

Osteonecrosis of the Jaw and the Role of Macrophages

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Nitrogen-containing bisphosphonates have been associated with the development of osteonecrosis of the jaws (ONJ), but the lack of reliable epidemiological data and appropriate animal models has restricted our understanding of ONJ pathophysiology and limited its management. The best available information is from histopathologic findings, which implicate bone necrosis and infection, although it is not clear which is primary. However, there are data suggesting that macrophages could well be the central factor in allowing the infection to develop first, followed by local necrosis, which could also account for the development of ONJ in patients treated with denosumab, a human monoclonal antibody to the receptor activator of nuclear factor- κ B ligand. This review examines the evidence that macrophages could play a prominent role in development of ONJ and the proposal that it may be more appropriate to view ONJ as a drug and not only a bisphosphonate-related complication.

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Osteonecrosis of the jaws (ONJ) is primarily considered to be a complication of radiotherapy in patients with head and neck cancer. A similar pathology, the “phossy jaw,” was observed in the 19th and early 20th centuries in workers exposed to the metabolically active white phosphorous used in matchmaking factories (1). In addition, oral infections, such as osteomyelitis of the jaw, could produce a similar clinical picture. In 2003 and 2004, two reports (2,3), one a comprehensive description of 63 ONJ case patients (3), suggested an association between ONJ and nitrogen-containing bisphosphonates (N-BPs). Since then, case reports and case series (4) have established an association between N-BPs, such as alendronate, risedronate, ibandronate, pamidronate, or zoledronate, and ONJ. This association has been strengthened further by the elimination of cancer itself as a risk factor. In a prospective phase III trial (AZURE-BIG 01-04) (5), 3340 women with stage II/III breast cancer, treated with (neo)adjuvant chemotherapy and/or endocrine therapy, were randomly assigned to receive either no additional treatment or 4 mg of zoledronate administered intravenously after each chemotherapy cycle for 60 months. Eleven cases of ONJ were confirmed in the zoledronate arm (0.7%; 95% confidence interval = 0.3 to 1.1), but no ONJ cases were seen in the control group ($P < .001$). However, little progress has been made in understanding the pathophysiology of bisphosphonate-related ONJ (BPr-ONJ), for which a causal relationship has yet to be shown (4). Several reasons could account for this slow progress, including the lack of an appropriate animal model (6). Moreover, there is uncertainty about the incidence of ONJ in the general population because the *International Classification of Diseases* code for ONJ has been introduced only recently (7), and thus, retrospective studies are not currently feasible. To complicate matters further, the diagnosis of ONJ requires current or recent exposure to bisphosphonates (8,9). This requirement could introduce a strong bias in the selection of case patients because ONJ has also

been described in individuals never exposed to bisphosphonates (10). Finally, the current diagnosis of BPr-ONJ is reminiscent of the time when osteoporosis was only diagnosed after a fracture had occurred. Thus, what we diagnose today as ONJ may be the end stage of the pathology of a chronic process.

Review Criteria

A comprehensive PubMed search of the English-language literature was performed for relevant articles using the Medical Subject Heading (MeSH) terms “bisphosphonates,” “alendronate,” “risedronate,” “ibandronate,” “zoledronic acid,” “denosumab,” “adverse effects,” “osteonecrosis,” “osteomyelitis,” “osteoclasts,” “monocytes,” and “macrophages” in various combinations. The reference lists of retrieved articles were assessed for additional articles. Abstracts and reports from meetings were included only when they related directly to previously published work.

Definition and Clinical Features of ONJ

The American Association of Oral and Maxillofacial Surgeons (AAOMS) (8) and the American Society of Bone and Mineral Research (ASBMR) (9) proposed the current widely accepted working definition of BPr-ONJ, which requires all of the following three characteristics to be present: 1) current or previous treatment with a bisphosphonate; 2) exposed necrotic bone in the maxillofacial region, which has been present for at least 8 weeks; and 3) no history of radiation therapy to the jaws. In addition, the ASBMR definition uses the label “suspected” ONJ when the exposed bone has been present for less than 8 weeks. The stage 0 proposed by the AAOMS (8), “no clinical evidence of necrotic bone, but non-specific clinical findings and symptoms” is so broad that it could only serve as a reminder of a possible presence of ONJ

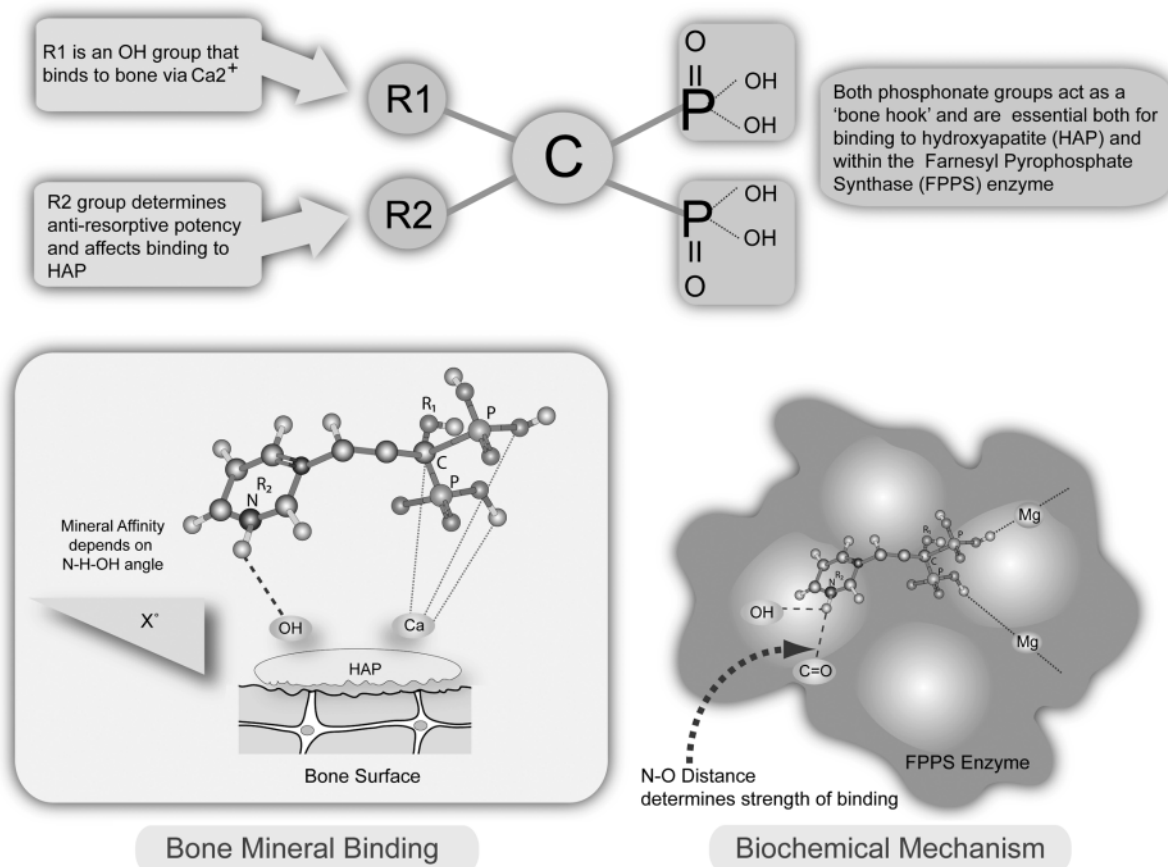


Figure 1. Bisphosphonate structure, bone mineral binding, and biochemical mechanisms. Reproduced from Pazianas et al. (28) with permission from the American Society for Bone and Mineral Research.

in patients treated with bisphosphonates. Therefore, in clinical practice, we are dealing almost exclusively with case patients with end-stage disease (11,12).

Involvement of the mandible is twofold more common than that of the maxilla, but both sites can be affected in the same patient. Exposed bone is the main clinical feature, and, if local infection is not evident, patients could be asymptomatic and unaware of having BPr-ONJ (4). In the majority of patients, however, infection is present, with the damaged bone colonized mostly by oral flora, especially those found in periodontal, pulpal, periapical (bacterial), and mucosal (fungal) pathologies. This infection could be complicated by pain and paresthesia, followed by purulent discharge with fistula formation (4).

ONJ Epidemiology and Risk Factors

Following the initial reports on BPr-ONJ (2,3), retrospective analyses of patient records, mainly those of patients treated with intravenous bisphosphonates for multiple myeloma or metastatic bone disease, failed to establish an accurate assessment of the incidence and prevalence of BPr-ONJ (13). All these retrospective studies and population-based surveys had methodological limitations such as possible inclusion of patients with maxillofacial pathology other than ONJ, as well as patients for whom no formal validation or adjudication of ONJ was possible. Furthermore, post marketing surveillance for three of the approved N-BPs, that is,

alendronate, risedronate, and ibandronate has not been of any help because adverse dental events were not included in the reporting. However, the HORIZON (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly) pivotal fracture trial, the only prospective study to examine the presence of ONJ in patients treated with a bisphosphonate, reported no risk (14). In 3889 osteoporotic women (with a mean age of 73 years), matched with 3876 control subjects and treated with a single annual infusion of 5 mg zoledronic acid over a 3-year period, only one incident of ONJ across both groups (treated and placebo) was described.

Overall, patients with multiple myeloma or metastatic bone disease, treated frequently with intravenous bisphosphonates and therefore receiving high cumulative doses, 12–15 times higher than the patients treated for osteoporosis or Paget bone disease, are considered to be at high risk of developing ONJ. The incidence of ONJ in these patients is estimated at 1%–12% at 3 years of exposure (15,16). Patients treated for osteoporosis with oral or intravenous bisphosphonate regimens receive substantially less exposure to bisphosphonates, and therefore, the risk could be described as negligible. Indeed, the incidence is thought to be less than 1 per 100 000 person-years of exposure (15,17), although in a recent study, it was estimated at 1 per 1000 (18). Major risk factors identified so far include the intravenous use of the N-BPs zoledronate and pamidronate, the cumulative dose of bisphosphonates, preexisting infection (eg, periodontitis) and oral trauma in general, including dentoalveolar surgery such as tooth extraction (19).

Pathophysiology

BPr-ONJ has been described by some as osteomyelitis of the jaw (20,21), and the presence of infection is a common feature. The risk of inflammatory conditions, osteomyelitis, and surgical procedures of the jaw and facial bones is increased in patients treated with intravenous bisphosphonates (22). However, the debate continues as to whether the low bone turnover attributable to bisphosphonate treatment causes necrosis, followed later by an infection, or if the treatment's direct toxic effects on the oral mucosa allow oral pathogens to reach the bone surface and cause infection followed by necrosis.

Pharmacology of Bisphosphonates

Bisphosphonates are currently used as first-line treatment for osteoporosis or Paget disease of the bone (23) and are administered routinely in patients with multiple myeloma or metastatic bone disease (24). The affinity of bisphosphonates for bone mineral and their inhibitory effect on osteoclast cell function results in a strong antiresorptive action, a reduction in the risk of osteoporotic fractures, and an improvement in the overall bone health in cancer patients (25,26). Bisphosphonates may also exert direct effects on bone marrow monocytes (the macrophage/osteoclast precursors) *in vivo* (27).

Bisphosphonates are stable analogs of naturally occurring inorganic pyrophosphates (Figure 1). They are resistant to chemical and biological degradation because a carbon atom in the pyrophosphate backbone has replaced the oxygen atom that connects the two phosphates (P-C-P). Two side chains, R1 and R2, are attached to the carbon. R1 is an OH group that binds to bone via Ca^{2+} . The R2 chain determines antiresorptive potency and affects binding to hydroxyapatite. In the second generation of bisphosphonates, that is, alendronate, risedronate, ibandronate, pamidronate, and zoledronate, the presence of nitrogen or an amino group in the R2 chain greatly increases antiresorptive potency (29). The N-BPs but not the bisphosphonates lacking nitrogen, such as etidronate or clodronate, affect the function and survival of the osteoclasts by inhibiting the farnesyl pyrophosphate synthase enzyme from the mevalonate pathway that is responsible for cholesterol synthesis (30) (Figure 2). The same pathway is inhibited by statins, albeit upstream, at the level of mevalonate synthesis. Zoledronate is the most potent inhibitor of farnesyl pyrophosphate synthase among the N-BPs currently in use (31).

Oral administration of bisphosphonates is characterized by poor gastrointestinal absorption (<1%). After bisphosphonate enters the circulation, approximately 50% of the dose is incorporated into bone. Most of the remainder is excreted unchanged in urine via filtration and proximal tubular secretion, and only a negligible amount is transiently exposed to other tissues. During cycles of bone remodeling, bisphosphonates are slowly released and reenter the systemic circulation unmetabolized (32).

Imaging Data

Panoramic dental radiographs, a routine imaging available in any dental practice, computed tomography, cone-beam computed

tomography, or magnetic resonance imaging are usually obtained after the onset of the clinical picture (33). Among the most frequently reported imaging features, albeit not specific for ONJ, are varying degrees of osteosclerosis and osteolysis on a mottled trabecular pattern, periosteal reaction, bone fragmentation, and sequestration. In addition, a thickening or loss of the lamina dura, a widening of the periodontal ligament space, and persistent extraction sockets are common findings (4,34). Imaging studies have also shown involvement of the affected jaw extending beyond what is clinically apparent (11,35,36).

Radionuclide scintigraphy, although lacking specificity and high resolution, has been used to diagnose BPr-ONJ. Generally, isotope uptake can take place in a metabolically active area where blood flow is not substantially interrupted, which is not the case in necrotic bone. However, sites around necrotic areas with metabolic activity, whether reflecting inflammatory changes or infection involving increased bone turnover, will take up isotope. Indeed, F-18 FDG PET (2-deoxy-2- ^{18}F fluoro-D-glucose positron emission tomography) imaging, which identifies tissues with high metabolic activity, has been positive in the vast majority of the ONJ patients investigated. Even scans that are more bone specific, such as $^{99\text{m}}\text{Tc}$ -bisphosphonate and NaF-PET (^{18}F sodium fluoride) imaging, showed increased bone uptake in affected areas of the jaw (37–39). Therefore, osteonecrosis is only part of the spectrum of pathologies in BPr-ONJ, and infection/inflammation is another important component.

Histological Findings

There is no evidence of toxicity throughout the skeleton in patients treated with sustained high doses of bisphosphonates. In BPr-ONJ, the bone lesion, by definition, is a necrotic area. Therefore, no viable bone cells (ie, osteoclasts, osteoblasts, or osteocytes) are expected to be found. Notably, biopsies performed in the affected areas of the jaw produced a wide range of findings, with an increase in bone activity being a frequent finding. However, extensive surface bacterial colonization (commonly actinomyces) was present when bone remodeling was taking place. The ONJ lesions were free of metastatic elements except in three patients (40,41) out of all of those examined histologically in a number of published studies.

The gross pattern of necrosis in BPr-ONJ is very similar to that described by Boonyapakorn et al. (42) in a prospective study of patients with multiple myeloma and other malignancies such as acellular bone or sequestrum formation with osteoclastic activity at irregular bone surfaces, surrounded by inflammatory cellular infiltration. Furthermore, in the necrotic region in BPr-ONJ, the vasculature is still present (43,44), and, therefore, the term 'avascular' necrosis of the jaw is inappropriate and should not be used.

Current Understanding

Two schools of thought have suggested how bisphosphonates could initiate the development of ONJ (4): either through suppression of bone turnover or through an antiangiogenic effect. However, the lack of an established animal model of ONJ has hampered our attempts to delineate its pathophysiology. Mice and

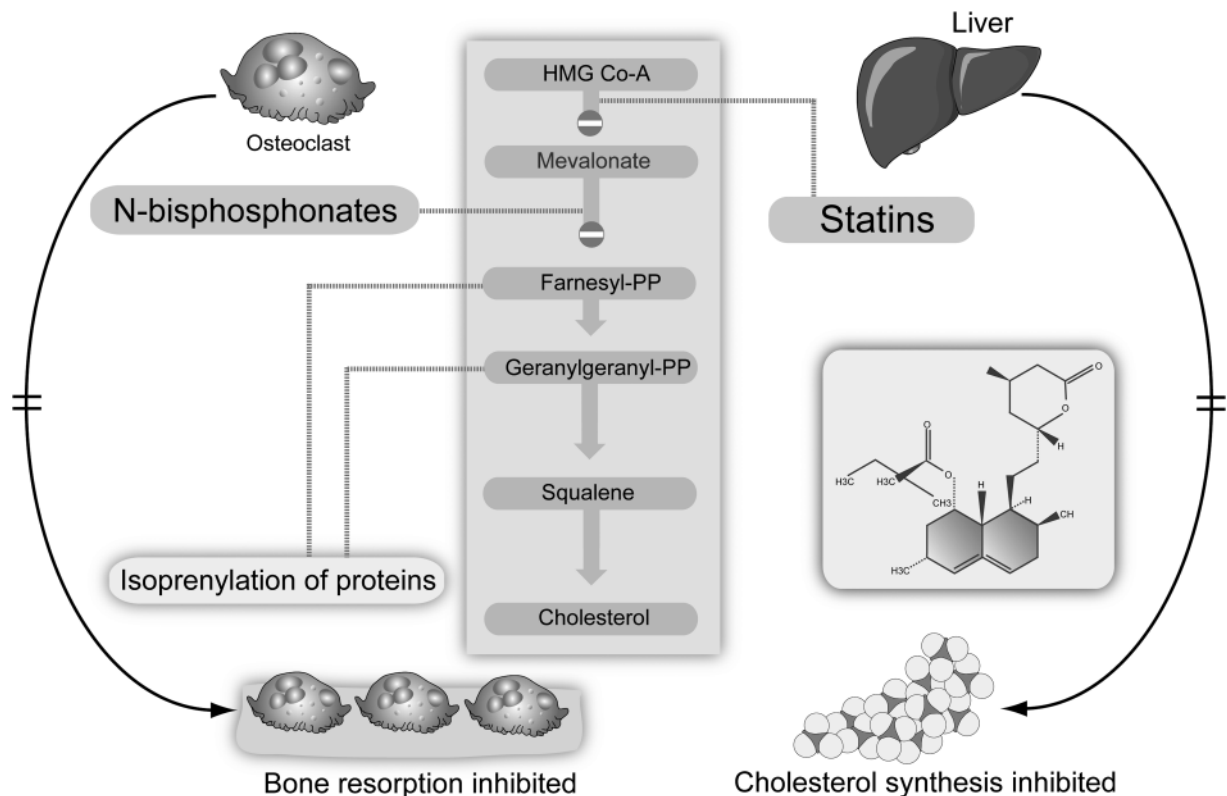


Figure 2. Inhibition of the mevalonate pathway by statins and bisphosphonates. HMG Co-A = 3-hydroxy-3-methylglutaryl-coenzyme A. Reproduced from Pazianas et al. (28) with permission from the American Society for Bone and Mineral Research.

rats are not considered appropriate models because, in addition to their well-known differences from humans in general bone remodeling processes, neither of these species has intracortical remodeling in the mandible under normal circumstances (45). Furthermore, it is difficult to combine conditions implicated in the development of ONJ to mimic human conditions (6).

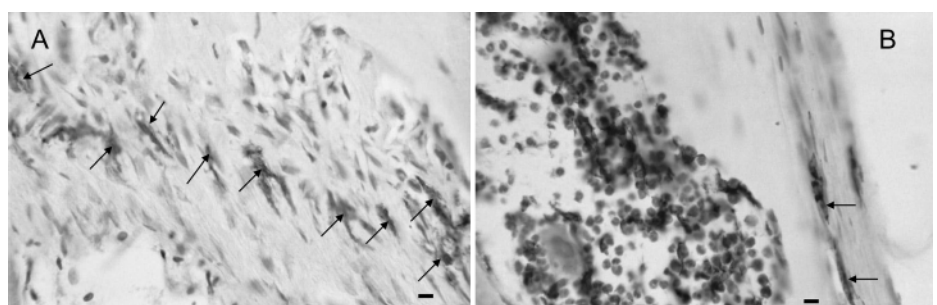
Necrotic Bone Attributable to Direct Action of Bisphosphonates on Bone Cells

The most commonly accepted view implicates the clinically important reduction of bone turnover caused by bisphosphonates as the initiating factor and proposes that the reduction in osteoclastic activity is followed by a proportional reduction in bone-forming activity by the osteoblasts, leading finally to areas of necrotic bone (4). This hypothesis is flawed for several reasons. Osteoblasts appear to be the least affected of the bone cells after

3 years of daily treatment with oral alendronate using either the standard dose for osteoporosis treatment or a fivefold higher dose (43). Osteocyte apoptosis is prevented by bisphosphonates at doses consistent with those used for osteoporosis (46,47). In addition, denosumab, a human monoclonal antibody to receptor activator for nuclear factor- κ B ligand (RANKL), causes greater suppression of bone turnover in osteoporotic patients than that caused by bisphosphonates. Moreover, only recently with administration of denosumab in increased doses and frequency has the development of ONJ been reported and at the same rate as bisphosphonates (48).

Even stronger arguments could be raised against the oversuppression theory by the fact that in patients with osteopetrosis, a bone pathology attributable to absence of osteoclasts or presence of nonfunctional osteoclasts, the bone is not necrotic, and ONJ is not a complication. Instead, osteomyelitis of the jaw has been described in approximately 10% of these patients (49–51).

Figure 3. Bone surface and macrophages. **A)** Section of the surface of the femur at the point of attachment of muscle. At the center of this view, there is a line of large stellate F4/80-positive macrophages (arrows) spread in the plane of the bone surface. Scale bar = 10 μ m. **B)** The bone marrow space, with large F4/80-positive cells spread out in the center of hematopoietic islands. The F4/80-positive macrophages can be seen spread in the plane of the bone surface, within the osteoblast layers. Scale bar = 10 μ m. Reproduced with permission from Hume et al. (The Roslin Institute, University of Edinburgh, UK) (70).



Therefore, even if bisphosphonate treatment in some patients could lead to a complete neutralization or elimination of the osteoclasts, the outcome should be osteopetrosis and not osteonecrosis. Furthermore, in a good number of case patients with reported ONJ, the bone turnover markers are not suppressed and remain close to or above the postmenopausal range (52). Thus, if low bone turnover does play a role in the development of ONJ, it could be via the reduction of the active bone remodeling sites, which leads to a reduced skeletal uptake of bisphosphonates and thus increases the chances for cells of the phagocytic lineage other than osteoclasts to be exposed longer to bisphosphonates.

Necrotic Bone Attributable to Reduction of Bone Blood Supplies Caused by Bisphosphonates

Evidence for the antiangiogenic effects of bisphosphonates is primarily from *in vitro* or animal studies. Zoledronic acid inhibited proliferation of human endothelial cells (53) and induced a 50% reduction of the revascularization of the prostate gland in rats (54). In beagle dogs, after 3 years of daily oral bisphosphonate treatment, the necrotic regions were void of patent canaliculi but had retained their vasculature (43). In cancer patients, a single 4 mg zoledronate infusion induced considerable and long-lasting modifications of circulating angiogenic factors, vascular endothelial growth factor and platelet-derived growth factor (55). However, histological examination of samples obtained from patients diagnosed with BPr-ONJ showed patent vessels in the majority of the patients (44,56). Furthermore, development of ONJ following chemotherapy with much more potent antiangiogenic agents than bisphosphonates (bevacizumab, bortezomib, and thalidomide) has been reported in only a few patients on bevacizumab (57–60), although combination with a bisphosphonate may increase the risk (61). In addition, medications that do not affect angiogenesis such as denosumab could cause ONJ as well (62).

Necrotic Bone Attributable to Infection Secondary to Toxic Effects of Bisphosphonates on Oral Mucosa

The alternative hypothesis incriminates a disruption of the oral mucosa, with the direct toxic action of bisphosphonates as the initiating factor. As a result, oral pathogens are able to pass through defective or severely damaged oral mucosa and infect the bone, eventually leading to its necrosis (63).

Indeed, there is clear documentation of bisphosphonate toxicity to gastrointestinal epithelia through the inhibition of farnesyl pyrophosphate synthase (64). Bisphosphonate pretreatment of murine oral mucosal cells inhibited proliferation and wound healing at clinically relevant doses (65). Clinically, gastrointestinal intolerance is one of the most recognizable side effects of oral preparations of N-BPs, that is, alendronate, risedronate, and ibandronate. They could cause irritation of the esophageal mucosa if they do not reach the stomach quickly.

This alternative hypothesis provides an explanation of how pathogens might be able to breach the first line of defense, that is, the oral mucosa. However, this is only the first step in reaching the

bony tissue and by itself is not enough to be a serious threat to the bone, as evidenced by the fact that trauma to the oral mucosa, including dental procedures, is common in both normal individuals as well as cancer or immunocompromised patients, but ONJ is not common at all. This hypothesis does not explain how the second line of localized defense, where monocytes and macrophages are central gatekeepers, could be compromised.

ONJ and Macrophages

Despite the fact that all of the groundbreaking work (66) on the effects of bisphosphonates on osteoclasts has been performed on macrophages and macrophage-like cells, we still have been very slow to incorporate macrophages into clinical thinking. It is even more remarkable that the macrophages of the J774 cell line used extensively in these studies (66) never mature to fully functional bone-resorbing osteoclasts (67).

After osteoclasts, monocytes and macrophages are the cells most likely to be affected by the administration of bisphosphonates (27). Indeed, when J774 macrophages were co-cultured with rabbit osteoclasts, J774 cells that were adjacent to resorbing osteoclasts frequently internalized more fluorescently labeled alendronate analog (FL-ALN) than J774 cells more distant from the osteoclasts. In addition, J774 macrophages occupying resorption pits internalized more FL-ALN than those on unresorbed surfaces (67).

Macrophages are remarkably similar to osteoclasts. Activated macrophages display increased membrane ruffling, spreading, adhesion, and lysosomal enzyme activity. They also develop phagolysosomes, an acidic compartment full of hydrolases. All of these characteristics resemble those in osteoclasts. In addition, both macrophages and osteoclasts contain tartrate-resistant acid phosphatase, a lysosomal protein that participates in bone resorption and in the inflammatory response of the macrophages (68).

Under physiological conditions, monocytes migrate into virtually all tissues of the body and differentiate into resident tissue macrophages. Infection, inflammation, and tissue injury trigger a rapid recruitment of monocytes from peripheral blood to the affected area. These monocytes then differentiate into immune macrophages that drive innate and adaptive immune responses (69). The presence of F4/80+ macrophage-like cells on osteal surfaces was reported by Hume et al. in 1984 (70), and this observation was extended recently by Chang et al. (71), when they established that periosteal and endosteal tissues contain a discrete population of resident tissue macrophages (Figure 3, A and B). Macrophages are present in the oral mucosa as well (72), and infection increases macrophage recruitment to the mucosa of the oral cavity (73).

The detrimental effects of bisphosphonates on macrophages have been well documented. J774 macrophage-like cells, as previously mentioned, were used to study the effects of bisphosphonates on osteoclasts. Bisphosphonates are internalized into J774 macrophage-like cells in the same way that they are internalized by the osteoclasts (74). After they gain entry, N-BPs inhibit cholesterol synthesis, described for the first time by Amin et al. (75). The same cell line was also used to document the ability of N-BPs to induce apoptosis (76) in a similar way to statins (30). Furthermore, protein prenylation was almost completely inhibited in J774 cells by rise-

dronate at a concentration of 10^{-5} M, which is similar to the concentration of N-BPs that affects osteoclast viability in vitro and could be achieved within the osteoclast resorption area (66).

ONJ and Proposed Mechanism

Following repeated bisphosphonate administration, the number of sites of skeletal metabolic activity could, at some point, become considerably reduced. As a result, the overall skeletal binding of bisphosphonates may become low enough to allow cells from the phagocytic lineage other than osteoclasts, that is, monocytes and macrophages, to be exposed for extended periods to these agents, leading to reduced functional capacity and numbers. This could cause severe defects in the second line of defense, with the first line being the epithelium of the oral mucosa, for example.

The oral cavity is one of the most susceptible areas to bone infection because of its numerous potentially pathogenic organisms, as well as frequent opportunities for injury and close proximity to the bone. However, compromised integrity of the mucosal epithelium alone is not enough to allow uninterrupted access to the bone surface; the local immune response must also be compromised. Since bisphosphonates do not affect neutrophils, the risk of systemic infection is minimal. However, the reduced function or presence of monocytes and macrophages could become critical for the development of local infection, that is, osteomyelitis.

Infection is present in the majority of the samples obtained from BPr-ONJ patients (77). In those specimens in which conventional microbiological and histological techniques have failed to demonstrate microorganisms, their presence could not be excluded because these methods usually miss biofilm bacteria. These are microbial cells attached to a surface and are embedded in a matrix of extracellular polymeric substances that they have produced to connect to and communicate with each other (77). Microbial biofilms are not just present on the bone surface exposed to the oral cavity but could also be found in the deeper structure of the bone as well (77), which could account for the chronic infectious nature of BPr-ONJ and at the same time could explain the resistance to current conventional therapeutic approaches. The infection could go undetected for long periods until it presents itself as exposed bone and is eventually diagnosed as what we now clinically describe as ONJ.

A large number of microbial pathogens were observed in resorption pits on the bone surface, and the depth of the pits varied with the amount of bacteria present. No eukaryotic cells such as osteoclasts were seen in or near resorption pits (entirely explained by the fact that these patients are on bisphosphonate treatment), suggesting a direct role for biofilms in the resorption process (77). Indeed, several species of bacteria could cause alveolar bone destruction, and their products (eg, lipopolysaccharides) could be the mediators (20).

The substantial involvement of monocytes and macrophages in the pathophysiology of BPr-ONJ could be further supported by the observation that BPr-ONJ is a local, not systemic, infection or inflammation, which would not be expected if neutrophils, for example, were affected. Bisphosphonates, at least the currently administered regimens, exclusively affect the phagocytic lineage and not other types of cells.

Furthermore, in osteopetrosis, osteomyelitis of the jaw is a complication in approximately 10% of patients. It is known that a

defect in the chloride channel 7 (*CLC7*) gene in the osteoclast could be the cause of the most common form of osteopetrosis, the autosomal dominant type II (Albers-Schonberg Disease) (78). The *CLC7* gene is present in macrophages, and it should be suspected that the macrophages could be defective as well. Therefore, this genetic defect could be another pathology sharing the same pathogenetic pathway with BPr-ONJ.

In addition, vitamin D could be involved in the development of ONJ through macrophages. The active form of vitamin D [$1,25(\text{OH})_2\text{D}_3$] is required for certain immune or anti-infectious responses to be activated in macrophages, which express CYP27B1, a cytochrome P450-containing hydroxylase that converts 25-hydroxyvitamin D to $1,25(\text{OH})_2\text{D}_3$ (79). Therefore, low 25-hydroxyvitamin D concentrations typical in vitamin D-deficient patients could increase the risk of ONJ. More specifically, the innate immune response involves the activation of toll-like receptors (TLRs) in polymorphonuclear cells, monocytes, and macrophages, as well as in a number of epithelial cells. TLRs are an extended family of host-pathogen recognition receptors that interact with specific membrane patterns shed by infectious agents that trigger the innate immune response in the host. Cluster of differentiation 14 (CD14, a monocyte marker) serves as a coreceptor for a number of these TLRs. Activation of TLRs leads to the induction of antimicrobial peptides and reactive oxygen species, which kill the organism. Among those antimicrobial peptides is cathelicidin, and its expression is induced by $1,25(\text{OH})_2\text{D}_3$. In addition, $1,25(\text{OH})_2\text{D}_3$ induces the coreceptor CD14. Stimulation of TLR2 by an antimicrobial peptide in macrophages or stimulation of TLR2 in keratinocytes by wounding results in increased expression of CYP27B1, which in the presence of adequate substrate, 25-hydroxyvitamin D, stimulates the expression of cathelicidin. Lack of 25-hydroxyvitamin D or CYP27B1 blunts the ability of these cells to respond to a challenge with respect to cathelicidin and/or CD14 production (80).

Animal data suggest that vitamin D could indeed be involved in ONJ. After zoledronate treatment, four out of six vitamin D-deficient rats developed exposed necrotic bone compared with one out of seven vitamin D-sufficient animals; none of the untreated normal or vitamin D-deficient rats developed ONJ (81). Furthermore, necrotic bone sequestra in the vitamin D-deficient rats were associated with actinomyces superinfection and pseudoepitheliomatous hyperplasia, another common finding in BPr-ONJ (81).

Denosumab, Sunitinib, Statins, and Macrophage Involvement in ONJ

A central role for monocytes and macrophages in the development of the BPr-ONJ provides a common mechanism that could explain the incidence of ONJ reported in patients on denosumab or sunitinib and provides new opportunities to introduce an effective treatment for this complication, pushing the boundaries of research to well beyond BPr-ONJ.

Denosumab

ONJ may develop in patients with advanced cancer treated with denosumab. In three head to head prospective randomized controlled trial phase III studies across a broad spectrum of advanced cancer patients, 4 mg of zoledronate administered intravenously

or 120 mg of denosumab injected subcutaneously were given monthly to 5677 patients for a mean of 12.1 (range 5.5–19.4) and 12.6 (range 5.6–19.4) months, respectively (48). Positively adjudicated cases of ONJ were recorded in 37 (1.3%) of those treated with zoledronate compared with 52 (1.8%) treated with denosumab. Notably, more patients on zoledronate (22%) were treated with antiangiogenic agents, a proposed risk factor for ONJ, than those on denosumab (12%), yet the number of patients who developed ONJ was higher in the denosumab group. Moreover, a meta-analysis of the data from 10 randomized controlled trials involving 18 197 participants showed that the risk of serious infection was statistically significantly increased in patients treated with denosumab (Mantel–Haenszel risk ratio = 1.26, 95% confidence interval = 1.01 to 1.57; $P = .04$, heterogeneity [I^2] = 22.8%) (82–84).

Human peripheral blood monocytes express RANK on the cell surface. Its ligand RANKL increases production of proinflammatory cytokines such as tumor necrosis factor α and interleukin 1 β , T-cell activation cytokines like interleukin 12 and 6, and chemokines such as macrophage inflammatory protein-1 α (85). Furthermore, RANKL protects monocytes from apoptosis by induction of the anti apoptotic proteins B-cell lymphoma extra large (Bcl-xl) and myeloid cell leukemia sequence 1 (Mcl-1), members of the B-cell lymphoma-2 family (85–87). RANKL also induces migration in human total peripheral blood mononuclear cells (PBMC) and CD14+ purified PBMC (88). Blockade of the RANK–RANKL interaction by a RANKL antibody such as denosumab could affect monocyte migration and function and decrease the survival and numbers of these cells, a situation similar to that created by bisphosphonates.

Sunitinib

The receptor tyrosine kinase inhibitor sunitinib, which is prescribed for gastrointestinal stromal tumors and metastatic renal cell carcinoma, may also increase the risk of developing ONJ, which was described in a patient who was treated with sunitinib (89) but never with a bisphosphonate. Macrophage colony-stimulating factor receptor, which is required for development, survival, proliferation, and differentiation of the monocyte–macrophage development series is a member of the receptor tyrosine kinase type III family, and its activity is inhibited by sunitinib (90). Angiogenesis is also inhibited by sunitinib through suppression of the vascular endothelial growth factor receptors, which could be an additional risk factor in the development of ONJ (91).

Statins

Statins induce apoptosis in J774 macrophage-like cells (30). In patients on frequent intravenous bisphosphonate infusions, statins, especially at high doses, might have an additive detrimental effect on the function and survival of monocytes and macrophages, which may increase the risk of infection in the jaw bones.

Treatment of ONJ

Effective preventive treatment or management of established BPr-ONJ could be achieved by discontinuation of BP treatment if the cancer activity level allows it. Because of the long half-life of BP compounds, their temporary discontinuation is not expected to help the recovery of already damaged bone. However, discontinuation

may prove critical in the recovery of monocyte and macrophage production or function, and it could improve the healing of the oral mucosa (65). Another treatment may be a more aggressive management of vitamin D deficiency. In osteoporotic patients, vitamin D supplementation is an obligatory addition to any antiresorptive regimen. In patients with metastatic bone disease where the risk of ONJ is greater, vitamin D replenishment should be part of the routine management, with careful monitoring of serum calcium to avoid hypercalcemia. The use of locally or systemically administered monocyte colony-stimulating factor or monocyte–macrophage colony-stimulating factor is another possible treatment option that may help the acceleration of the healing of oral mucosa. A temporary amplification of the numbers of functional monocytes and macrophages could increase the natural defenses against infection substantially. Any undesirable increase in the number of osteoclasts will not have any detrimental effects in cancer patients because the skeleton is already saturated by bisphosphonates (65). Furthermore, in non cancer osteoporotic patients with ONJ, concurrent treatment with intermittent administration of parathyroid hormone could revitalize the bone and increase the chances of treating ONJ (92).

Conclusions

ONJ in patients on N-BPs, as well as those treated with the RANKL antibody denosumab, remains a serious clinical challenge with no important breakthrough since its first description in 2003. Direct detrimental effects of N-BPs or denosumab on monocytes and macrophages could provide a new comprehensive explanation of its pathophysiology and thereby greatly increase potential treatment options.

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Notes

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