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Bisphosphonate-related osteonecrosis of the jaw: an overview

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Bisphosphonates are widely used in the management of metastatic disease to bone and in diseases of altered bone turnover. Recently, multiple-case series and retrospective studies have established a relationship between necrotic bone lesions localized to the jaw and the use of chronic bisphosphonate therapy. This condition has been named bisphosphonate-related osteonecrosis of the jaw (BRONJ). To evaluate the potential risks associated with this new and emerging complication, stage-specific management strategies and guidelines have been developed. In view of the widespread use of chronic bisphosphonate therapy, the observation of an associated risk of osteonecrosis of the jaw should alert practitioners to monitor for this previously unrecognized complication and to reevaluate the indications for and the duration of bisphosphonate therapy in patients with osteopenia/osteoporosis and cancer. Morbidity associated with BRONJ might be prevented or reduced by implementing prevention strategies and establishing early diagnostic procedures. The current widespread use of bisphosphonates as an inhibitor of bone resorption is directly attributable to their efficacy in improving the quality of life for patients with metastatic bone cancer, osteoporosis, and Paget's disease.

Keywords: osteonecrosis; bisphosphonates; BRONJ; ONJ

Bone metastasis to the axial skeleton, pelvis, femora, and ribs is a common occurrence for many malignancies.[1–3] The primary mechanism responsible for osteolysis in these patients is the excessive resorption of bone by osteoclasts. Cancer cells that have metastasized to bone produce a variety of cytokines such as interleukins, prostaglandins, parathyroid hormone-related peptide, and tumor necrosis factor. These agents can stimulate osteoclasts to resorb bone in an uncontrolled manner and result in skeletal destruction.[2,4,5] Myeloma-related lytic disease is now understood to be secondary to increased osteoclastic activity and impaired osteoblastic activity. Myeloma cells are known to secrete both stimulators of osteoclast activation such as receptor activator of nuclear-kB ligand (RANKL) and soluble molecules such as dickkopf 1 (DKK) that inhibit osteoblastic activity.[6] Bisphosphonates inhibit osteoclast function and therefore block the formation of "punched out" lytic bony lesions and consequent manifestations of lytic bony disease.

Osteopenia and osteoporosis are diseases that result from an unbalanced level of bone remodeling. The function and activity of osteoblasts and osteocytes are modulated by sex hormones, a variety of cytokines, and physiologic mechanical stress. Age-related changes in physical activity and sex hormones levels result in an increase in the number of osteoclasts and bone resorption sites. This overwhelms the production of new bone by osteoblasts.[7] The end result is an overall decrease in bone mass and bone strength.

The pathophysiology of Paget's disease is also centered on an imbalance of bone remodeling where the bone resorbing function of the osteoclast is enhanced. This is due to osteoclastic hyperplasia coupled with an overall increase in osteoclastic bone resorbing activity. The reciprocal response by the osteoblast is to increase bone formation, but the

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response is inadequate and disorganized, resulting in a disfigured and structurally weak skeleton.[2]

The aforementioned complications associated with metastatic bone disease, osteoporosis, and Paget's disease are all related to perturbations in osteoclast function. Therefore, it is not surprising that bisphosphonates, which are potent inhibitors of osteoclast function, have demonstrated clinical efficacy in all of these diseases. Bisphosphonate use has dramatically increased over the past few years as new indications for their use continue to be identified. Bisphosphonate therapy has made a significant impact in the palliation of cancer morbidity by reducing bone pain, hypercalcemia, and skeletal complications, such as pathologic fractures. The efficacy of intravenous bisphosphonates in decreasing osteoclast-mediated lysis of bone in disease secondary to multiple myeloma, advanced breast cancer, and other solid tumors has been well established in clinical trials.[8–14]

Thus, intravenous bisphosphonates are frequently administered to patients with osteolytic metastases, especially if there is risk for significant morbidity. A determination, based on clinical practice guidelines established by the American Society of Clinical Oncology, is that the use of bisphosphonates is considered the standard of care for treatment of (1) moderate to severe hypercalcemia associated with malignancy, and (2) metastatic osteolytic lesions associated with breast cancer and multiple myeloma in conjunction with antineoplastic chemotherapeutic agents.[15,16] The Food and Drug Administration has broadened the indications for intravenous bisphosphonates to include bone metastases from any solid tumor. In 2005, it was estimated that over 2.8 million cancer patients worldwide had received intravenous bisphosphonates since their introduction to the marketplace.[17]

As a potent suppressor of osteoclast activity, bisphosphonates slow the remodeling process and increase bone mineral density thereby reducing the risk of fracture in women with osteopenia and osteoporosis.[18,19] All bisphosphonates currently approved for osteoporosis treatment have been shown to significantly reduce the risk of osteoporotic fractures.

Bisphosphonates and jaw necrosis

Despite these benefits, osteonecrosis of the jaw has recently emerged as a significant complication in a subset of patients receiving these drugs. A finding, based on a growing number of case reports and institutional reviews, is that bisphosphonate therapy may cause exposed and necrotic bone that is isolated to the jaw.

Since 2003 numerous reports have been published highlighting the adverse effect profile of this class of agents including the development of osteonecrosis of the jaw in patients treated with bisphosphonates.[20–33] Although the exact mechanism of bisphosphonate-induced osteonecrosis has not yet been determined, several hypotheses have been proposed. The prevailing hypothesis focuses on a drug-induced defect in jawbone physiologic remodeling or wound healing. The profound inhibition of osteoclast function inhibits normal bone turnover to an extent that local micro damage from normal mechanical loading or injury (tooth extraction) cannot be repaired.[34] This can ultimately results in bone necrosis. The recent reports of jaw necrosis in patients receiving Denosumab®, a monoclonal antibody that targets osteoclasts by a completely different mechanism than bisphosphonates, supports the hypothesis osteoclast inhibition might be the primary event in the pathogenesis of this complication.[35,36] Consideration has also to be given to the antiangiogenic properties of certain bisphosphonates. Zolendronic acid has been demonstrated to exert an inhibitory effect on circulating levels of vascular endothelial growth factor (a potent stimulator of angiogenesis).[37,38] These properties may affect the local bone blood supply contributing to the apparent ischemic changes noted in the affected patients' jawbones or operate in concert with the metabolic changes mediated by osteoclast suppression to produce local jawbone necrosis. Other studies have focused on the soft tissue response and demonstrated that bisphosphonates can be directly toxic to the oral mucosa, which may result in mucosal fenestration and bone exposure.[39] Because only a minority of bisphosphonate users develop bone necrosis, it is also possible that individual genetic variations in drug metabolism or skeletal homeostasis may confer susceptibility or resistance to developing BRONJ.[40] These theories and suppositions need to be validated by evidence-based clinical and basic science research.

The apparent selective involvement of the maxilla and mandible may be a reflection of the unique environment of the oral cavity. Typically, healing of

an open bone wound (e.g., extraction socket) in the presence of normal oral microflora occurs quickly and without complication. However, when the healing potential of the mandible or maxilla is compromised either by tumorcidal radiation doses or some other agent(s) or pathologic process, then minor injury or disease in these sites increases the risk for osteonecrosis and possible secondary osteomyelitis. Also, bisphosphonates are preferentially deposited in bones with high turnover rates; given that the maxilla and mandible are sites of significant bone remodeling, it is possible that the levels of bisphosphonate within the jaw are selectively elevated. It is interesting to note that to date this complication of bisphosphonate-related bone necrosis has not been reported within bones outside the craniofacial skeleton.

Several retrospective clinical studies have identified potential risk factors associated with the development of BRONJ.[41–49] These include a history of dentoalveolar trauma, duration of bisphosphonate exposure, and the type of bisphosphonate. In the majority of BRONJ cases reported to date, recent dentoalveolar trauma was the most prevalent and consistent risk factor.[23,41,44] Patients with a history of inflammatory dental disease (e.g., periodontal and dental abscesses) are at a sevenfold increased risk for developing BRONJ.[50] In a case series, the use of chronic steroids in conjunction with bisphosphonates has also been identified as a potential risk factor.[51] The duration of bisphosphonate therapy also appears to be related to the likelihood of developing necrosis with longer treatment regimens associated with a greater risk of developing disease.[41,50] In addition, the more potent intravenous bisphosphonates such as pamidronate and especially zolendronic acid appear to be significantly more problematic as compared with the oral bisphosphonate medications. In a pharmacoepidemiological study comparing large numbers of cancer patients, there was a significantly increased risk of jaw and facial bone surgery and an increased risk of developing osteomyelitis of the jaws in those patients exposed to intravenous bisphosphonates.[52]

Initially, BRONJ was seen only with the use of the more potent intravenous forms of the drug, however, their have been reports of osteonecrosis in patients on the less potent oral forms.[23,31,53] This alarming finding may have significant implications as the number of patients on oral bisphosphonates increases. Although found in both sexes, the literature reports more cases of BRONJ in females than males. This is likely a reflection of the large number of cases reported in breast cancer patients. With postmenopausal osteoporosis as an indication for bisphosphonate use, a large percentage of the female population may also be at risk for developing BRONJ. Patients receiving oral bisphosphonate therapy for osteoporosis that develop BRONJ have typically been exposed to these agents for a longer period of time (greater than 3 years) or were also exposed to steroid therapy.[51]

Current incidence data for BRONJ are limited to retrospective studies with limited sample sizes. The current difficulty in establishing exact incidence data stems from several factors, including a nonstandardized definition and inconsistencies in case recognition and reporting. With that understanding, the estimate of cumulative incidence of BRONJ in patients receiving intravenous bisphosphonates for malignant disease ranges from 0.8% to 12%.[51] For those patients exposed to oral bisphosphonates, the incidence appears to be significantly less.[51] Merck, the manufacturer of alendronate, calculated the incidence of BRONJ to be 0.7 cases per 100,000 person years of exposure.[51] This was derived from the number of reported (not confirmed) cases that were deemed to likely represent BRON divided by the number of alendronate pills prescribed, since approval of the drug, and converted to number of patient years. However, because these cases were not confirmed there may be serious problems with this methodology. In a survey study, based on prescription data in Australia, the estimated frequency of BRONJ for patients treated weekly with alendronate was 0.01–0.04%. If extraction were performed, the calculated frequency increased to 0.09–0.34%.[53]

In 2005, the Food and Drug Administration responded to the growing number of BRONJ cases by issuing broad drug class warning of this complication for all bisphosphonates. This has also prompted a change in clinical practice. With the benefit of bisphosphonate therapy beyond 5 years coming into question for patients with low to moderate risk of an osteoporotic fracture[54,55] coupled with the growing concern about long-term suppression of bone turnover,[56,57] some clinicians have emphasized the importance of a drug holiday. Bisphosphonate treatment algorithms for the oncology patient have also

been modified in some institutions. In a consensus statement from the Mayo Clinic, the use of bisphosphonates in the treatment of multiple myeloma was modified to limit the exposure of intravenous bisphosphonates and minimize the potential for developing BRONJ.[58] The efficacy of these new treatment strategies in decreasing the incidence of BRONJ remains to be determined. In the patient group receiving oral bisphosphonates, the benefit will be especially difficult to establish given the low incidence of BRONJ.

Clinical presentation and staging

Because a universally acceptable term for this complication has not been established, it has been referred to by several names in the literature. A decision by the American Association of Oral and Maxillofacial Surgeons (AAOMS), based on the pattern of association between bisphosphonate therapy and jaw necrosis that has been established in numerous retrospective clinical case studies, was made to adopt the term bisphosphonate-related osteonecrosis of the jaw (BRONJ) for this entity. Standardization of diagnostic criteria for BRONJ is also important to facilitate future clinical and epidemiological research. In addition, a uniform definition for BRONJ will serve to distinguish this new clinical entity from other delayed intraoral healing conditions. The working definition of BRONJ that was established by the AAOMS is the most widely used.[51] In that definition, patients may be considered to have BRONJ if all of the following three characteristics are present: (1) current or previous treatment with a bisphosphonate; (2) exposed, necrotic bone in the maxillofacial region that has persisted for more than eight weeks; and (3) no history of radiation therapy to the jaws.

Signs and symptoms that may occur before the development of clinically detectable osteonecrosis include pain, tooth mobility, mucosal swelling, erythema, and ulceration. Most case series have described this complication at regions of previous dental surgery (i.e., extraction sites) however exposed bone has also been reported in patients with no history of trauma or in edentulous regions of the jaw. This is similar to data extrapolated from a single institutional database at Long Island Jewish Medical Center where the occurrence of BRONJ has been monitored since 2001. One hundred and eighty-six patients with a mean age range of 66 met the criteria. The typical presenting lesions were either a nonhealing extraction socket or spontaneously exposed jawbone; both were refractory to conservative debridement and antibiotic therapy. Eighty percent of the subjects (148) had received intravenous bisphosphonates and 20% (38) were exposed only to an oral bisphosphonates. Dentoalveolar trauma had preceded the development of bone necrosis in 87% of the patients (162).[59]

A clinical staging system, developed by Ruggiero[30] and subsequently updated in the 2009 AAOMS guidelines,[51] has served to more accurately categorize patients with BRONJ, direct rational treatment guidelines, and collect data to assess the prognosis and treatment outcome in patients who have used either IV or oral bisphosphonates (Table 1). Patients with no evidence of exposed or necrotic bone are considered to be "at risk" if they have been exposed to either IV or oral bisphosphonates. The potency of the bisphosphonate used, the duration of exposure, and dentoalveolar surgery appear to be the main determinates in assessing the risk of developing BRONJ. The recent addition of a *Stage 0* category includes those patients with no clinical evidence of necrotic bone but display a variety of nonspecific clinical signs and symptoms such as odontalgia, bone pain, or osteosclerosis that may be a precursor for clinical disease.

Patients with *Stage 1* disease have exposed bone but are asymptomatic. There is no evidence of significant adjacent or regional soft tissue inflammatory swelling or infection. It is possible that patients may have symptoms of pain prior to the development of radiographic changes suspicious for osteonecrosis or clinical evidence of exposed bone (Fig. 1). *Stage 2* disease is characterized by exposed bone with associated pain, adjacent or regional soft tissue inflammatory swelling, or secondary infection (Fig. 2). Patients with *Stage 3* disease (Figs. 3A–C) have exposed bone associated with pain, adjacent or regional soft tissue inflammatory swelling or secondary infection in addition to a pathologic fracture, or an extraoral fistula or radiographic evidence of osteolysis extending to the inferior border. The likelihood of a patient with Stage 1 or Stage 2 disease progressing to a more advanced stage has not been determined but may be dependant on several variables such as the duration of bisphosphonate exposure and whether the patient is still receiving bisphosphonate therapy.

Table 1. Staging of bisphosphonate-related osteonecrosis of the jaw

At risk category	No apparent exposed/necrotic bone in patients who have been treated with either oral or IV bisphosphonates
Stage 0	Nonspecific clinical findings and symptoms such as jaw pain or osteosclerosis but no clinical evidence of exposed bone
Stage 1	Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection
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
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 or sinus floor

Clinical management

In broad terms, managing patients with BRONJ can be very challenging because most surgical and medical interventions may not eradicate this process. The position papers of the AAOMS[51] and the ASBMR[60] provide an adequate assessment of our current level of knowledge about BRONJ and introduce reasonable treatment strategies and risk assessment guidelines that are consistent with the available data. It is important for patients and clinicians to realize that a cure may not be a realistic expectation. The goal of treatment for patients at risk of developing BRONJ or who have active disease is to preserve the quality of life by controlling pain, managing infection, and preventing the development of new areas of necrosis. This has to be balanced with the oncologic management of the patient with osteolytic metastases and the risk of pathologic fracture in the osteoporotic patient. Stopping the intravenous bisphosphonate therapy for the cancer patient provides no short-term benefit given the fact that these agents remain incorporated within the bone for an extended period of time. The benefit of long-term cessation of bisphosphonate treatment may be of some value in controlling jaw necrosis provided that it does not compromise the oncologic management.[59,61]

The focus of management is to minimize the risk of developing BRONJ by optimizing the dental health for those patients who will receive or are receiving bisphosphonate therapy. This can be easily achieved by informing patients of the low risk of developing BRONJ and strongly encouraging regular dental visits and prophylactic dental treatment.

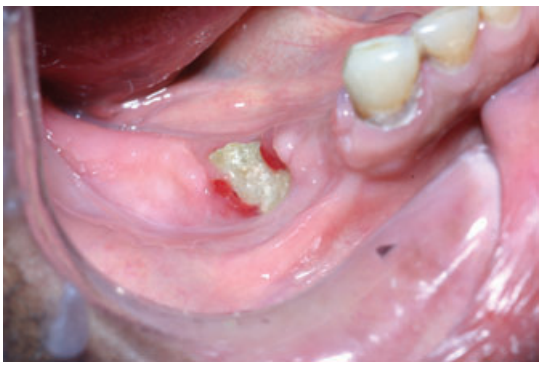

Figure 1. Asymptomatic, nonhealing extraction site in a patient with metastatic prostate cancer and a history of zolendronate therapy (Stage 1 BRONJ).

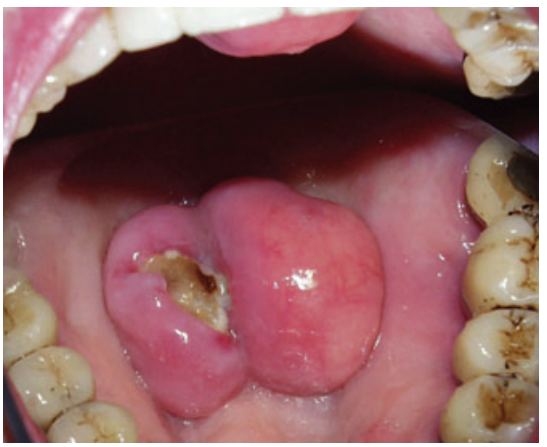

Figure 2. Exposed, necrotic palatal torus associated with localized mucosal inflammation in a patient with a long history of alendronate exposure (Stage 2 BRONJ).

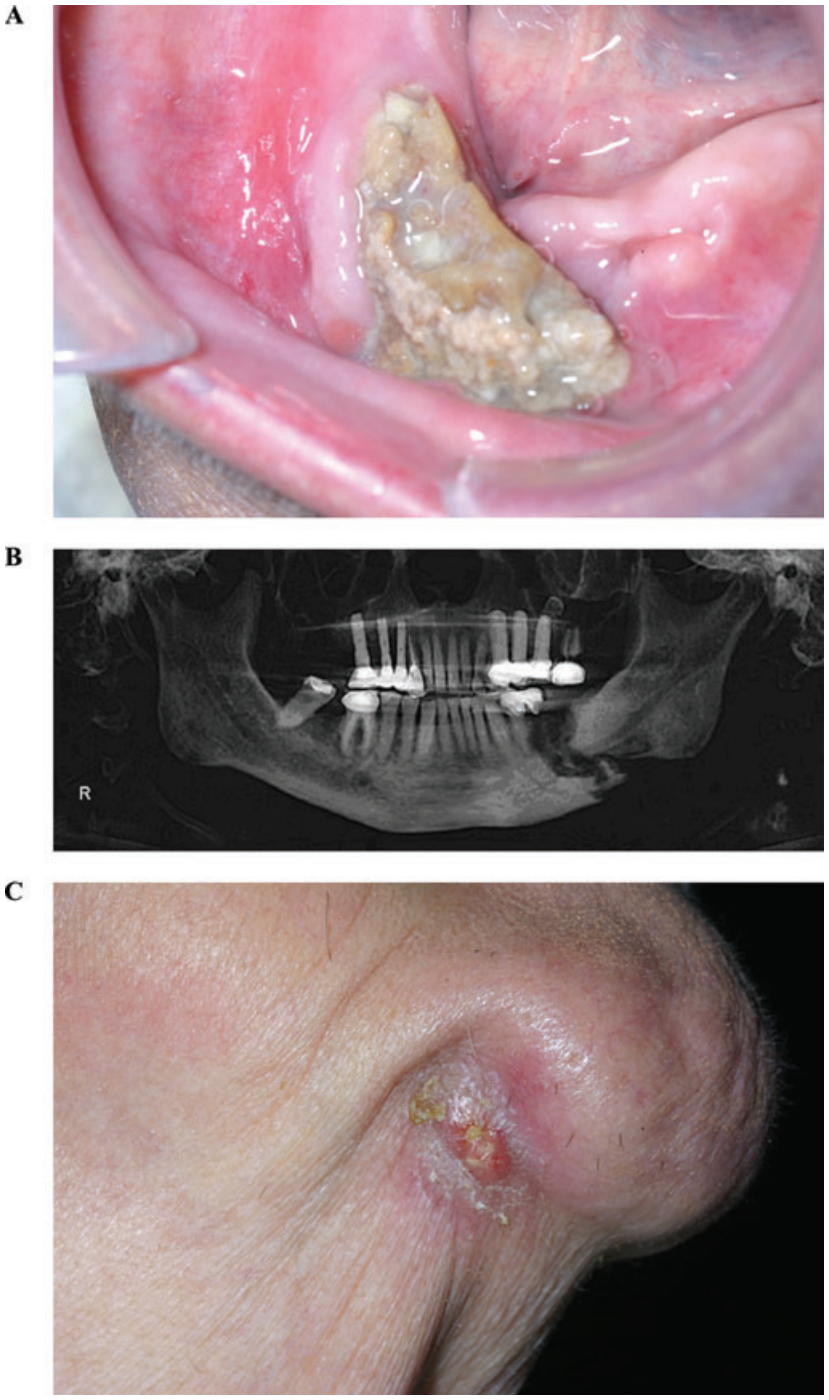

Figure 3. (A) Large segment of necrotic right mandible in a patient with end-stage breast cancer and a history of zolendronate exposure (Stage 3 BRONJ). (B) Panoramic radiograph of the mandible demonstrating a pathologic fracture and a large region of osteolysis. (C) Draining extraoral fistula in the region of the right mandible where the displaced bone has protruded through the skin.

Utilizing measured levels of surrogate markers of bone resorption to quantify BRONJ risk remains controversial.[62–68] The rationale for this approach is based on extrapolated data from a study by Bone[69] in which markers for bone remodeling began to increase within months following withdrawal of oral bisphosphonate medications in osteoporotic women thereby suggesting that osteoclastic function and bone remodeling was normalizing. However, these markers are a reflection of total bone turnover throughout the entire skeleton and are not specific to the maxilla or mandible where it is suspected that the bone turnover rate may be more severely depressed from prolonged bisphosphonate exposure. From a more practical perspective, using bone turnover markers to estimate the level of bone turnover suppression is only meaningful when compared to baseline, pretreatment levels and these are rarely obtained in clinical practice. In addition, using bone resorption marker levels to assess BRONJ risk can be misleading for the small cohort of patients that develop osteoporosis despite a normal baseline level of bone resorption.

Patients with BRONJ Stage 1 disease are by definition asymptomatic and therefore require no intervention other than periodic antibiotic oral rinses and close clinical follow up. No surgical treatment is indicated unless areas of exposed bone are a physical irritant to the surrounding soft tissue. Patients with Stage 2 BRONJ have exposed necrotic bone that is painful and secondarily infected. These patients benefit from oral antimicrobial rinses in combination with antibiotic therapy. In a case series reported by Marx, 90% of BRONJ patients with Stage 1 or Stage 2 disease were stabilized with oral rinses and systemic antibiotic therapy.[23] Patients with Stage 3 disease have pain and infection that significantly impacts the quality of life. The large burden of necrotic bone results in extra oral fistulization, pathologic fracture, or extensive sinusitis that is typically refractory to antibiotic therapy. At this stage, aggressive surgical management (partial or complete jaw resection) is required so that palliation with resolution of acute infection and pain can be achieved.

Conclusion

Osteonecrosis of the jaw is a complication of bisphosphonate therapy that is associated with significant morbidity and often requires symptomatic management for palliation in certain patients. This has caused individual clinicians and certain institutions to reevaluate the indications for and the duration of bisphosphonate therapy for osteopenia/osteoporosis and cancer patients.

Despite the strong clinical correlation between jaw necrosis and bisphosphonate therapy, a definitive casual relationship has yet to be established. Retrospective and prospective case studies have certainly established an association between bisphosphonates and jaw necrosis but the true incidence of this complication remains unknown. Clinical studies in the form of practitioner surveys or retrospective and prospective cohort investigations are needed to establish a more meaningful assessment of the associated risk factors and incidence of this problem in the population at risk. In addition, basic science research with the development of animal model system is needed to elucidate the cellular, molecular, and genetic mechanisms responsible for this process. Ideally, this would include studies that examine the role of regional differences in bisphosphonate bioavailability, wound healing, and bone metabolism of the jaw in the presence of bisphosphonates and the efficacy of systemic or preferably local jaw bone markers in monitoring disease and assessing risk. Also, the development of an animal model for this disease process is important to establish treatment strategies that are evidenced based and associated with valid outcome data.

The efficacy of these agents in treating and preventing the significant skeletal complications associated with osteoporosis and bone metastases has had a major positive impact for patients and is responsible for their widespread use in medicine. A more complete understanding of BRONJ will allow clinicians to predict who will benefit most from bisphosphonate therapy and to make more accurate judgments about risk, prognosis, treatment selection, and outcome.

Conflicts of interest

The author is a consultant for Amgen.

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