Oral Diseases (2008) 14, 277–285. doi:10.1111/j.1601-0825.2007.01381.x

http://www.blackwellmunksgaard.com

ORIGINAL ARTICLE

Updates on bisphosphonates and potential pathobiology of bisphosphonate-induced jaw osteonecrosis

J Sarin, SS DeRossi, SO Akintoye

Department of Oral Medicine, School of Dental Medicine, University of Pennsylvania, Philadelphia, PA, USA

Osteonecrosis of the jaws is a major complication associated with long-term use of bisphosphonates. While osteonecrosis can arise from other precipitating conditions, bisphosphonate-induced jaw osteonecrosis (BJON) is highly associated with long-term administration of pamidronate (Aredia®) and zoledronic acid (Zometa®), which are two intravenous bisphosphonate formulations. The underlying pathogenesis of BJON and its site-specific presentation still remain to be fully elucidated. This review will discuss clinically available bisphosphonates, current opinions, pathogenesis, and management guidelines for bisphosphonate-induced jaw osteonecrosis.
Oral Diseases (2008) **14**, 277–285

Keywords: bisphosphonates; jaw; osteonecrosis; biology; bone marrow

Introduction

'Osteonecrosis' is a term commonly used to describe death of bone cells – the osteocytes in the cortical bone and the cells of the bone marrow organ residing in the hematopoietic compartment of trabecular bone. These include hematopoietic stem cells (HSCs), bone marrow stromal cells (BMSCs), pre-osteoblasts, mature osteoblasts, lining cells, and osteoclasts. Osteonecrosis also destroys bone endothelial cells and vasculature leading to impairment of blood flow within the bone. So, osteonecrosis alone is not considered a disease but the end result of disrupted blood flow caused by other factors. Bisphosphonates, in particular, pamidronate (Aredia®) and zoledronic acid (Zometa®) have been widely associated with osteonecrosis of the jaw bones (ONJ), a condition characterized by tissue dehiscence, chronic bone devitalization, hypocellularity, and lytic radiographic features. Anecdotal reports and case series suggest that it is often refractory to therapy (Ruggiero *et al*, 2004; Marx *et al*, 2005; Migliorati *et al*, 2005a, 2006), but prospective clinical studies have not been conducted. Other types of osteonecrosis are associated with the infiltrative process of Gaucher's disease, physiologic changes in pregnancy, pathological processes of trauma, and thromboembolism while others are characterized as idiopathic (Katz *et al*, 1996; Montella *et al*, 1999; Bjorkman *et al*, 2004). In the maxillofacial complex, osteonecrosis can arise as a complication of several therapeutic regimens. In particular, osteoradionecrosis is a distinct type of osteonecrosis that results as a complication of high-dose radiation therapy, whereas osteomyelitis can cause osteonecrosis from protracted microbial invasion of bone. Less closely associated with the maxillofacial complex is steroid-induced osteonecrosis described as avascular necrosis in patients on long-term glucocorticoid therapy (Calvo-Alen *et al*, 2006).

The term 'osteonecrosis of the jaw' has been used to describe cases of bisphosphonate-induced osteonecrosis (Marx *et al*, 2005) because all previously reported cases have been located in the jaw bones except one case in the auditory canal (Polizzotto *et al*, 2006). As jaw osteonecrosis can arise from factors other than bisphosphonate therapy, ONJ specifically caused by bisphosphonates can be referred to as 'bisphosphonate-induced jaw osteonecrosis' (BJON). Some reports have indicated a high susceptibility of BJON in regions of thin and friable oral mucosa such as tissue covering a torus mandibularis or torus palatinus (Marx *et al*, 2005; Odvina *et al*, 2005; Woo *et al*, 2006). An example is a 60-year-old female multiple myeloma patient on long-term pamidronate who was referred to our oral medicine practice to rule out BJON (Figure 1). She had never been aware of her torus palatinus until spontaneous tissue dehiscence occurred over the torus. She was asymptomatic for 4 months before complaining of unusual 'growth on the roof of her mouth'.

Although the underlying pathogenesis of BJON is yet to be clearly elucidated, it is clinically distinct from other types of osteonecrosis. The highest number of cases of BJON have been reported in patients treated with pamidronate and zoledronic acid which are widely used to treat hypercalcemia associated with malignancy, osteolytic lesions of cancer metastasis and multiple

Correspondence: SO Akintoye, Department of Oral Medicine, School of Dental Medicine, University of Pennsylvania, Philadelphia PA, USA. E-mail: akintoye@dental.upenn.edu
Received 18 October 2006; revised 20 November 2006; accepted 8 December 2006

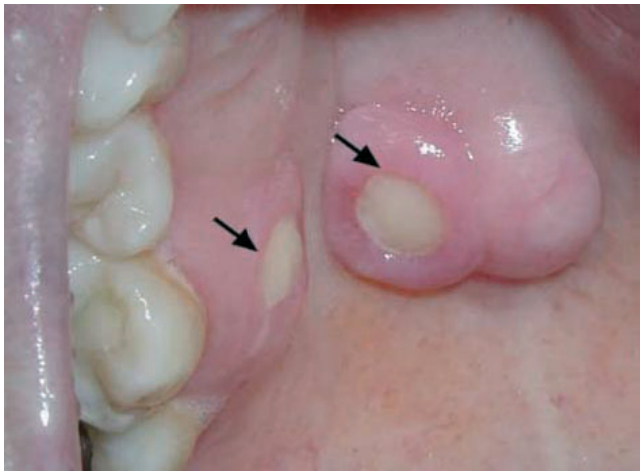

Figure 1 Bisphosphonate-induced osteonecrosis. This 60-year-old female patient diagnosed with multiple myeloma was on long-term treatment with pamidronate before developing osteonecrosis in relation to the torus palatinus and palatal exostosis (black arrows)

myeloma, and Paget's disease. The increasing number of BJON cases prompted the drug manufacturer (Novartis Pharmaceuticals, East Hanover, NJ, USA) to include ONJ in the patient information literature as a possible side effect of long-term administration of pamidronate and zoledronic acid (MedWatch, 2005). However, there are several reported cases of BJON associated with orally administered bisphosphonates such as alendronate (Fosamax®) and risedronate (Actonel®) (Ruggiero *et al*, 2004; American Dental Association Council on Scientific and Affairs, 2006). It is important for the clinician to be more conversant with different bisphosphonate formulations and current updates on pathogenesis and management of BJON to accurately counsel patients taking these medications. This review covers bisphosphonates currently approved for clinical use by the USA Food and Drug Administration (FDA) and presents an overview of current opinions on the pathogenesis and management of BJON.

Structure and properties of bisphosphonates

Bisphosphonates are analogs of pyrophosphate with oxygen replaced by carbon in the pyrophosphate bond to form a phosphate–carbon–phosphate (P-C-P) structural backbone (Figure 2). Different bisphosphonates were designed by changing the two side chains (R′ and R″) on the carbon atom in the P-C-P structure. The effectiveness and binding affinity of bisphosphonates to mineral structure is made possible by the phosphate ends of the P-C-P structure as it allows anchorage of bisphosphonate onto the bone surface. The two side chains (R′ and R″) dictate the anti-resorptive potency of an individual bisphosphonate and determine the extent of bisphosphonate binding to hydroxyapatite (Rodan and Fleisch, 1996). Generally, bisphosphonates have high affinity for hydroxyapatite, remaining unmetabolized for long periods of time (Jung *et al*, 1973; Fleisch, 1998). This physicochemical property is due to the binding of the phosphate ends to metal ions, including

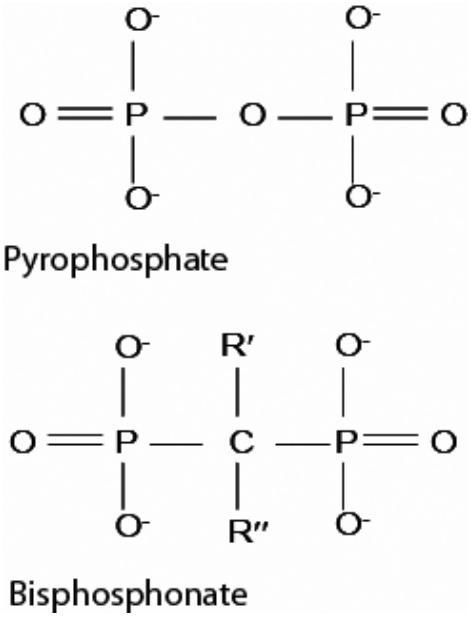

Figure 2 Chemical structure of pyrophosphate and bisphosphonate (adapted from Fleisch, 2000)

calcium, forming both soluble and insoluble complexes and the resistance of their P-C-P structural backbone to heat, most chemicals and enzymatic hydrolysis (Fleisch, 2000). In addition to avid binding to hydroxyapatite, bisphosphonates prevent hydroxyapatite crystal formation, aggregation, and dissolution (Fleisch, 2000).

Bisphosphonates inhibit bone resorption and therefore improve bone mineral density by decreasing bone turnover. This action is not due to their physicochemical properties but due to cellular mechanisms that decrease frequency and resorption depth of bone remodeling units (Schenk *et al*, 1973; Fleisch, 2000). Bisphosphonates have direct effects on osteoclasts, reducing recruitment and proliferation of osteoclast precursors and inducing osteoclast apoptosis. During bone turnover, matrix-bound bisphosphonate is phagocytosed by osteoclasts and the accumulation of bisphosphonates in osteoclasts changes their cytoskeleton, disrupts their ruffled border and induces apoptosis (Hughes *et al*, 1995). The nitrogen-containing bisphosphonates inhibit the mevalonate pathway in cholesterol biosynthesis. They inhibit farnesylpyrophosphate synthase, an enzyme that catalyses the conversion of geranylpyrophosphate to farnesylpyrophosphate (Figure 3). This decreases formation of isoprenoid lipids used for post-translational prenylation (covalent addition of multiprenyl units or fatty acid chains) of several proteins required for cellular functions. The final outcome is a reduction in osteoclast activity and increased apoptosis (Luckman *et al*, 1998). In a similar fashion, non-nitrogen-containing bisphosphonates can also induce osteoclast apoptosis. Because they are structurally close to a pyrophosphate, they can be easily integrated into the phosphate chain of ATP-containing compounds so that the P-C-P containing ATP compound becomes non-hydrolyzable and accumulates intracellularly to induce apoptosis (Rogers, 2003).

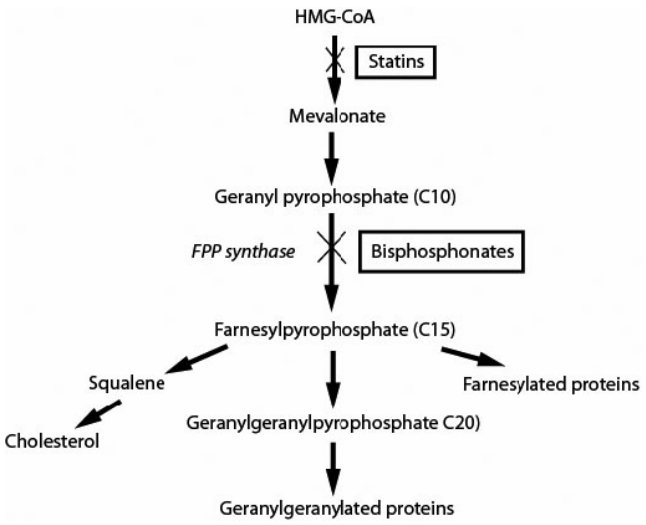

Figure 3 Effect of bisphosphonates. Nitrogen-containing bisphosphonate mediate their action by inhibiting the mevalonate pathway involved in cholesterol synthesis. Statins clinically used to lower cholesterol level inhibit formation of mevalonate, but bisphosphonates inhibit farsnesylpyrophosphate (FPP) synthase, an enzyme that catalyzes conversion of geranyl pyrophosphate to farnesylpyrophosphate (adapted from Fleisch, 2000)

Bisphosphonates also inhibit osteoclastic activity indirectly through bone marrow stromal cells (BMSCs) and osteoblasts. Normally, osteoblasts enhance osteoclast recruitment and activation by interaction of osteoblast cell surface 'receptor activator of NFκB ligand' (RANKL) with RANK on hematopoietic osteoclast precursor cells. To keep this interaction in check, osteoblasts also secrete osteoprotegerin (OPG), a soluble decoy receptor that competes with RANKL for RANK to inhibit osteoclast recruitment and control osteoclast–osteoblast balance (Lacey *et al*, 1998; Kostenuik, 2005). Bisphosphonates inhibit RANKL expression and enhance OPG production by bone marrow stromal cells and osteoblasts so that RANK–RANKL interaction is disrupted. These synergistic actions lead to suppression of osteoclast recruitment and reduction of bone resorption (Viereck *et al*, 2002; Nishida *et al*, 2005).

Several bisphosphonates have been tested for clinical use, but it is difficult to directly compare them because each bisphosphonate has distinct physicochemical and biological characteristics. Currently, there are nine bisphosphonates approved for clinical use by the FDA in the USA (Table 1). Seven of the nine bisphosphonates have been approved for oral administration while pamidronate and zoledronic acid are given intravenously. Alendronate (Fosamax®, Merck, Whitehouse Station, NJ, USA), risedronate (Actonel®, Roche, Nutley, NJ, USA), pamidronate (Aredia®, Novatis, East Hanover, NJ, USA), zoledronic acid (Zometa®, Procter & Gamble, Cincinnati, OH, USA) and ibandronate (Boniva®, Sanofi-aventis, Bridgewater, NJ, USA) are aminobisphosphonates; they have a much higher potency because they contain nitrogen in the R′ side chain (Table 1) (Woo *et al*, 2006). Since 1995, there has been an increasing use of intravenous bisphosphonates for the treatment of cancer bone metastasis (Michaelson and Smith, 2005). It is therefore noteworthy, that both pamidronate and zoledronic acid have been involved in as many as 600 reported cases of BJON, which led to the association of BJON with long-term administration of intravenous bisphosphonates. Presented below is a short summary on each bisphosphonate based on available drug monographs (RxList, 2006a).

Alendronate (Fosamax®)

Alendronate is a nitrogen-containing, orally administered bisphosphonate that was approved by the FDA in the USA since 1995. It is one of the top 50 prescribed

Table 1 List of bisphosphonate approved for clinical use by United States of America Food and Drug Administration (FDA), route of administration and common side effects

Generic name	*Brand name*	*Route of administration*	*Manufacturer*	*FDA approval*	*Common side effects*
Alendronate sodium	Fosamax	Oral	Merck	1995	Gastrointestinal intolerance, headache, hypocalcemia, hypophosphatemia
Aldendronate sodium plus Vitamin D	Fosamax plus D	Oral	Merck	2005	Gastrointestinal intolerance, headache, bone pain, dizziness
Etidronate disodium	Didronel	Oral	Procter & Gamble	1977	Gastrointestinal intolerance, bone pain, fever, increased serum creatinine
Ibandronate sodium	Boniva	Oral/Intravenous	Roche and GlaxoSmithKline	2003	Gastrointestinal intolerance, headache, bone pain, hypercholesterolemia, dizziness
Pamidronate disodium	Aredia	Intravenous	Novartis	1991	Fever, fatigue, nausea, hypophosphatemia, hypokalemia, infusion site reaction
Risedronate sodium	Actonel	Oral	Procter & Gamble	1998	Gastrointestinal intolerance, headache, pain, rash, urinary tract infection, arthralgia, back pain, hypertension
Risedronate sodium plus calcium carbonate	Actonel with calcium	Oral	Procter & Gamble	2005	Infection, back pain, abdominal pain, hypertension, arthralgia
Tiludronate disodium	Skelid	Oral	Sanofi-aventis	1997	Gastrointestinal intolerance, dizziness, paresthesia, chest pain, edema, rhinitis, sinusitis
Zoledronate acid	Zometa	Intravenous	Novartis	2001	Gastrointestinal intolerance, bone pain, fever, fatigue

drugs in the USA with 17 915 000 prescriptions in 2005 and 20 972 548 in 2004 (RxList, 2006a,b). Uptake of alendronate by osteoclasts is 10-fold that of osteoblasts. Although, it does not hinder osteoclast recruitment or attachment, alendronate inhibits osteoclast activity. By binding to sites of active bone resorption by osteoclasts, alendronate disrupts the osteoclast-ruffled border and its ability to resorb bone. Increasing deposition of normal bone over hydroxyapatite-bound alendronate traps it within the bone matrix, making it pharmacologically inactive. Therefore, it is necessary for patients to continuously take alendronate to suppress newly formed resorption surfaces. Alendronate reduces bone turnover by reducing the number of bone remodeling sites. It allows bone formation to surpass bone resorption at bone remodeling sites; as a result, alendronate enhances progressive increase in bone mass. The mean bioavailability of alendronate after oral intake is 0.64% compared with its intravenous equivalent; however, this is further reduced if alendronate is taken with meals. Metabolism of alendronate in animals or humans is still unclear, but it is partially eliminated in urine. The half-life of alendronate in humans is over 10 years, which is an indication that alendronate is slowly released from bone. Alendronate is used for prevention and treatment of osteoporosis in postmenopausal women. It promotes increase in bone mass, which results in marked reduction in fracture incidence in postmenopausal women. It is also used to increase bone mass in men with glucocorticoid-induced osteoporosis and to treat bone lesions of Paget's disease. However, it is not indicated for use in children with osteogenesis imperfecta. About 170 cases of alendronate-induced jaw osteonecrosis have been reported worldwide, with at least 29 cases reported in the US alone (American Dental Association Council on Scientific Affairs 2006). All cases of alendronate-related BJON occurred in patients who had been taking alendronate for several years. This most likely represents a low incidence of alendronate-related osteonecrosis considering the high number of alendronate annual prescriptions and its long half-life. Recently, a new form of alendronate fortified with vitamin D (Fosamax plus D) was approved by the FDA.

Pamidronate (Aredia®)

Pamidronate is a nitrogen-containing bisphosphonate with an amino group attached at the R′ position. It is one of two bisphosphonates approved by the FDA for intravenous administration. As a strong inhibitor of bone resorption, it attaches to hydroxyapatite to block mineral dissolution and inhibit osteoclast activity. Pamidronate is not metabolized by humans but eliminated from the body by renal clearance. It is highly effective for treatment of cancer-associated hypercalcemia because of its ability to inhibit bone resorption without affecting bone formation and mineralization. Pamidronate is used for the treatment of hypercalcemia of malignancy, Paget's disease, and osteolytic bone metastases of cancers such as breast cancer and multiple myeloma, but it has not been approved in the US for treatment of osteoporosis. However, in clinical studies, pamidronate administered intravenously has been shown to prevent bone loss in patients with postmenopausal osteoporosis, recently menopausal women and patients with corticosteroid-induced osteoporosis (Boutsen *et al*, 2001). About 211 cases of pamidronate-induced jaw osteonecrosis have been reported worldwide.

Zoledronic acid (Zometa®)

Zoledronic acid is also a nitrogen-containing bisphosphonate with an imidazole ring attached at the R′ position. Like pamidronate, zoledronic acid is administered intravenously. It has potent anti-resorptive properties by binding to bone to inhibit resorption of hydroxyapatite. It also inhibits osteoclast activity and induces osteoclast apoptosis. Zoledronic acid is not metabolized in humans but excreted intact by the kidneys. It is mainly used for the treatment of cancer-associated hypercalcemia and osteolytic bone metastases of cancers such as breast cancer and multiple myeloma. It is also not currently approved by the FDA for treatment of osteoporosis in the USA; however, about 219 cases of zoledronic acid-induced jaw osteonecrosis have been reported worldwide.

Risedronate (Actonel®)

Risedronate is also a nitrogen-containing bisphosphonate with high affinity for hydroxyapatite. It inhibits osteoclast activity by preventing formation of osteoclast-ruffled border, thereby reducing bone resorption and bone turnover. Absorption after an oral dose is relatively rapid, with a bioavailability of 0.63% compared with the equivalent intravenous dose, but this is reduced by 55% if taken with meals. Risedronate is taken up by bone while the remainder is excreted in urine. Risedronate is an effective inhibitor of osteoclastic bone resorption. It was FDA-approved for the prevention and treatment of postmenopausal osteoporosis, glucocorticoid-induced osteoporosis and Paget's disease. It was also among the top 100 prescribed drugs in the USA in 2005 with 9 660 000 prescriptions (RxList, 2006b). Risedronate is provided as either daily or weekly oral formulations. A combination of risedronate and calcium was FDA-approved in 2005 as the first-prescription osteoporosis therapy to include calcium. It is indicated specifically for the prevention and treatment of postmenopausal osteoporosis. The addition of calcium improves its efficacy as it is essential for maintaining bone health. There have been approximately 12 reported cases of risedronate-related BJON causing jaw osteonecrosis (American Dental Association Council on Scientific and Affairs, 2006; Van den Wyngaert *et al*, 2006).

Ibandronate (Boniva®)

Ibandronate is a third-generation nitrogen-containing oral bisphosphonate. In 2005, it became the first FDA-approved bisphosphonate to be taken once a month. While it is primarily administered orally, it also has an intravenous formulation. Ibandronate has high affinity for hydroxyapatite and inhibits osteoclast activity. It

reduces bone resorption and bone turnover, leading to a net gain in bone mass. Absorption of ibandronate after oral administration is about 0.6% of comparable intravenous dose, but its bioavailability is decreased by 90% if taken with meals. Ibandronate is not metabolized in humans, but is taken up either by the bone matrix or excreted in urine. It is used for treatment and prevention of osteoporosis. In postmenopausal women, a daily dose of 2.5 mg day^{-1} increased bone mineral density by 5% in the spine and 3–4% in the hip bones; but when the 2.5 mg day^{-1} dose was compared with 100- and 150-mg monthly doses, the monthly formulations demonstrated similar or better improvements in bone mineral density (Miller *et al*, 2005). Therefore, a monthly formulation of ibandronate has also been approved for patient care. There has been one reported case of ibandronate-related BJON (American Dental Association Council on Scientific and Affairs, 2006).

Etidronate (Didronel®)

The chemical structure of etidronate does not contain nitrogen. Unlike other bisphosphonates, etidronate increases bone density by acting directly on bone and not through osteoclasts or osteoblasts. It acts by chemisorption to calcium phosphate to inhibit formation, growth, and dissolution of hydroxyapatite. These actions are dose-dependent, but its ability to inhibit hydroxyapatite dissolution is best at low doses. Bioavailability of etidronate after oral intake is about 3% of comparable intravenous dose but half of absorbed etidronate resides in bone. The bone-bound etidronate is gradually eliminated from bone in about 165 days. Etidronate has not been approved by the FDA for treatment of osteoporosis. Rather, it is used for treatment of bone lesions of Paget's disease and for prevention and treatment of heterotopic ossification (ectopic calcification) that commonly occurs in 50% of patients who undergo total hip replacement. However, it is noteworthy that some studies have shown that intermittent cyclical etidronate therapy prevents bone loss in menopausal women (Storm *et al*, 1990; Watts *et al*, 1990). There are currently no reported cases of etidronate-related BJON.

Tiludronate (Skelid®)

Tiludronate is a bisphosphonate that does not contain nitrogen in its chemical structure. It also prevents bone resorption by inhibiting osteoclast activity. However, it acts by reducing the enzymatic transport processes that results in bone resorption. Tiludronate mediates its inhibition of osteoclast activity by either inhibiting protein-tyrosine-phosphatase to make osteoblast detach from the bone surface or by inhibiting the osteoclastic proton pump. After oral administration, bioavailability of tiludronate is 6% relative to an intravenous reference dose but this is reduced by 90% if taken with meals. Tiludronate is not metabolized by humans; it is mainly excreted in urine. Tiludronate was approved by the FDA to treat Paget's disease but it is not prescribed as commonly as other bisphosphonates. In a large trial of postmenopausal women, oral tiludronate did not demonstrate effectiveness in fracture prevention probably due to use of doses that were considered suboptimal (Black and Rosen, 2006). There are currently no reported cases of BJON associated with patients treated with tiludronate.

Other bisphosphonates

Other bisphosphonate formulations not approved for use in the USA are currently being tested or, in other countries, for different skeletal disorders. Clodronate disodium is readily available in both oral and intravenous formulations in Canada for treatment of malignancy-associated hypercalcemia. Other bisphosphonates include EB-1053, icandronate, minodronate, neridronate, and olpadronate. There are still ongoing studies on efficacy of icandronate in patients with multiple myeloma, but minodronate has demonstrated some effectiveness in patients with osteogenesis imperfecta (Ochiai *et al*, 2005; Hanai *et al*, 2006). Additionally, intravenous formulations of neridronate and olpadronate are being tested in patients with breast cancer and Paget's disease, respectively (van der Pluijm *et al*, 1996; Roldan *et al*, 1998). As there are still no conclusive data on their safety and efficacy, it is not surprising that these drugs have not yet been approved by the FDA for use in the USA.

The most common side effects of the nine approved bisphosphonates are gastrointestinal intolerance, bone pain, and flu-like symptoms (Table 1). Gastrointestinal symptoms are common with orally administered bisphosphonates. This is a side effect difficult to overcome because absorption of oral bisphosphonates is drastically reduced if taken with food. Flu-like febrile symptoms are more common with pamidronate and alendronate but limited to only about a day before disappearing. Other common side effects include dizziness, nausea, vomiting, and headaches.

Bisphosphonate-induced osteonecrosis of jaws

Long-term use of pamidronate and zoledronic acid have been associated with up to 600 cases of BJON (Ruggiero *et al*, 2006; Woo *et al*, 2006). The strong association with these two bisphosphonate formulations may relate to the higher bioavailability of intravenously administered bisphosphonates compared with oral formulations. At least 50% of intravenous bisphosphonates is bioavailable for incorporation into the bone matrix compared with an average of 1% of oral bisphosphonates absorbed by the gastrointestinal tract (Ezra and Golomb, 2000). BJON is considered the first described long-term complication of bisphosphonate therapy. Most cases were diagnosed after dental procedures such as tooth extraction, though a few cases occurred spontaneously (Migliorati *et al*, 2005b). BJON can present clinically as painful, soft tissue swelling and infection, loosening of teeth, drainage, exposed bone, or it may be asymptomatic (Marx, 2003). There are still conflicting reports on the bone more commonly affected between the maxilla and mandible. Nonetheless, these reports agree that intra-oral sites with bone covered by thin and friable

Table 2 Stage-specific treatment recommendations for management of bisphosphonate-induced jaw osteonecrosis (*Adapted from Ruggiero *et al*, 2006)

Staging	*Clinical features*	*Treatment strategies*
Pre-BJON	No apparent exposed/necrotic bone in patients who have been treated with either oral or intravenous bisphosphonates	No treatment indicated. Patient education
Stage 1	Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection	Antibacterial mouth rinses. Clinical follow up on a quarterly basis. Patient education and review of indications for continued bisphosphonate therapy
Stage 2	Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	Symptomatic treatment with broad-spectrum oral antibiotics, e.g. penicillin, cephalexin, clindamycin, or first-generation fluoroquinolone Oral antibacterial mouth rinses. Pain control. Only superficial debridement to relieve soft-tissue irritation
Stage 3	Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border	Antibacterial mouth rinses. Antibiotic therapy and pain control. Surgical debridement or resection for long-term palliation of infection and pain

Adapted from Ruggiero *et al* (2006).

mucosa such as torus mandibularis or torus palatinus (Figure 1) are more susceptible (Migliorati *et al*, 2005b; Woo *et al*, 2006). It is important to clinically monitor orofacial complex of patients taking bisphosphonate for early signs of BJON. As a guide to management, clinical staging of BJON was recently proposed based on the absence or presence of symptoms (Table 2) (Ruggiero *et al*, 2006).

Theories related to BJON pathogenesis

Mechanisms underlying the pathogenesis of BJON are active areas of investigation. Currently, several theories have been proposed to explain the pathogenesis of BJON.

Jaw susceptibility

It has been proposed that the jaw bones are highly susceptible to osteonecrosis, based on several anatomical and physiological factors (Marx *et al*, 2005). First, bisphosphonates tend to be highly concentrated in the jaws rather than other skeletal sites because of their high vascularity and bone turnover. Secondly, the forces of masticatory functions and periodontal ligament around numerous teeth mandate rapid bone turnover around the periodontium and can easily induce microfractures in bisphosphonate-induced acellular and avascular bone. Thirdly, the thin oral mucosa can be easily traumatized or breached during surgical procedures, allowing oral microbes to track into the necrotic bone.

Anti-osteoclast activity

The inhibitory effect of bisphosphonates on osteoclasts causes cessation of bone remodeling and bone turnover. Pamidronate and zoledronic acid, possibly, are highly associated with BJON because they are potent inhibitors of osteoclasts, unlike oral bisphosphonates (e.g. alendronate) that are less potent and resist osteoclast function less severely. After long-term administration of bisphosphonates, the inability of osteoclasts to resorb old bone causes the osteoblast and osteocytes to die leaving an acellular bone matrix. This is followed by degeneration of the small capillaries, avascularity, and high susceptibility to microfractures (Marx *et al*, 2005). Inadvertent trauma to the thin overlying oral mucosa can introduce oral microbes into the avascular bone matrix leading to osteonecrosis.

Anti-angiogenesis action

Bisphosphonates are also known to exhibit anti-angiogenic property (Santini *et al*, 2003). This is one reason for their use in the management of metastatic cancer. Theoretically, the ability of bisphosphonates to inhibit vascular endothelial growth factor and formation of new capillaries (Ferretti *et al*, 2005) may be accentuated in the jaw bones with high vascularity and bone turnover. The end result is avascular necrosis. However, other antiangiogenic drugs are not associated with osteonecrosis in any skeletal site.

Uncoupling of osteoblast–osteoclast equilibrium in jaw bones

Bone marrow stromal cells (BMSCs), a putative population of postnatal stem cells within the bone marrow organ can differentiate into multiple cell types including pre-osteoblasts and osteoblasts. Because BMSCs express RANKL on their cell surface, they also indirectly modulate osteoblast–osteoclast balance. It has been shown that the superior proliferative ability (Akintoye *et al*, 2006) of orofacial marrow stromal cells (OFMSCs) resident in the maxilla and mandible compared with axial skeletal site (iliac crest) make them more susceptible to high doses of pamidronate (Stefanik *et al*, 2006), an intravenous bisphosphonate implicated in BJON. Osteoblastic differentiation of OFMSCs was reduced after pamidronate treatment, but when OFMSCs were pre-treated with pamidronate and co-cultured with $CD34^+$ hematopoietic stem cells (HSCs), there was an appreciable increase in osteoclast number compared with marrow stromal cells derived from iliac crest of the same individuals. The same study suggested

that, in addition to enhancing the osteoclast-recruiting capacity of OFMSCs, pamidronate can also suppress OFMSC osteoblastic differentiation. Thus, unlike its action on iliac crest BMSCs, pamidronate may act within the jaw bones to uncouple the osteoblast–osteoclast balance by simultaneously suppressing bone formation while enhancing bone resorption. There is also additional evidence that osteoclast activity is elevated in patients on long-term bisphosphonates because they demonstrate low serum calcium despite elevated levels of parathyroid hormone (Ardine *et al*, 2006).

'Band-wagon' effect

In the absence of other stress-inducing factors, pamidronate-treated BMSCs are able to recover and form ectopic bone after transplantation into immunocompromised mice (Sarin *et al*, 2006; Stefanik *et al*, 2006). But in clinical situations, several co-morbid factors may promote BJON because patients with osteolytic lesions of cancer metastasis may be taking multiple medications including chemotherapy (Migliorati *et al*, 2006; Woo *et al*, 2006). Dexamethasone is a commonly used adjuvant in cancer therapy and some reports indicated that chronic administration of oral glucocorticoids and estrogen in addition to bisphosphonates may increase the risk of BJON (Marx *et al*, 2005; Odvina *et al*, 2005). Other stress-inducing co-morbidities in cancer patients include alcohol, smoking, and advanced age and suggested dental co-morbidities are periodontal disease, dental caries, and root canal therapy. It is possible that the synergistic effect of the combination of chemotherapy, bisphosphonate-induced cellular stress on OFMSCs due to long-term use, cancer related co-morbid factors, uncoupling of osteoblast–osteoclast equilibrium, reduced vasculature, bone microfractures, and tracking of oral microbes through the periodontium may act in concert to produce a 'bandwagon effect' (Sarin *et al*, 2006) that raises disease burden and lower susceptibility threshold in favor of BJON.

Management Guidelines

There are currently no evidence-based guidelines on the management of BJON, therefore emphasis is placed on preventive measures. Patients on bisphosphonates and physicians prescribing them should be educated on potential oral complications and risks of BJON. Before commencing bisphosphonate therapy, the patient should be referred for a thorough dental evaluation to identify and treat any potential sources of infection. The dentist should emphasize oral hygiene instructions and routine dental prophylaxis to insure optimal dental health (Table 2).

If possible, bisphosphonate therapy should be delayed when dental health is sub-optimal. Invasive dental procedures should be completed, non-restorable teeth with poor prognosis should be extracted, and bisphosphonate therapy can be started 4–6 weeks later to allow appropriate bone healing (Ruggiero *et al*, 2006). Risks of BJON associated with oral bisphosphonates are far lower than intravenous formulations but more dependent on the duration of treatment. Elective dental treatment is not currently contraindicated in this patient population (American Dental Association Council on Scientific and Affairs, 2006) but they should be educated on the relative low risks associated with oral bisphosphonates, the maintenance of optimal oral health and the need to promptly inform their dental healthcare provider if oral symptoms develop. If a patient is already on bisphosphonate therapy with no evidence of osteonecrosis, it is paramount to emphasize good oral hygiene and preventive dental care. Routine dental care including prophylaxis, scaling, and root planning, and minor restorations can be carried out without added risks for developing BJON. However, dental extractions and other oral surgical procedures should be avoided as bone healing may be compromised (Migliorati *et al*, 2005b). Patients with removable dentures should be examined for areas of mucosal trauma, especially along the internal mylohyoid ridge area. If BJON has already developed, dental management will depend on the severity of the lesion. Treatment objectives for these patients will be directed at eliminating pain, controlling soft and hard tissue infections, and minimizing progression of osteonecrosis. Unfortunately, these patients do not respond well to established treatment algorithms for osteomyelitis or osteoradionecrosis that include surgical intervention and hyperbaric oxygen therapy. Surgical debridement of necrotic bone to create well-vascularized bone conducive to healing is difficult because the entire jawbone has been exposed to the pharmacologic effect of bisphosphonate. Therefore, surgical treatment should be delayed if possible. Patients with established BJON should avoid elective dento-alveolar surgical procedures, because the surgical sites may result in additional areas of exposed necrotic bone. Patients with mild, asymptomatic, or stage 1 disease may benefit from use of antimicrobial rinses such as 0.12% chlorhexidine, while a patient with exposed bone associated with pain and/or secondary infection or stage 2 disease will require oral antimicrobial rinses combined with antibiotic therapy based on culture and sensitivity tests (Table 2). Finally, patients with painful exposed necrotic bone, soft tissue swelling, and infection may also have pathologic jaw fracture (stage 3 disease); these patients should be treated by surgical debridement of necrotic bone, antimicrobial therapy, analgesics, and daily oral antimicrobial rinses (Table 2) (Ruggiero *et al*, 2006).

The benefits of bisphosphonate therapy are well established. Their ability to prevent bone fracture reaches a peak only after long-term use, so patients are still instructed to keep taking bisphosphonates for an extended amount of time. It is imperative for health professionals to carefully consider the risks and benefits before taking patients off bisphosphonates as a preventive measure for jaw osteonecrosis. The dentist and physician managing the patient must adopt an interdisciplinary approach that will result in the

formulation of an effective patient-specific management protocol.

Conclusions

There is increasing evidence that bisphosphonates preferentially increase osteoclast activity in orofacial bones and sites that eventually succumb to both BJON and osteoradionecrosis (Hansen *et al*, 2006; Sarin *et al*, 2006). Moreover, osteoclast activity is elevated in patients on long-term bisphosphonates because they demonstrate low serum calcium despite elevated levels of parathyroid hormone (Ardine *et al*, 2006). As bisphosphonates act on osteoclasts to modulate bone resorption, future research to conclusively elucidate pathogenesis of BJON will continue to focus on the biochemical changes that disrupt osteoblast–osteoclast balance in patients taking bisphosphonates. Current BJON management guidelines are based on expert opinions, but an understanding of mechanisms that underlie pathogenesis of BJON will enhance development of evidence-based management guidelines.

Acknowledgements

The authors thank Drs Phoebe Leboy and Ellis Golub for their useful comments in the preparation of this manuscript. This report was partly supported by the United States Department of Health and Human Services research grant 1K08CA120875-01 from the National Cancer Institute, National Institute of Health, Bethesda, MD 20892, USA.

References

Akintoye SO, Lam T, Shi S, Brahim J, Collins MT, Robey PG (2006). Skeletal site-specific characterization of orofacial and iliac crest human bone marrow stromal cells in same individuals. *Bone* **38:** 758–768.

American Dental Association Council on Scientific and Affairs (2006). Dental management of patients receiving oral bisphosphonate therapy: expert panel recommendations. *J Am Dent Assoc* **137:** 1144–1150.

Ardine M, Generali D, Donadio M *et al*. (2006). Could the long-term persistence of low serum calcium levels and high serum parathyroid hormone levels during bisphosphonate treatment predispose metastatic breast cancer patients to undergo osteonecrosis of the jaw? *Ann Oncol* **17:** 1336–1337.

Bjorkman A, Svensson PJ, Hillarp A, Burtscher IM, Runow A, Benoni G (2004). Factor V leiden and prothrombin gene mutation: risk factors for osteonecrosis of the femoral head in adults. *Clin Orthop Relat Res* **425:** 168–172.

Black D, Rosen CJ (2006). Bisphosphonates for the prevention and treatment of osteoporosis. In: Favus MJ, ed. *Primer on the metabolic bone diseases and disorders of mineral metabolism*. American Society of Bone and Mineral Research: Washington DC, pp. 277–282.

Boutsen Y, Jamart J, Esselinckx W, Devogelaer JP (2001). Primary prevention of glucocorticoid-induced osteoporosis with intravenous pamidronate and calcium: a prospective controlled 1-year study comparing a single infusion, an infusion given once every 3 months, and calcium alone. *J Bone Miner Res* **16:** 104–112.

Calvo-Alen J, McGwin G, Toloza S *et al*. (2006). Systemic lupus erythematosus in a multiethnic US cohort (LUMINA): XXIV. Cytotoxic treatment is an additional risk factor for the development of symptomatic osteonecrosis in lupus patients: results of a nested matched case-control study. *Ann Rheum Dis* **65:** 785–790.

Ezra A, Golomb G (2000). Administration routes and delivery systems of bisphosphonates for the treatment of bone resorption. *Adv Drug Deliv Rev* **42:** 175–195.

Ferretti G, Fabi A, Carlini P *et al*. (2005). Zoledronic-acid-induced circulating level modifications of angiogenic factors, metalloproteinases and proinflammatory cytokines in metastatic breast cancer patients. *Oncology* **69:** 35–43.

Fleisch H (1998). Bisphosphonates: mechanisms of action. *Endocr Rev* **19:** 80–100.

Fleisch H (2000). *Bisphosphonates in bone disease: from the laboratory to the patient*, 4th edn. Academic Press: San Diego, CA.

Hanai Y, Tokuda H, Takai S, Harada A, Ohta T, Kozawa O (2006). Minodronate suppresses prostaglandin F2alpha-induced vascular endothelial growth factor synthesis in osteoblasts. *Horm Metab Res* **38:** 152–158.

Hansen T, Kirkpatrick CJ, Walter C, Kunkel M (2006). Increased numbers of osteoclasts expressing cysteine proteinase cathepsin K in patients with infected osteoradionecrosis and bisphosphonate-associated osteonecrosis-a paradoxical observation? *Virchows Arch* **449:** 448–454.

Hughes DE, Wright KR, Uy HL *et al*. (1995). Bisphosphonates promote apoptosis in murine osteoclasts in vitro and in vivo. *J Bone Miner Res* **10:** 1478–1487.

Jung A, Bisaz S, Bartholdi P, Fleisch H (1973). Influence of pyrophosphate on the exchange of calcium and phosphate ions on hydroxyapatite. *Calcif Tissue Res* **13:** 27–40.

Katz K, Horev G, Grunebaum M, Yosipovitch Z (1996). The natural history of osteonecrosis of the femoral head in children and adolescents who have Gaucher disease. *J Bone Joint Surg Am* **78:** 14–19.

Kostenuik PJ (2005). Osteoprotegerin and RANKL regulate bone resorption, density, geometry and strength. *Curr Opin Pharmacol* **5:** 618–625.

Lacey DL, Timms E, Tan HL *et al*. (1998). Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell* **93:** 165–176.

Luckman SP, Hughes DE, Coxon FP, Graham R, Russell G, Rogers MJ (1998). Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including Ras. *J Bone Miner Res* **13:** 581–589.

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

Marx RE, Sawatari Y, Fortin M, Broumand V (2005). Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg* **63:** 1567–1575.

MedWatch (2005). *Safety Information, U.S Food and Drug Administration*. http://www.fda.gov/medwatch/SAFETY/2005/zometa_deardentite_5–5-05.pdf.

Michaelson MD, Smith MR (2005). Bisphosphonates for treatment and prevention of bone metastases. *J Clin Oncol* **23:** 8219–8224.

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

Migliorati CA, Schubert MM, Peterson DE, Seneda LM (2005b). Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone: an emerging oral complication of supportive cancer therapy. *Cancer* **104:** 83–93.

Migliorati CA, Siegel MA, Elting LS (2006). Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. *Lancet Oncol* **7:** 508–514.

Miller PD, McClung MR, Macovei L *et al*. (2005). Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. *J Bone Miner Res* **20:** 1315–1322.

Montella BJ, Nunley JA, Urbaniak JR (1999). Osteonecrosis of the femoral head associated with pregnancy. A preliminary report. *J Bone Joint Surg Am* **81:** 790–798.

Nishida S, Tsubaki M, Hoshino M *et al*. (2005). Nitrogen-containing bisphosphonate, YM529/ONO-5920 (a novel minodronic acid), inhibits RANKL expression in a cultured bone marrow stromal cell line ST2. *Biochem Biophys Res Commun* **328:** 91–97.

Ochiai N, Yamada N, Uchida R *et al*. (2005). Combination therapy with thalidomide, incadronate, and dexamethasone for relapsed or refractory multiple myeloma. *Int J Hematol* **82:** 243–247.

Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY (2005). Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab* **90:** 1294–1301.

van der Pluijm G, Vloedgraven H, van Beek E, van der Wee-Pals L, Lowik C, Papapoulos S (1996). Bisphosphonates inhibit the adhesion of breast cancer cells to bone matrices in vitro. *J Clin Invest* **98:** 698–705.

Polizzotto MN, Cousins V, Schwarer AP (2006). Bisphosphonate-associated osteonecrosis of the auditory canal. *Br J Haematol* **132:** 114.

Rodan GA, Fleisch HA (1996). Bisphosphonates: mechanisms of action. *J Clin Invest* **97:** 2692–2696.

Rogers MJ (2003). New insights into the molecular mechanisms of action of bisphosphonates. *Curr Pharm Des* **9:** 2643–2658.

Roldan EJ, Perez-Llore A, Ferretti JL (1998). Olpadronate: a new amino-bisphosphonate for the treatment of medical osteopathies. *Expert Opin Investig Drugs* **7:** 1521–1538.

Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL (2004). Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* **62:** 527–534.

Ruggiero SL, Fantasia J, Carlson E (2006). Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **102:** 433–441.

RxList (2006a). *RxList Monographs*. http://www.rxlist.com; accessed 16 October 2006. RxList.

RxList (2006b). *The Top 300 Prescriptions for 2005 by Number of US Prescriptions Dispensed*. http://www.rxlist.com/top200.htm; accessed 7 October 2006. RxList.

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

Sarin J, Stefanik D, Lam T *et al*. (2006). Bisphosphonate-Induced Jaw Osteonecrosis: Skeletal Site-Specific Effects of Pamidronate on Osteogenic Differentiation of Human Bone Marrow Stromal Cells. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **102:** 325.

Schenk R, Merz WA, Muhlbauer R, Russell RG, Fleisch H (1973). Effect of ethane-1-hydroxy-1,1-diphosphonate (EHDP) and dichloromethylene diphosphonate (Cl 2 MDP) on the calcification and resorption of cartilage and bone in the tibial epiphysis and metaphysis of rats. *Calcif Tissue Res* **11:** 196–214.

Stefanik D, Sarin J, Vogell A, Levin L, Leboy PS, Akintoye SO (2006). Effects of pamidronate on oro-facial human bone marrow stromal cells. *J Dent Res* **85:** 430.

Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH (1990). Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. *N Engl J Med* **322:** 1265–1271.

Van den Wyngaert T, Huizing MT, Vermorken JB (2006). Bisphosphonates and osteonecrosis of the jaw: cause and effect or a post hoc fallacy? *Ann Oncol* **17:** 1197–1204.

Viereck V, Emons G, Lauck V *et al*. (2002). Bisphosphonates pamidronate and zoledronic acid stimulate osteoprotegerin production by primary human osteoblasts. *Biochem Biophys Res Commun* **291:** 680–686.

Watts NB, Harris ST, Genant HK *et al*. (1990). Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med* **323:** 73–79.

Woo SB, Hellstein JW, Kalmar JR (2006). Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* **144:** 753–761.