Bisphosphonates and osteomyelitis of the jaw: a pathogenic puzzle

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SUMMARY

The maxillary and mandibular bones undergo high-turnover remodeling to maintain mechanical competence. Common dental or periodontal diseases can increase local bone turnover. Bisphosphonates (BPs) accumulate almost exclusively in skeletal sites that have active bone remodeling. The maxillary and mandibular bones are preferential sites for accumulation of BPs, which become buried under new layers of bone and remain biologically inactive for a long time. Surgical odontostomatological procedures create open bony wounds that heal quickly and without infection, as a result of activation of osteoclasts and subsequently osteoblasts. Once BPs are removed from the bone via activation of osteoclasts after a tooth extraction or a periodontal procedure, they induce osteoclast apoptosis. This inhibition of osteoclast bone resorption impairs bone wound healing because of decreased production of cytokines derived from the bone matrix, and the bone is exposed to the risk of osteomyelitis and necrosis. The pathogenic relationship between BPs and osteonecrosis of the jaw is unclear, but there is evidence to indicate an association between high-dose BP treatment and exposure to dental infections or oral surgical procedures. A better knowledge of the interactions between BPs and jaw and maxillary bone biology will improve clinical and therapeutic approaches.

KEYWORDS bisphosphonates, jaw, maxillary bone, osteomyelitis, osteonecrosis

REVIEW CRITERIA

Data for this review were identified by searching the PubMed and MEDLINE databases. The search was limited to articles published in English and indexed up until 1 July 2006. The search terms used alone or in combination were "aminobisphosphonates", "zoledronic acid", "pamidronate", "ibandronate", "alendronate", "osteonecrosis of the jaw", "angiogenesis", "pharmacokinetics", "pharmacodynamic", "maxillary and mandibular bone", "bone resorption marker", "risk factors", "osteomyelitis", "apoptosis induction" and "bone metastases". Full articles were obtained and references were checked for additional material when necessary. The reference list was updated in March 2007 to reflect data published since acceptance.

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INTRODUCTION

Bisphosphonates (BPs) are widely used as the first treatment choice for osteoporosis, Paget's disease of bone, bone cancer metastasis, and hypercalcemia of malignancy. Nowadays, amino-BPs such as zoledronate (zoledronic acid), pamidronate (disodium pamidronate), ibandronate (ibandronic acid), alendronate (alendronic acid) and risedronate (risedronate sodium), are preferred to non-amino-BPs (e.g. clodronate [sodium clodronate], etidronate [disodium etidronate]) because of their greater potency, faster efficacy, and more-persistent inhibitory effects on bone turnover. There is a growing body of evidence indicating the antineoplastic activity of these agents.[1,2] In patients with bone metastases, intravenous infusion of zoledronate, pamidronate or ibandronate is preferred, and at doses 12–20-fold greater than those utilized in osteoporotic patients.[3]

Studies have shown an increasing incidence of a new clinical entity associated with BP treatment; this condition has been termed avascular necrosis—also known as osteonecrosis or osteomyelitis—of the mandibular and maxillary bone.[4–7] Osteonecrosis is a severe clinical condition characterized by difficulty in eating and speaking, oral pain, infection, and bone necrosis. The condition commonly manifests as a painful exposed nonhealing bone, and is a challenging clinical and surgical management problem. Osteonecrosis of the jaw (ONJ) is a rare complication in patients with cancer who are receiving radiation therapy, chemotherapy, or other cancer treatment regimens. In the past 10 years, several million patients have been treated with a variety of BPs, but ONJ has only been reported recently.[4–7] The ONJ occurrence rate is quite low; however, as awareness of this condition grows, the reporting of new cases of ONJ in cancer patients treated with BPs could increase. The incidence of ONJ associated with BP treatment in patients with cancer is unknown, but the reported frequency of cases in this population ranges from 0.15% in controlled clinical

trials to 9.1% in a postal survey.[8] A planned retrospective review is in progress at the MD Anderson Cancer Center, Houston, TX.[9] Hence, there is no consensus on the diagnostic criteria for and therapeutic approach to ONJ, and, importantly, the pathogenesis of this condition is not completely understood.

BIOLOGICAL CHARACTERISTICS OF THE MAXILLARY AND MANDIBULAR BONES

The most peculiar feature of ONJ associated with BP treatment is the exclusive localization of osteonecrosis to the mandibular and maxillary bones. There are no reports of other skeletal sites being affected by this form of osteonecrosis. The only other condition with features similar to BP-induced ONJ is osteoradionecrosis. Why are BPs associated with osteonecrosis exclusively at the mandibular and/or maxillary bones? The answer to this question relates to some peculiarities of the biology of the jaw and the maxillary bone, and to the pharmacokinetic and pharmacodynamic properties of BPs.

The jaw and maxillary bone, particularly the alveolar bone and periodontium, are examples of skeletal sites that are characterized by a particularly high bone turnover. The bones maintain a high remodeling status throughout life in response to continuous mechanical stress or as a result of tooth movements or loss.[10–13] In response to mechanical force, osteocytes and osteoblasts of the alveolar bone activate bone remodeling by stimulating local overexpression of various cytokines, which in turn induce maturation of numerous new osteoclasts from the medullary monocyte precursor and recruit them to the bone surface.[14,15] Human gingival fibroblast (HGF) and human periodontal ligament (HPDL) cells present in periodontal tissue might also have a role in osteoclastogenesis through the expression of receptor activator of nuclear factor kappa B ligand (RANKL) on their cell surface. It has been shown that mechanical stress increases the expression of RANKL on HPDL cells.[16] Formation of the osteoclasts requires the interaction between receptor activator of nuclear factor kappa B, which is expressed on the surface of osteoclast precursors, and its ligand. In addition, HGF and HPDL cells secrete a certain amount of osteoprotegerin, a decoy tumor necrosis factor receptor, which is able to bind to RANKL and inhibit osteoclastogenesis. HGF and HPDL cells thereby contribute actively to the bone balance of the periodontium.[17]

Mandibular and maxillary bone remodeling increases with age; periodontal disease and elevated systemic bone turnover are the most important reasons for this effect.[18] In total, 5–20% of the general population has severe, generalized periodontitis, and mild to moderate disease affects the majority of adults.[19] High levels of RANKL have been found in the gingival crevicular fluid samples of patients with chronic periodontitis, indicating a role for RANKL in the pathogenesis of periodontal disease characterized by alveolar-bone and tooth loss.[20,21] Periodontal bone loss gradually increases with age and is most pronounced in the maxilla, especially surrounding the molars. In randomly selected orthopantomograms, considerable alveolar-bone loss of greater than 4–6 mm was noted in 50% of individuals aged 50 years or older.[22] Alveolar-bone loss is an independent predictor of incident tooth loss, with 1 mm of alveolar-bone loss at baseline being associated with a threefold increased risk of tooth loss. Among postmenopausal women, 3–11% each year spontaneously lose at least one tooth.[20] When a tooth is lost or extracted, bone resorption is activated in the extraction sockets.[12,13] The residual-ridge alveolar bone undergoes life long osteoclastic resorption, even after rapid wound healing.[11,12,23]

STRUCTURE AND INTERACTIONS OF BISPHOSPHONATES

BPs are the most effective inhibitors of bone resorption. These agents are synthetic analogs of inorganic pyrophosphate in which the oxygen molecule that binds the two phosphate molecules (P-O-P) is substituted by a carbon (P-C-P) atom with two additional groups, termed R1 and R2. Several properties contribute to BP potency and efficacy, mainly affinity for hydroxyapatite crystals and inhibition of osteoclast activity. It is known that the affinity of BPs for mineralized tissue occurs through bidentate or tridentate binding via the phosphate groups and via the R1 side chain. BPs that contain hydroxy or amino groups in R1 show higher binding affinity for mineralized tissue than compounds lacking an R1 substitution or with other substitutions, such as chlorine or hydrogen.[24]

The R2 side chain is responsible for the molecular mechanism of action of BPs. Bone resorption can be inhibited by BPs because they induce osteoclast apoptosis. BPs with non-nitrogen-containing R2 groups, such as clodronate and etidronate, are metabolized intracellularly into methylene that contains toxic analogs of ATP, which

probably inhibit ATP-utilizing enzymes and induce osteoclast death. BPs with nitrogen-containing R2 groups can inhibit the enzyme farnesyl pyrophosphate synthase, which functions in the mevalonic acid pathway. The inhibition of farnesyl pyrophosphate synthase leads to prenylation of small GTPase signaling proteins that are essential for osteoclast activity and survival.[24] Studies have indicated that the R2 side chain of amino-BPs can also influence the molecule's overall bone affinity, indicating that the entire BP molecule is important for the action on bone resorption.[25] Furthermore, amino-BPs inhibit recruitment and differentiation of osteoclasts from medullary monocyte precursors.[26]

BPs are characterized by their high affinity for bone and their preferential binding to active bone remodeling sites.[27] It is believed that BPs are distributed into two compartments: the bone surface, the main site of active bone remodeling; and within the bone. The acid pH created by osteoclast activity in the resorption lacuna releases BPs from the bone surface, which are endocytosed by nearby active osteoclasts.[28] It remains unclear whether cell types in the bone microenvironment other than osteoclasts can internalize amino-BPs from bone surface, but recent data demonstrate that amino-BPs have no detectable effect on non-osteoclast bone cells *in vivo* at doses that cause a robust inhibition of prenylation in osteoclasts.[29]

After BP uptake at the bone surface, a proportion of BPs are embedded in the bone during the formation phase, where they remain dormant for a long time and do not affect bone turnover.[25] Following resumption of bone remodeling at previously exposed sites, the embedded BPs are liberated from the mineral layer of the bone matrix by the resorbing osteoclasts.[27] It is not known to what extent the released BPs are used again for the suppression of bone. Several clinical studies have shown a persistent effect of a single infusion of zoledronate,[30,31] or a prolonged inhibition of bone turnover after cessation of treatment with amino-BPs.[32–34] These results support the hypothesis that some of the embedded amino-BPs released from bone are active again at the bone surface. Another possible explanation of the lasting effects of amino-BPs could be that high doses result in a more general distribution of the drug to both active and other sites of bone resorption. Amino-BPs that adhere to the bone beneath the lining cells remain at or near the surface, where they exhibit an antiresorptive action when a resorption cycle is initiated at that site.[35] Both hypotheses are probably true, the former being more likely in focal bone disease such as Paget's disease or bone metastasis, and the latter in systemic bone disease such as osteoporosis.

Differences in the inherent binding affinity of amino-BPs affect their uptake, distribution and long-term retention in bone. Furthermore, the amount of amino-BP uptake and retention in the skeleton depends on renal function and the rate of bone turnover.[36] A relationship between the number of metastases and whole-body retention of pamidronate has been demonstrated.[37] It should be noted that the amount of BP retained in the skeleton varies markedly between patients. This variation in BP retention is particularly apparent in those with relatively high variation in rate of bone turnover, such as patients with Paget's disease of bone or metastatic bone disease. The different response to treatment observed in patients during intravenous or oral treatment might be attributable to these bone turnover and retention differences.[36,38,39]

EFFECTS OF BISPHOSPHONATES IN THE MANDIBULAR AND MAXILLARY BONES

The mandibular and maxillary bones, particularly the periodontal and alveolar bone surfaces, have a relatively high rate of bone remodeling, and are sites of high BP uptake and accumulation. In patients with cancer, it is likely that BP accumulation increases not only as a result of high-dose or long-term BP treatment, but also because maxillary and jaw bone remodeling is frequently activated by tooth mobilizations or extractions, or periodontal infections.[27] In most of the reported cases of BP-induced ONJ, the patients had undergone previous dental procedures;[4–7] in the study reported by Migliorati and colleagues, all patients had some degree of local oral infection.[6] One patient with osteoporosis who was treated with oral alendronate developed ONJ after several dental extractions and preparation for dental implant placement.[6]

In recent years, several reports of various experimental models assessing the effects of BPs on alveolar-bone resorption have demonstrated that a single systemic administration or short-term treatment of amino-BPs markedly affects local bone remodeling, which then influences osteoclast number and activity.[40,41] BPs have been proposed as a therapeutic option for the prevention of various types of alveolar-bone loss or movement, and their effects on osteoclast activity in alveolar bone are well

established.[40,41] In patients with cancer who exhibit susceptibility to infection and receive high doses of BPs for prolonged periods, these agents could have a different outcome to that seen in experimental models or in clinical trials.

Tooth extractions, or any other surgical odontostomatological procedures, can create an open bony wound (e.g. an extraction socket), which, despite the presence of oral microflora, might heal quickly and without infection. Following tooth extraction, the bone healing process includes an initial inflammatory response that actives bone remodeling. Osteoclast bone resorption is prominent throughout the bone surfaces around and within the extraction sockets, and is followed by new bone formation by osteoblasts.[40] Osteoclast activity is a response to mechanical forces or sites of compression in orthodontic tooth movement.[42] Osteoclast activity is essential for bone healing, begins during the early phases, and is believed to be involved in the regulation of bone formation via communication with osteoblasts.[43] The bone healing process is regulated by many cytokines and growth factors including platelet-derived growth factors, bone morphogenic proteins, members of the transforming growth factor β superfamily, and members of the insulin-like growth factor family. These growth factors and cytokines are produced and deposited in the bone matrix by preosteoblasts and mature osteoblasts.[44] Spatial and temporal localization of these growth factors correlates with histologic events that contribute toward healing.[45–47] The concentration of these molecules in the microenvironment of the bone remodeling site is a critical regulator of cellular proliferation and differentiation, and of extracellular matrix deposition and mineralization; moreover, these growth factors and cytokines are responsible for the coupling of bone resorption and bone formation, which is necessary for bone healing.[13,48]

A history of dental extraction at the site of osteonecrosis is reported in most cases of ONJ.[49] Tooth extraction, tooth loss or periodontitis induces osteoclast activation in the alveolar bone, which is the first part of the healing process. It is likely that amino-BPs that accumulate in the alveolar bone during treatment induce osteoclast apoptosis and slow the wound healing process, leaving the lesion prone to infection that can cause widespread osteomyelitis and osteonecrosis. The effect of local or daily BP on the osteoclasts of the alveolar bone following tooth extraction is well documented.[40] Patients with bone metastases receive pamidronate or zoledronate infusions once monthly. It is possible to speculate that, because of their very short plasma half-life, BPs could inhibit the osteoclast activity in the healing wound only if the infusion is carried out within a short time of dental surgery. Alternatively, the local reactivation of BPs deposited in the alveolar bone could account for the inhibition of osteoclasts, and could also explain how discontinuation of these agents does not seem to exert any effect on the healing of ONJ (Figure 1).[50]

The use of therapeutic doses of amino-BPs in animal models and in humans has not been associated with markedly delayed healing of peripheral and axial bones;[51] however, animal model studies of very high doses of BPs show accumulation of these agents, leading to damage and a delay in fracture healing.[52–54] The jaw and maxillary bone, particularly alveolar bone, are characterized by active remodeling. Amino-BPs might accumulate at these sites preferentially, thus resulting in concentrations that exceed those found elsewhere in the skeleton and that reproduce the effects obtained in the experimental models of delayed fracture healing.

IS BONE CELL DEATH OR ISCHEMIA A PATHOGENIC MODEL OF OSTEONECROSIS?

BP-induced ONJ has striking clinical and behavioral similarities to osteoradionecrosis, such as exposed bone and nonresponsiveness to conventional surgical management. In osteoradionecrosis, the pathogenesis of chronic, nonhealing wounds is based on hypoxia, hypovascularity and hypocellularity. It has been suggested that BPs could lead to local impairment of the response to localized bone injury through the decrease they cause in cellularity and blood flow in bone.[4–7] In ONJ associated with amino-BP treatment, large numbers of osteoclasts have been detected close to actively resorbing bone, and this accumulation is likely to mimic the healing process. Large numbers of osteoclasts have also been detected in patients with infected osteoradionecrosis,[55] but in such cases their accumulation contributed to sequestration and resolution. In other types of osteomyelitis (i.e. those associated with chemotherapy), BP treatment has occasionally been reported to be an effective therapy.[56,57]

Alterations in the intraosseous blood flow have been hypothesized as a pathogenic cause of osteoradionecrosis and BP-induced ONJ.[4–7,50] The effect of these alterations has been named

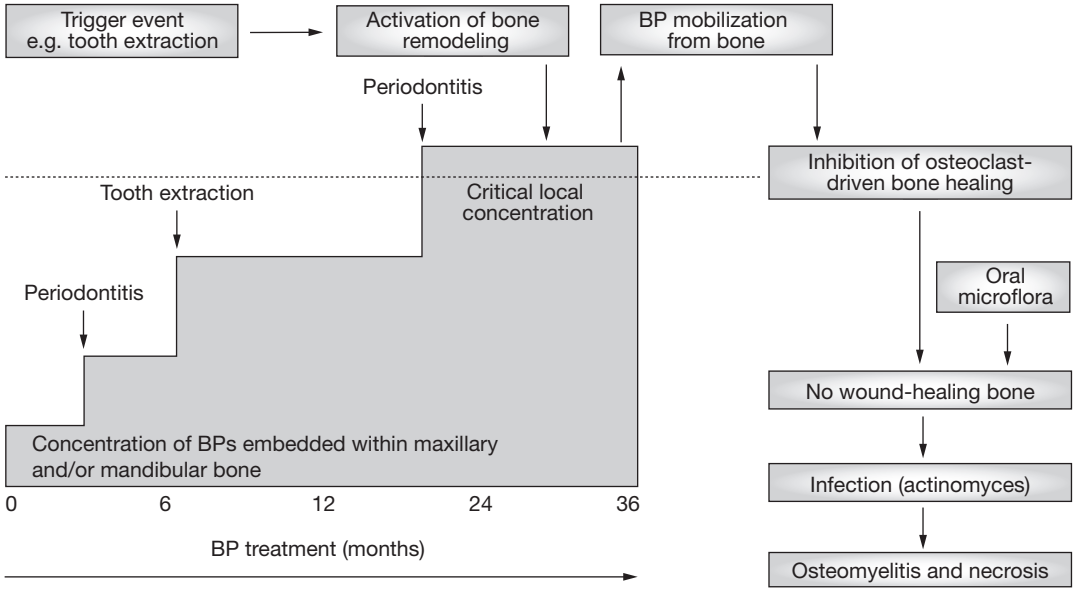

Figure 1 Mechanism of bisphosphonate accumulation in the jaw and a hypothetical pathogenic role in osteonecrosis. During BP treatment, dental procedures or periodontal pathology that induce high cellular turnover in alveolar bone facilitate the preferential accumulation of BPs in the maxillary and/or mandibular bone. When a critical concentration of BP in the bone is achieved, a trigger event (e.g. a tooth extraction) activates bone remodeling and may release locally pharmacological doses of BPs that then inhibit osteoclast-driven bone healing. The contamination of the bony wound by oral microflora (i.e. by a member of the *Actinomyces* genus) induces necrotic osteomyelitis. The timing of BP treatment is provided as an example. Abbreviation: BP, bisphosphonate.

'drug-induced avascular necrosis of bone'.[5–7] This pathogenic hypothesis was formulated almost exclusively on the basis of common histopathological finding of tissue necrosis in patients with BP-induced ONJ. The blood flow in the jaw and maxillary bone could be altered by BPs via inhibition of intraosseous angiogenesis.[4–7] This mechanism seems unlikely for many reasons. The presence of necrosis is a common histopathological finding in all reported cases of BP-induced ONJ, and is not just confined to conditions of ischemic tissue damage but is also common in osteomyelitis, in which intraosseous blood flow is not notably altered. In fact, bone necrosis could be related to bacterial superinfection and not be directly dependent on BP action. Interestingly, despite the presence of vascularized bone at the resection margins, Ruggiero *et al.* found progressive necrosis in patients with ONJ.[58] Moreover, Hellstein and Marek described the histopathological features of several cases of ONJ, reporting intact vascular channels, even in areas with acute inflammatory infiltrates and bacterial overgrowth; non-vital bone fragments with reduced evidence of osteoclastic action, but without any vascular alteration, were also noted by the authors.[59]

To explain osteoradionecrosis, the hypothesis of hypovascularity and hypoxia has been revisited. It has been suggested that the selective suppression of osteoclasts in radiated bone is a key pathogenic element of bone necrosis, and the restoration of suppressed bone remodeling is considered an essential process to healing.[60] A typical pathogenic model of regional bone disease attributable to ischemia induced by arteriolar vasoconstriction is reflex sympathetic dystrophy or post-traumatic complex regional pain syndrome (algodystrophy or Sudeck's atrophy). Interestingly, in this typical ischemic bone disease, bone necrosis does not occur; instead, acute osteoporosis is the common outcome, and treatment with BPs is the first treatment choice.[61]

The recently reported antiangiogenic properties of BPs might explain the apparent ischemic changes in ONJ. Antiangiogenic effects of BPs have been demonstrated *in vitro* and in animal models but only in pathologic tissue (i.e. neoplastic or Paget's-disease tissue).[62–64] In patients with cancer, pamidronate and zoledronate have been shown to have antiangiogenic properties, as indicated by decreased circulating VEGF.[63,65] Antiangiogenic effects of BPs are mainly observed in soft tissues,

and there is no evidence that BPs inhibit angiogenesis in axial or appendicular bone; therefore, BPs do not influence bone growth or remodeling, or fracture repair. In addition, there is a lack of data on angiogenesis in the jaw bone. Deckers and co-workers studied the *in vivo* effects of BPs on bone angiogenesis in two mouse models of suppressed bone resorption: mice treated with clodronate and osteoporotic mice.[66] Interestingly, the authors observed that treatment with clodronate completely abolished osteoclastic bone resorption, whereas angiogenesis remained unaffected, observations recently confirmed by other investigators.[55]

LOCAL AND SYSTEMIC RISK FACTORS FOR OSTEONECROSIS OF THE JAW

The potential risk factors for ONJ are multiple and have not been precisely identified. In patients with cancer, specific risk factors include treatment with cytotoxic drugs, therapy with steroids, chemotherapy, impaired immunity, and immunotherapy. Other nonspecific risk factors include vascular disorders, diabetes, blood dyscrasias, arthritis, alcohol abuse, smoking, and malnutrition.[4,7] All these factors are associated with ONJ and are known causes of dental abscesses, sinus infections, denture sore spots, periodontal diseases, and oral infections. Oral infections (e.g. mucositis, gingivitis, periodontitis) are a considerable problem in patients with cancer treated with intensive chemotherapy regimens, including hematopoietic stem-cell transplant procedures.[67] These infections are caused by the complex interaction between the toxicity of cancer chemotherapy for oral mucosal tissues, myelosuppression and the oral microflora.[68] Frequently in patients with cancer, subgingival colonization by putative periodontal pathogens leads to the development of periodontitis. As dental plaques migrate in the apical direction, the periodontal attachment apparatus is degraded and alveolar bone is reabsorbed. Periodontitis progression is associated with a limited number of pathogenic Gram-negative anaerobic bacteria including *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythensis, Fusobacterium nucleatum*, and organisms of the *Treponema* genus. Infections of the periodontium might also be associated with enteric bacilli, *streptococci* and *pseudomonas*, or with fungi such as *Candida albicans* and members of the *Aspergillus* genus.[69] Interestingly, *A. actinomycetemcomitans*, the most frequently isolated bacterium in ONJ cases,[5,6,55,58] produces large amounts of lipopolysaccharide and several inflammatory cytokines. Lipopolysaccharide is the major pathogenic factor in alveolar bone destruction, inducing the activation of HPDL cells that express matrix metalloproteinase-2 and RANKL (Figure 2).[70]

Patients with cancer can spontaneously lose teeth and frequently require tooth extraction, root-canal treatments and other surgical interventions. In the majority of reported cases of BP-induced ONJ, removal of a tooth or an oral surgical procedure triggers the exposed nonhealing bone.[4–6] 'Spontaneous' ONJ is rare and only few cases have been described.[6] In patients with neutropenic cancer, periodontal infections can easily be overlooked or misdiagnosed because symptoms of inflammation are absent as a result of a lack of neutrophils. Most importantly, in patients with severe periodontitis the infection affects the deep parts of the periodontium, and such an infection cannot be diagnosed by visual inspection.[69] In individuals with underlying impaired immune responses, if the infection extends beyond the mucogingival junction and into the adjacent mucosa and bone, acute necrotizing periodontitis or necrotizing stomatitis might occur;[71] the possibility that the infection itself induces nonhealing necrosis in maxillary or mandibular bone should not be excluded.

DO DIFFERENT AMINO-BISPHOSPHONATES HAVE DIFFERENT ROLES?

Most cases of ONJ have been noted in cancer patients receiving intravenous pamidronate or zoledronate, and some have been reported in osteoporotic patients receiving oral alendronate.[4] Amino-BPs (i.e. alendronate, risedronate, ibandronate, pamidronate and zoledronate) and non-amino-BPs (i.e. etidronate and clodronate) are quite different in their potency, and considerable differences also exist among the amino-BPs.[28,72] The *in vivo* pharmacological effects of BPs depend upon their apoptotic potency on osteoclasts and the amount of drug uptake in the remodeling site of the skeleton. The amount of BP on the bone surface depends on its binding affinity for the bone and the dose administered, which in turn influence the skeletal retention of BPs. Among the amino-BPs tested *in vitro* for relative potency with respect to inhibition of osteoclast activity, zoledronate was the most potent, followed by risedronate, ibandronate, alendronate and pamidronate.[72,73] The affinity of these agents for the

bone differs—bone retention is higher for zoledronate (64% after 24 h) than for pamidronate, ibandronate, alendronate (about 55% after 24 h for all) and risedronate (35% after 24 h).[36] These data could explain the varying clinical outcomes seen in head-to-head clinical trials of BPs. In postmenopausal women with osteoporosis, the effects of a single infusion of 4 mg zoledronate were comparable to those of 10 mg/day alendronate given orally for 1 year.[30] In Paget's disease of bone, the suppressive effect on bone remodeling of a single infusion of 5 mg zoledronate was comparable to that of 30 mg risedronate given daily for 6 months.[33] Moreover, differences in bone affinity might explain the twofold greater suppression of bone turnover observed in postmenopausal women receiving alendronate compared with that seen in women receiving the more potent compound risedronate.[74]

The route of administration of BPs (intravenous or oral) contributes to the amount of agent that enters the bone. In fact, the bioavailability of oral BPs, which is similar among the amino-containing compounds alendronate, ibandronate and risedronate, is not dose-dependent and is significantly lower than that of BPs dosed intravenously.[36] Furthermore, following oral absorption all amino-BPs exhibit a high degree of interindividual variability.[75,76] Considerably higher doses should be given to patients with bone metastases or Paget's disease of bone, who have a high bone turnover; therefore, infusion of BPs is preferred in these situations. An oral formulation is generally reserved for relatively low bone turnover diseases such as osteoporosis.[77]

Several BPs, including clodronate, pamidronate, ibandronate, and zoledronate have demonstrated marked benefits compared with placebo in cancer patients with bone metastases; however, intravenous pamidronate and zoledronate have demonstrated the most consistent clinical benefit across multiple end points and tumor types.[77,78] Pamidronate and zoledronate have, therefore, become the standard of care for bone metastases,[77] and it is not surprising that almost all cases of ONJ are associated with these BPs. Ibandronate has only recently been approved in the European Union and the US for bone metastases in patients with breast cancer and for those with osteoporosis.[79] One case of ONJ has been reported to be associated with ibandronate use.[80]

From a pathogenic point of view, a crucial risk factor for ONJ could be the cumulative dose of BPs rather than the route of administration. ONJ associated with BP use has been reported to occur at a cumulative dose of 9,060 mg for alendronate, 3,285 mg for pamidronate and 62 mg for zoledronate.[8] The critical doses should be confirmed in prospective manner, and it would be very useful to stratify the associated risk of ONJ. It is likely that if all amino-BPs are used at high doses and for a long duration, they could be associated with ONJ despite the route of administration, as is suggested by the cases of ONJ in patients treated with oral alendronate, risedronate and ibandronate.[4,6]

DOES OSTEONECROSIS OF THE JAW ONLY OCCUR IN CANCER PATIENTS?

The epidemiological estimate of the incidence of ONJ is calculated on the basis of incomplete data. From a review of all case reports and case series of ONJ reported in the literature, data indicate that BP use was present in 46% of ONJ cases with multiple myeloma, 39% of cases with metastatic breast cancer, 6% in those with prostate cancer, 4.1% of those with osteoporosis, 3.5% of those with other metastatic diseases, and 1% of those with Paget's disease of bone.[4,81] The exact prevalence of ONJ in cancer patients, however, remains uncertain. The frequency of ONJ associated with BPs was recently estimated in Australia by a postal survey in 2004 and 2005.[8] The results of this study revealed prevalence rates of 0.88–1.15% for patients with bone malignances, 0.26–1.8% for those with Paget's disease, and 0.01–0.04% for those with osteoporosis. The remarkable difference in the incidence of ONJ among patients with cancer and that among patients using BPs for other indications is due to the type and dose of BPs used, despite specific risk factors for ONJ such as concomitant chemotherapy and susceptibility to infection. Patients with bone metastases are commonly treated with zoledronate, or are switched from pamidronate to zoledronate. The standard zoledronate schedule for such patients is 4 mg/month, which is almost 12-fold higher than the dose used for osteoporosis.[30] Osteoporotic patients represent the largest population exposed to amino-BPs. Among the several million patients with osteoporosis who have received oral BP treatment, however, only a few cases of ONJ have been reported to date.[4,8] A reasonable estimate for the incidence of ONJ is 1 case every 100,000 patient years,[82] but the real incidence is unknown. Oral therapy with amino-BPs is characterized by remarkable differences in the amount of compound reaching the skeleton because of the high interindividual variability in skeletal

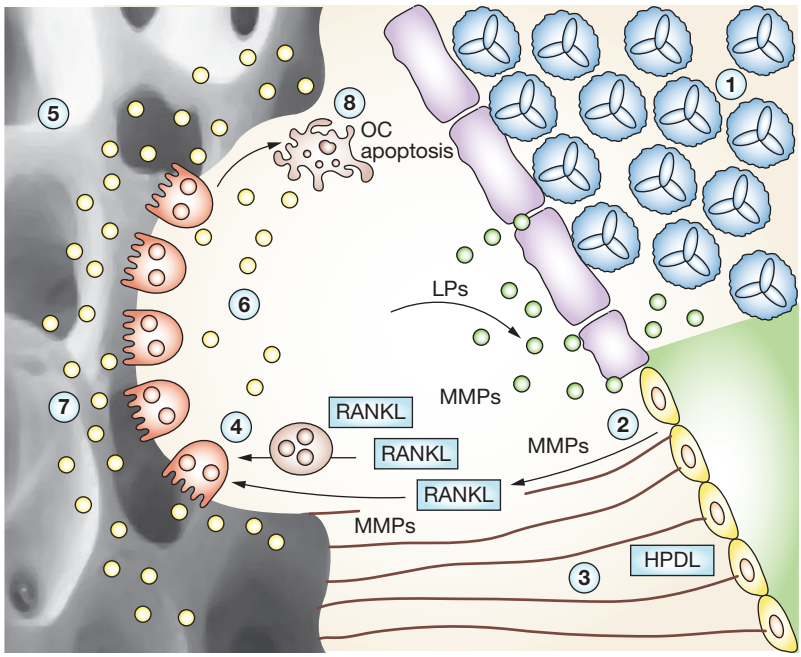

Figure 2 Schematic representation of the interaction between periodontitis, bisphosphonates and alveolar bone. Actinobacillus actinomycetemcomitans (1; blue cells) is the most common periodontal pathogen and causes chronic periodontitis. The bacterium acts via LPS (green dots) to induce HPDL cells (yellow cells) (2) to express large amounts of MMPs that destroy periodontal ligament (3) and RANKL that activates OC (brown cells) bone resorption (4) in the alveolar bone (5). BPs (6; yellow dots) continuously accrue in the active remodeling bone (7) and inhibit OC activity by causing osteoclast apoptosis (8). A large amount of BPs in the bone should impair the OC-driven healing after tooth extraction. Abbreviations: BPs, bisphosphonates; HPDL, human periodontal ligament; LPS, lipopolysaccharide; MMPs, matrix metalloproteinases; OC, osteoclast; RANKL, receptor activator of nuclear factor kappa B ligand.

retention, relatively low compliance rates, and long duration of therapy. Alendronate is the BP most frequently associated with ONJ in patients with osteoporosis. Among the oral amino-BPs, alendronate is the standard therapy for osteoporosis, and is more potent at inhibiting bone turnover and is retained in the skeleton for a longer period than risedronate.[83]

In a randomized clinical trial of more than 7,000 postmenopausal women, 5 mg/year zoledronate for 3 years caused 1 case of ONJ, and 2 cases of ONJ were observed in the placebo group.[84] These data indicate that the risk of ONJ associated with intravenous and oral amino-BPs should be verified in prospective controlled studies. The majority of patients with ONJ have a history of dental disease, dental surgery or trauma, or periodontitis.[3–8] For patients with cancer or osteoporosis who are taking amino-BPs, the same recommendations to prevent ONJ are suggested, although there are substantial differences between the groups in the degree of risk.[4] Dental and periodontal pathology, and associated treatment, seem to promote BP accumulation in alveolar bone, thereby activating bone remodeling and triggering ONJ. We can speculate that theoretically all individuals who have taken critical cumulative doses of BPs (albeit different for each amino-BP), have dental pathology or have undergone dentoalveolar surgery, or have other potential risk factors that facilitate infections, are potentially at risk of ONJ.

CONCLUSIONS

Considerable benefits to patients with bone metastases are provided by BPs, which decrease skeletal complications, reduce bone pain and improve patient quality of life; therefore, these agents are becoming the standard of care for bone metastases.[3] In addition, the role of BPs in the treatment of patients with cancer continues to expand, and there is evidence that both clodronate and pamidronate can prevent or delay development of bone metastases. Ongoing trials are evaluating the efficacy of adjuvant zoledronate given after radical treatment of primary tumors. Preclinical evidence indicates that the potential direct antitumor effects of BPs, and their application in this respect, are promising.

The development of ONJ in cancer patients treated with BPs is rare, but is a clinically dramatic event without an effective therapy. The association of ONJ with BP treatment is suggestive but far from conclusive. The biological features of maxillary and mandibular bone *per se* and the pharmacokinetic and/or pharmacodynamic profile of BPs could constitute a rationale for ONJ development. Dental and/or periodontal infections and/or odontostomatological surgery could be critical events leading to ONJ in nonhealing bone lesions. We can surmise that the high interindividual variability in bone retention of BPs could explain the discrepancies between the large cancer population treated with these compounds and the low occurrence of ONJ.

Many questions remain concerning the underlying pathogenesis of ONJ, but the most interesting one relates to the accumulation of notable doses of BPs at skeletal sites different to the therapeutic bone metastasis target. Bone turnover has been found to be related to the risk of skeletal complications, disease progression or death in patients with bone metastases,[85] and there is some evidence to suggest that the rate of

inhibition of bone turnover by BPs could provide valuable prognostic information in patients with bone metastases.[86] Markers of bone turnover could be potential surrogate markers for individual patient benefit and might provide a useful means by which to monitor the pharmacological effect of BPs in patients with cancer. In addition, the prevalent rate of bone turnover is a crucial regulator of the amount of BP taken up by the skeleton.[36,39] Although a specific pharmacokinetic and/or pharmacodynamic model for metastatic bone disease remains to be developed, it is most likely that the apparent relationship between BP skeletal retention and antiresorptive effects could have implications for the optimization of the dosing schedule on the basis of bone turnover rate at baseline, and during therapy for individual patients.[36,39] This approach of BP schedule modification might decrease the risk of excessive accumulation at skeletal sites other than those affected by metastases.

KEY POINTS

- Osteonecrosis of the jaw or maxillary bone associated with bisphosphonate (BP) treatment is a relatively rare but severe clinical condition; however, a clear pathogenic relationship between osteonecrosis of the jaw and BPs has not been established
- The jaw and the maxillary bone are characterized by high bone turnover that is constantly stimulated by mechanical stress, tooth movements or loss, periodontitis, and odontostomatological procedures, which are particularly frequent in cancer patients
- Treatment with an amino-BP over long time periods causes the drug to accumulate in an inactive state within the alveolar bone
- Physical trauma or infection activates local bone remodeling, releasing pharmacological doses of BPs that inhibit the osteoclast-driven bone healing
- The nonhealing wound exposes the alveolar bone to the risk of infection by commensal flora and the wound can progress to necrotic osteomyelitis; there is no convincing evidence that a direct necrotic effect is mediated through inhibition of angiogenesis
- The possibility of accumulation of substantial doses of BPs at skeletal sites other than those affected by bone metastases could have implications for the optimization of BP schedules to improve response in patients

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