the forefront to early diagnose the BRON condition.

References

1 Mcleod NMH, Davies BJB, Brennan PA. Bisphosphonates osteonecrosis of the jaws; an increasing problem for the dental practitioner. *British Dent J* 2007; **203:** 641–644.

2 Chiandussi S, Biasotto M, Dore F *et al.* Clinical and diagnostic imaging of bisphosphonate-associated osteonecrosis of the jaws. *Dentomaxillofac Radiol* 2006; **35:** 239–243.

3 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:** 1567–1575.

4 Fleisch H. Bisphosphonates: mechanisms of action. *Endocr Rev* 2002; **19:** 80–100.

5 Fournier P, Boissier S, Filleur S *et al.* Bisphosphonates inhibit angiogenesis *in vitro* and testosterone-simulated vascular regrowth in the ventral prostate in castrated rats. *Cancer Res* 2002; **62:** 6538–6544.

6 Marx RE. Pamidronate(Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003; **61:** 1115–1117.

7 Santini D, Vespasiani GU, Vincenzi B *et al.* The antineoplastic role of bisphosphonates: from basic research to clinical evidence. *Ann Oncol* 2003; **14:** 1468–1476.

8 Cartsos V, Zhu S, Zavras A. Bisphosphonates use and the risk of adverse jaw outcomes: a medical claims study of 714,217 people. *JADA* 2008; **139:** 23–30.

9 Woo SB, Hellstein JW, Kalmar JR. Narrative review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006; **144:** 753–761.

10 Clarke BM, Boyette J, Vural E, Suen JY, Anaissie EJ, Stack BC Jr. Bisphosphonates and jaw osteonecrosis: the UAMS experience. *Otolaryngol Head Neck Surg* 2007; **136:** 396–400.

11 Freiberger JJ, Padilla-Burgos R, Chhoeu AH *et al.* Hyperbaric oxygen treatment and bisphosphonate-induced osteonecrosis of the jaw: a case series. *J Oral Maxillofac Surg* 2007; **65:** 1321–1327.

12 AAOMS Position Paper. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 2007; **65:** 369–376.

13 Migliorati CA, Casiglia J, Epstein J, Jacobsen PL, Siegel MA, Woo SB. Managing the care of patients with bisphosphonate-associated osteonecrosis: an American Academy of Oral Medicine position paper. *J Am Dent Assoc* 2005; **136:** 1658–1668.

14 American Dental Association council on Scientific Affairs. Dental management of patients receiving oral bisphosphonates therapy. *J Am Dent Assoc* 2006; **137:** 1144–1150.

15 American Academy of Periodontology *American Academy of Periodontology Statement of Bisphosphonates*. http://www.perio.org/resources-products/bisphosphonates.htm (accessed 26 August 2005).

16 Weinberg MA. Bisphosphonates-associated osteonecrosis of the jaws: impact on oral health. *US Pharm* 2006; **5:** 62–69.

17 Cheng A, Mavrokokki A, Carter G. The dental implications of bisphosphonates and bone disease. *Aust Dent J* 2005; **50 (Suppl. 2):** S4–S13.

18 Black DM, Schwartz AV, Ensrud KE. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension – a randomized trial. *JAMA* 2006; **296:** 2927–2938.