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Updates on Osteonecrosis of the Jaw

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Abstract

Purpose of review—Osteonecrosis of the Jaw (ONJ) in an uncommon condition noted to occur in patients with cancer receiving intravenous bisphosphonates. The etiology of ONJ remains unknown. The leading hypotheses addressing the mechanism of ONJ are reviewed here.

Recent findings—The present clinical data suggests that ONJ may occur in approximately 5% of patients with metastatic bone disease. The ability to predict an individual's risk of developing ONJ remains elusive. It is likely that an altered bone microenvironment and/or host defense mechanisms effected by medications used to treat patients with metastatic bone disease contributes to the development of ONJ. Medications that significantly reduce osteoclastic activity are associated with ONJ. Preclinical models of ONJ are being developed, but to establish such an intricate systemic condition in animals is challenging.

Summary—The ONJ field has progressed via knowledge gained by case reports, population-based studies and emerging animal models. Still, there are myths that need to be resolved and important clues that need to be investigated. Understanding the pathophysiology of this condition will be critical to improve patient care. Communications between oncologists, dentists, basic scientists and patients are central to effective treatment and research for this condition.

Keywords

necrotic bone; bisphosphonate; antiangiogenesis; immunomodulation

Introduction

Osteonecrosis of the jaw (ONJ) is an uncommon problem, which appears to occur in approximately 5% of patients receiving intravenous bisphosphonate in the management of metastatic bone disease. Much of what is known about ONJ has come from case reporting where the incidence of ONJ in patients with metastatic bone disease ranges from 1–18% (1, 2). ONJ appears to occur much less frequently in patients receiving oral bisphosphonates in the management of osteoporosis or Paget's disease of the bone (3). The incidence of ONJ in the general public is unknown.

Risk factors associated with the development of ONJ appear to include bone invasive dental procedures, comorbid conditions (most notably cancer), bisphosphonate exposure, lifestyle and behaviors (tobacco, alcohol) and antecedent factors (60% occurring after a dentoalveolar surgery or extractions) (4,5). Although the etiology of ONJ remains undefined, potential mechanisms have been proposed and include over suppression of bone turnover, immune dysfunction, and suppressed angiogenesis. [Table 1] A review of the recent clinical, translational, and basic science literature is presented here.

Clinical: Oversuppression of Bone Turnover

The intravenous nitrogen containing bisphosphonates (IV-NBP) are potent inhibitors of osteoclast function and are used in to decrease the risk of skeletal complications of malignancy in patients with metastatic bone disease. Case reports of ONJ suggest that it is more common in patients exposed to the higher potency bisphosphonates for a longer period of time (5). Bone remodeling is critical to the healing process and it has been hypothesized that ONJ is associated with over suppression of bone resorption and disruption of the bone remodeling (6). Clinically, the apparent increased risk of ONJ with zoledronic acid, a highly potent IV-NBP, and the affect of cumulative dosing, supports the hypothesis that strong inhibition of bone remodeling is associated with ONJ (4).

If ONJ is associated with profound osteoclast inhibition, then ONJ may occur with other osteoclast inhibiting therapies, including the monoclonal antibody, denosumab, which targets receptor activator for nuclear factor κ B ligand, (RANKL). In two Phase III randomized, placebo controlled, clinical trials comparing zoledronic acid (4mg intravenously monthly) versus denosumab (120 subcutaneously monthly), ONJ occurred with equal frequency in both treatment arms. In the study of 2046 patients with metastatic breast cancer there were 14 patients in the zoledronic acid arm (1.4%) and 20 patients in the denosumab arm (2.0%) who developed ONJ (7). In the study of 1776 patients with metastatic bone disease from multiple myeloma, or solid tumors (excluding breast and prostate), ONJ was seen in 10 patients (1.1%) on denosumab and 11 patients (1.3%) on zoledronic acid (8). These prospective data suggest that the incidence of ONJ is approximately 1–2% over 2–3 years in patients with metastatic bone disease treated with potent osteoclast inhibitors. Phase III clinical trials exploring monthly versus every 3 monthly dosing of zoledronic acid are ongoing and incorporate assessments of oral health to evaluate whether the intensity of drug dosing alters the risk of ONJ. [Table 2]

Clinical: Immune Dysfunction

The mechanisms of action of the anticancer therapies used in patients with metastatic bone disease vary widely. The bulk of therapies can be associated with immuno-suppression either secondary to suppression of the bone marrow and hematopoiesis or due to the incorporation of high dose glucocorticoids into the regimen. It has been proposed that immuno-suppression and/or dysfunction may be a risk factor for ONJ. Although the role of vitamin D in immune function is still being defined, it is critical to bone health (9) and may serve as an immunomodulator. The role of vitamin D deficiency in ONJ has been suggested but not thoroughly evaluated. In patients with multiple myeloma there did not appear to be a correlation between serum levels of 25 hydroxyvitamin D and ONJ (10). Using a cut off of < 30 ng/ml, it is estimated that greater the 75% of the adult US population is vitamin D insufficient (11). Similarly, in patients with metastatic breast cancer receiving intravenous bisphosphonates, the frequency of vitamin D levels < 30 ng/ml is 67% (12). Given the frequency of vitamin D insufficiency (13–15) and the limitations of the existing ONJ data, it is difficult to comment on whether low levels of vitamin D link at all to ONJ.

Intertwined with the hypothesis of immune function effecting risk of ONJ is the question of how the oral microflora, particularly *Actinomyces* species and its associated range of pH, may

affect the risk of developing ONJ (5,16). Denture use is associated with ONJ, perhaps due to bisphosphonates negatively affecting mucosal healing and subsequently oral flora invading bone (17). Clinical research is ongoing to investigate the oral flora microenvironment. In a cohort study collecting gingival crevicular fluid from patients with prior intravenous bisphosphonate exposure with and without ONJ and a control group analysis of bacterial DNA suggested that there may be a shift in the bacterial profile in ONJ and IVBPs subjects as compared to healthy controls (18). The analysis of the microbial profiles continues and the significance of any change in bacterial profile is yet to be defined.

Clinical: Suppressed Angiogenesis

Angiogenesis has become a target for anticancer therapies (19) and both licensed and experimental therapies are in clinic (20). Due to the importance of the vasculature to wound healing, it has been hypothesized that drugs altering normal vascularization may impact on the risk of ONJ. Interestingly, cases of ONJ have been reported in patients treated with the monoclonal antibody to vascular endothelial growth factor (VEGF), bevacizumab, who have not received IV-NBP (21,22) as well as cases of ONJ occurring in patients treated with bevacizumab or sunitinib when used with IV-NBP (23,24). In a Phase II clinical trial exploring bevacizumab, docetaxel, thalidomide, and prednisone in men with chemotherapy naïve metastatic prostate cancer who were permitted concurrent zoledronic acid, the incidence of ONJ was 18% (2). This report raises the concern that regimens with bevacizumab may increase the risk of ONJ. However, an ad hoc evaluation of 3 Phase III clinical studies in 3,560 patients with locally recurrent or metastatic breast cancer receiving bevacizumab containing therapy observed a 0.9–2.4% incidence of ONJ (25). There was no statistical difference in the incidence of ONJ in the bevacizumab versus placebo arms. Similarly, there was not statistical difference in the incidence of ONJ in those treated with bisphosphonate, or not. The analysis is limited by the retrospective design and the use of adverse report forms used to generate the data. However, this data on bevacizumab and ONJ is consistent with the single center retrospective analysis where the incidence of ONJ in patients treated with bevacizumab without bisphosphonate was 0% and 2% in those treated with bevacizumab and bisphosphonate. (26)

A genome wide association study performed in 24 cases of ONJ and 651 controls identified 4 polymorphisms in CYP2C8 were associated with an increased risk of developing ONJ (27). In addition to affecting drug metabolism, CYP2C8 may play role in the cascade of angiogenesis (28) thus supporting the hypothesis of ONJ being associated with vascular disruption. To investigate whether hyperbaric oxygen (HBO) may be an adjunctive therapy for ONJ wound healing, clinical trials of HBO are ongoing with encouraging results to date (29). Clinical trials in patients with metastatic bone disease assessing ONJ are ongoing as illustrated in Table 2.

Preclinical

The development of an animal model is essential for understanding the etiology and pathophysiology of ONJ. Oncology patients with ONJ typically have a history of multiple different kinds of chemotherapy that have immunosuppressive and antiangiogenic effects. Therefore, it is likely that an altered bone microenvironment and/or host defense mechanisms effected by chemotherapeutic drugs contributes to the development of ONJ. It is also possible that the interaction between bisphosphonates and cancer plays a role in the pathophysiology of ONJ. However, to establish such an intricate systemic condition in animals is challenging. For instance, mice typically do not survive long enough to study the effect of long-term bisphosphonate therapy in established mouse models of metastatic cancer. Furthermore, a recent cohort study shows that the prevalence of ONJ is less than 10% (17). Such low incidence of ONJ also makes animal research difficult to design. Accordingly, animal models are currently lacking. However, advances have been made in ONJ research at the preclinical level

in the past few years. The preclinical studies exploring the 3 major hypotheses for the mechanism leading to ONJ are reviewed here.

Preclinical: Oversuppression of Bone Turnover

Bone is constantly remodeled by bone cells to maintain its integrity. Osteocytes, in particular, reside in mineralized matrices and communicate with neighboring osteocytes and other cells on the bone surface. Responding to signals from osteocytes in the bone, osteoclasts are activated and migrate into damaged bone sites to initiate bone remodeling (30). Thus, osteocytes and osteoclasts are cardinal in the early stage of bone remodeling. Bisphosphonates have site-specific affinity for bone (31). In the mouse mandible, bisphosphonates are mainly localized in the alveolar bone. Roelofs et al. found the deposition of bisphosphonates in osteocytes lacunae near vascular channels in mice (32). Since osteocytes are the only cells that reside in the lacunae, accumulated bisphosphonate would eventually alter the cellular activity of osteocytes. Allen and Burr reported that a large number of empty osteocyte lacunae developed in the canine mandible after three years of alendronate therapy while no empty osteocyte lacunae were noted in the control group (33). No ONJ was noted in their study. These findings suggest that long-term bisphosphonate therapy has an adverse effect on osteocyte viability.

Because microdamage accumulation is one of the factors which stimulate bone remodeling, it is thought that bone remodeling rates would vary in different skeletal sites. In canines, the bone remodeling rate is high in the jaw throughout life, while it declines with age in the femur (34), suggesting that the jaw requires steady bone turnover regardless of age. Since osteoclastic bone resorption is essential for bone remodeling, the inhibition of osteoclasts by bisphosphonates would have a greater impact on the health of the jaw bone than other bones in an aged population. A recent study demonstrated that the bone remodeling rate in canine mandible was significantly suppressed after the 3-month zoledronic acid administration and virtually no bone turnover noted in the mandible after the 6-month zoledronic acid therapy (35). Thus, in this hypothesis, microdamage occurs and induces local osteocyte death initially. Such local necrotic bone requires repair but due to osteoclast inhibition bone remodeling is not accomplished (36). With suppressed bone remodeling microdamage accumulates and local necrotic bone grows. This may eventually manifest as ONJ.

Preclinical: Immune Dysfunction

It is clear that osteoclasts are a main target of bisphosphonates. However, accumulating evidence indicates that bisphosphonates are able to activate other cell types, especially immune-modulating cells. $V\gamma 9V\delta 2$ T cells that play a major role in innate immunity have been shown to be activated by bisphosphonates (37,38). Using a fluorescent labeling technique Coxon et al. showed that non-bone resorbing phagocytotic cells, such as macrophages/monocytes, are able to take up small amounts of bisphosphonates *in vitro* (39). Roelofs et al. used a similar technique to investigate the effect of bisphosphonates on non-osteoclast cells *in vivo* and found that CD14 high bone marrow monocytes uptake bisphosphonates (32). When macrophages were sensitized with bisphosphonates, chemokine production was suppressed (40). Bisphosphonates are also able to modulate the maturation of dendritic cells (41). These findings support an immunomodulatory effect of bisphosphonates. In 2008 Sonis et al. reported that mice treated with bisphosphonates and dexamethasone developed ONJ-like lesions following tooth extraction (42). No ONJ-like lesions were detected in the group treated with bisphosphonate alone in the study. Considering that dexamethasone has an immunosuppressive effect, in this rat ONJ model immune dysfunction might play a role. In fact, immune dysfunction is one of the main characteristics of multiple myeloma (43) and a great number of ONJ patients have received immunosuppressive therapy. Kikuri et al. further investigated the mechanisms by which bisphosphonates and dexamethasone alter the immune system *in vivo*

and found that regulatory T cells that maintain immune homeostasis were suppressed and that T helper 17 cells (Th17) which play a role in autoimmunity were activated (44). When mesenchymal stem cells were infused into the animal, ONJ was healed or the animal was protected from ONJ development. Thus, dysregulation of the immune tolerance could be involved in the development of ONJ. A link between ONJ and the immune system was further supported in a study where bisphosphonate-treated animals with vitamin D deficiency developed ONJ-like lesions following tooth extraction (45). In addition to a critical role in calcium absorption, Vitamin D has an impact on immune function (46). Thus, altered immune responses could predispose oncology patients to the development of ONJ.

Preclinical: Suppressed Angiogenesis

A hypothesis has been proposed that the inhibition of blood vessel formation by bisphosphonates is partly responsible for the development of ONJ. Bisphosphonate therapy delays wound healing following tooth extractions by inhibiting angiogenesis *in vivo* (47,48). However, whether the anti-angiogenic effect of bisphosphonates comes via osteoclast inhibition or other cells, such as macrophages/monocytes, remains unknown. Osteoclasts are proposed as angiogenic cells (49). During bone remodeling angiogenesis follows osteoclastic bone resorption. Bone resorption releases matrix-bound angiogenic growth factors to stimulate blood vessel formation. Therefore, the inhibition of osteoclasts by bisphosphonates results in suppression of the release of angiogenic factors. Hirbe et al. investigated the mechanisms of an anti-tumor effect of bisphosphonates and showed that bisphosphonates inhibited tumor growth in an osteoclast independent manner (50). Thus, the mechanisms of suppressed angiogenesis in ONJ would be different from those in tumor growth. Tumor-associated macrophages may play a role in tumor growth and angiogenesis (51). Since macrophages can uptake bisphosphonates, the anti-tumor effect of bisphosphonates could be attributed to such altered macrophage function.

Osteoclasts are of hematopoietic origin and share some biological functions with macrophages/monocytes, hence, the suppression of osteoclasts by bisphosphonates could influence the host immune mechanisms and tissue remodeling including angiogenesis. Additionally, bacterial infection and subsequent biofilm formation exacerbate the condition of ONJ (52,53). Thus, the pathophysiology of ONJ is complicated and complex preclinical models are needed.

Along with angiogenesis, lymphangiogenesis has recently been highlighted as a potential consideration for the development of osteonecrosis of the jaw (36). In a mouse model of osteomyelitis, Li et al reported that antiresorptives limited draining lymph node size during the establishment of osseous infections. They drew parallels with the histopathology of ONJ. These findings warrant further investigation.

Summary and Future needs

Considering ONJ was apparently non-existent ten years ago, the field has progressed via knowledge gained by case reports, population-based studies and emerging animal models. Still, there are myths that need to be resolved and important clues that need to be investigated for our understanding of the pathophysiology to translate into improved patient care. Three lead areas worthy of investigation include the impact of antiresorptives on alveolar bone turnover, on immune dysfunction, and on altered angiogenesis.

There is promulgation in the literature of the tenet of higher turnover in the alveolar bone than other skeletal sites. However, there has never been a systematic study of bone turnover and bone formation in human alveolar bone versus other skeletal sites, nor has there been a study of the actions of bisphosphonates in human alveolar bone at the tissue or cellular level. Such studies are imperative to be able to understand the unique action of these drugs and their

association with ONJ. Furthermore, it is not clear whether there are stage specific effects of bisphosphonates during osseous wound healing. Osteoclasts are important during healing after a tooth extraction at two key stages (54). They are first seen after the influx of leukocytes at the margins of bone disrupted by the extraction trauma where they function to recontour the wound margins. Later, after woven bone is laid down, osteoclasts facilitate remodeling of immature bone into mature lamellar bone. Many clinicians recommend that patients take a drug holiday before and after an extensive dental procedure, yet this is still controversial and not based on scientific evidence. It would be prudent to know what the temporal implications are for anti-resorptives on osteoclast prominent events during wound healing.

The impact of anti-resorptives on the convergence of inflammation, immune dysfunction and response to microbial infection is a vital avenue for further investigation. Once an established well characterized animal model of ONJ is developed, studies in this area should become more feasible and lead to improved knowledge of these mechanisms. An important goal of such studies would be to formulate a base for the development of prudent preventive strategies when dental procedures are required in patients on high dose bisphosphonates. Antibiotic regimes and immunomodulation via vitamin D supplementation or other approaches may become more rational with a stronger base of information.

The literature on anti-resorptives and angiogenesis has not yet led to a clear indication of the contribution of vascular supply in the bone with development of osteonecrosis. Studies pro and con are apparent and suggest that better experimental approaches are needed. The vascular spaces in bone are unique and although angiogenesis studies in the cancer field are extensive, very little is known about the vascular supply within the marrow and how bisphosphonates impact this. Case reports of angiogenesis inhibitors and the development of ONJ are suggestive, but are far from definitive. With the advent of improved MR imaging techniques that can associate bone mineral density with vascular perfusion at various skeletal sites, it should be feasible to evaluate the impact of anti-resorptive therapies on vascular perfusion in bone (55).

Conclusion

As the emerging literature suggests that bisphosphonates may not be the only drugs associated with ONJ, better epidemiologic data of the incidence of ONJ in various populations is clearly needed. As more information is gathered regarding epidemiology, mechanisms identified in animal models and experience via case controlled studies, our clinical treatment guidelines need to be revisited and updated. Finally and importantly, sound and open lines of communication between oncologists, dentists, and patients are central to effective treatment for this condition.

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References

1. Reid IR. Osteonecrosis of the jaw Who gets it, and why? *Bone* 2009;44(1):4–10. [PubMed: 18948230]
- 2*. Aragon-Ching JB, Ning YM, Chen CC, et al. Higher incidence of Osteonecrosis of the Jaw (ONJ) in patients with metastatic castration resistant prostate cancer treated with anti-angiogenic agents. *Cancer Invest* 2009;27(2):221–6. A prospective study of patients with metastatic prostate cancer receiving docetaxel, bevacizumab, thalidomide, prednisone and zoledronic acid where the incidence of ONJ was 18% and suggests that anti-angiogenic and chemotherapy agents can predispose to the development of ONJ. [PubMed: 19235596]

3. Khosla S, Burr D, Cauley J, et al. Bisphosphonate-Associated Osteonecrosis of the Jaw: Report of a Task Force of the American Society for Bone and Mineral Research. *J Bone Min Research* 2007;22:1479–1491.
4. Almazrooa SA, Woo SB. Bisphosphonate and nonbisphosphonate-associated osteonecrosis of the jaw: a review. *J Am Dent Assoc* 2009;140(7):864–75. [PubMed: 19571050]
5. Gliklich R, Wilson J. Epidemiology of Bisphosphonate-Related Osteonecrosis of the Jaws: The Utility of a National Registry. *J Oral and Maxillofacial Surgery* 2009;67(5, Suppl):71–74.
6. Allen MR, Burr DB. The Pathogenesis of Bisphosphonate-Related Osteonecrosis of the Jaw: So Many Hypotheses, So Few Data. *Journal of Oral and Maxillofacial Surgery* 2009;67(5, Suppl):61–70. [PubMed: 19371816]
- 7* *. Stopeck A, Body JJ, Fujiwara Y, et al. Denosumab versus zoledronic acid for the treatment of breast cancer patients with bone metastases: results of a randomized phase 3 study. *European Journal of Cancer Supplements* September;2009 7(3):2. Phase III data suggesting that the incidence of ONJ is 1–2% in patients with metastatic breast cancer involving the bone treated with potent osteoclast inhibitors.
- 8*. Henry D, von Moos R, Vadhan-Raj S, et al. A double-blind, randomized study of denosumab versus zoledronic acid for the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *European Journal of Cancer Supplements* September;2009 7(3):11. Phase III data suggesting that the incidence of ONJ is 1–2% in patients with metastatic bone disease treated with potent osteoclast inhibitors.
9. Binkley N. Is Vitamin D the fountain of youth? *Endocr Pract* 2009;15(6):590–596. [PubMed: 19491061]
10. Badros A, Goloubeva O, Terpos E, et al. Prevalence and significance of vitamin D deficiency in multiple myeloma patients. *British J of Haemat* 2008;142:480–501.
11. Adams JS, Hewison M. Update in Vitamin D. *J Clin Endocrinol Metab* 2010;95:471–478. [PubMed: 20133466]
12. Wang-Gillam A, Miles DA, Hutchins LF. Evaluation of vitamin D deficiency in breast cancer patients on bisphosphonates. *Oncologist* 2008 Jul;13(7):821–7. [PubMed: 18614589]
13. Crew KD, Shane E, Cremers S, et al. High prevalence of vitamin D deficiency despite supplementation in premenopausal women with breast cancer undergoing adjuvant chemotherapy. *J Clin Oncol* 2009;27:2151–2156. [PubMed: 19349547]
14. Ng AC, Kumar SK, Rajkumar SV, Drake MT. Impact of vitamin D deficiency on the clinical presentation and prognosis of patients with newly diagnosed multiple myeloma. *Am J Hematol* 2009;84:397–400. [PubMed: 19415724]
15. Trump DL, Chadha MK, Sunga AY, et al. Vitamin D deficiency and insufficiency among patients with prostate cancer. *BJU Int*. 2009
16. Otto S, Schuler K, Ihrler S, et al. Osteonecrosis or Metastases of the Jaw or Both? Case Report and Review of the Literature *Journal of Oral and Maxillofacial Surgery*. *J Oral Maxillofac Surg* 2010 May;68(5):1185–8. [PubMed: 20144499]
- 17*. Vahtsevanos K, Kyrgidis A, Verrou E, et al. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. *J Clin Oncol* 2009;10;27(32):5356–62. This cohort study of 1621 Greek patients with metastatic bone disease receiving bisphosphonate therapy identified 80 cases of ONJ between January 2000 and October 2008. The investigators identified the following factors to be associated with ONJ: dentures, history of dental extraction, and use of zoledronic acid. The data did not demonstrate an association with smoking, periodontitis, or root canal treatment.
18. Abraham, F.; Saxena, D.; Dalvi, M., et al. Molecular Analysis of Bacteria Associated With Osteonecrosis of the Jaw Molecular Analysis of Bacteria Associated With Osteonecrosis of the Jaw IADR/AADR/CADR 87th General Session and Exhibition; April 1–4, 2009;
19. Folkman J. Clinical applications of research on angiogenesis. *N Engl J Med* 1995 Dec 28;333(26): 1757–63. [PubMed: 7491141]
20. Heath VL, Bicknell R. Anticancer strategies involving the vasculature. *Nature Reviews Clinical Oncology* 2009;6:395–404.

21. Greuter S, Schmid F, Ruhstaller T, Thuerlimann B. Bevacizumab-associated osteonecrosis of the jaw. *Ann Oncol* 2008;19(12):2091–2. Epub 2008 Oct 31. [PubMed: 18977851]
22. Estilo CL, Fornier M, Farooki A, et al. Osteonecrosis of the Jaw Related to Bevacizumab. *Journal of Clinical Oncology* 2008;26(24):4037–4038. [PubMed: 18711196]
23. Ayllon J, Launay-Vacher V, Medioni J, et al. Osteonecrosis of the jaw under bisphosphonate and antiangiogenic therapies: cumulative toxicity profile? *Ann Oncol* 2009;20(3):600–1. [PubMed: 19188135]
24. Brunello A, Saia G, Bedogni A, et al. Worsening of osteonecrosis of the jaw during treatment with sunitinib in a patient with metastatic renal cell carcinoma. *Bone* 2009;44:173–175. [PubMed: 18849018]
- 25*. Guarneri V, Miles D, Robert N, et al. Bevacizumab and osteonecrosis of the jaw: incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer. *Breast Cancer Res Treat On line*. The authors present data from adverse event reported from three large clinical trials investigating bevacizumab in the treatment of patients with locally advanced or metastatic breast cancer. The analysis included 3,560 patients and did not demonstrate an association between bevacizumab and risk of ONJ. 10.1007/s10549-010-0866-3
26. McArthur HL, Estilo C, Huryn J, et al. Osteonecrosis of the jaw (ONJ) among intravenous (IV) bisphosphonate- and/or bevacizumab-treated patients (pts) at Memorial Sloan-Kettering Cancer Center (MSKCC). *J Clin Oncol* 2008;26:9588.
27. Sarasquete ME, Garcia-Sanz R, Marin L, et al. Bisphosphonate-related osteonecrosis of the jaw is associated with polymorphisms of the cytochrome P450 CYP2C8 in multiple myeloma: a genome-wide single nucleotide polymorphism analysis. *Blood* 2008;112:2709–2712. [PubMed: 18594024]
28. Michaelis UR, Fisslthaler B, Barbosa-Sicard B, et al. Cytochrome P450 epoxigenases 2C8 and 2C9 are implicated in hypoxia-induced endothelial cell migration and angiogenesis. *J Cell Sci* 2005;118(23):5489–5498. [PubMed: 16291720]
29. Freiburger JJ. Utility of Hyperbaric Oxygen in Treatment of Bisphosphonate-Related Osteonecrosis of the Jaws. *J Oral Maxillofac Surg* 2009;67(Suppl 1):96–106. [PubMed: 19371820]
30. Cardoso L, Herman BC, Verborgt O, et al. Osteocyte apoptosis controls activation of intracortical resorption in response to bone fatigue. *J Bone Miner Res* 2009;24:597–605. [PubMed: 19049324]
- 31*. Kozloff KM, Volakis LI, Marini JC, Caird MS. Near-infrared fluorescent probe traces bisphosphonate delivery and retention in vivo. *J Bone Miner Res*. 2010 [Epub ahead of print] The deposition and retention of bisphosphonates was assessed using a fluorescent bisphosphonate marker in rats. The study found that the degree of bisphosphonate deposition and retention were affected by bone quantity and bone turnover rate. In the mandible the bisphosphonate marker was found mainly in the temporomandibular joints and alveolar bone surrounding the roots of the molars.
- 32**. Roelofs AJ, Coxon FP, Ebetino FH, et al. Fluorescent Risedronate Analogs Reveal Bisphosphonate Uptake by Bone Marrow Monocytes and Localization Around Osteocytes In Vivo. *J Bone Miner Res* 2010;25:606–616. The study demonstrated that bisphosphonates are deposited and localized in osteocytes lacunae either close to the bone surface or vascular channels in the cortical bone using fluorescently labeled risedronate. The study also showed evidence that CD14^{high} bone marrow monocytes are capable of uptake a large amount of bisphosphonates *in vivo*. [PubMed: 20422624]
33. Allen MR, Burr DB. Mandible matrix necrosis in beagle dogs after 3 years of daily oral bisphosphonate treatment. *J Oral Maxillofac Surg* 2008;66:987–994. [PubMed: 18423290]
34. Huja SS, Beck FM. Bone remodeling in maxilla, mandible, and femur of young dogs. *Anat Rec (Hoboken)* 2008;291:1–5. [PubMed: 18085627]
35. Allen MR, Kubek DJ, Burr DB. Cancer Treatment Dosing Regimens of Zoledronic Acid Result in Near Complete Suppression of Mandible Intra-Cortical Bone Remodeling in Beagle Dogs. *J Bone Miner Res* 2010;25:98–105. [PubMed: 19580463]
- 36*. Li D, Gromov K, Proulx ST, et al. Effects of antiresorptive agents on osteomyelitis: novel insights into the pathogenesis of osteonecrosis of the jaw. *Ann N Y Acad Sci* 2010;1192:84–94. This study describes an osteomyelitis animal model where anti-resorptive agents were utilized in a murine trans-tibial infected pin model. Anti-resorptives (alendronate and osteoprotegerin) were found to decrease lymphatic drainage and prevent the removal of necrotic bone harboring bacteria. Parallels were drawn to the condition of osteonecrosis of the jaw. [PubMed: 20392222]

37. Simoni D, Gebbia N, Invidiata FP, et al. Design, synthesis, and biological evaluation of novel aminobisphosphonates possessing an in vivo antitumor activity through a gammadelta-T lymphocytes-mediated activation mechanism. *J Med Chem* 2008;51:6800–6807. [PubMed: 18937434]
38. Agrati C, Cimini E, Sacchi A, et al. Activated V gamma 9V delta 2 T cells trigger granulocyte functions via MCP-2 release. *J Immunol* 2009;182:522–529. [PubMed: 19109184]
39. Coxon FP, Thompson K, Roelofs AJ, et al. Visualizing mineral binding and uptake of bisphosphonate by osteoclasts and non-resorbing cells. *Bone* 2008;42:848–860. [PubMed: 18325866]
40. Masuda T, Deng X, Tamai R. Mouse macrophages primed with alendronate down-regulate monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1 alpha (MIP-1 alpha) production in response to Toll-like receptor (TLR) 2 and TLR4 agonist via Smad3 activation. *Int Immunopharmacol* 2009;9:1115–1121. [PubMed: 19501197]
41. Chen YJ, Chao KS, Yang YC, et al. Zoledronic acid, an aminobisphosphonate, modulates differentiation and maturation of human dendritic cells. *Immunopharmacol Immunotoxicol* 2009;31:499–508. [PubMed: 19555208]
42. Sonis ST, Watkins BA, Lyng GD, et al. Bony changes in the jaws of rats treated with zoledronic acid and dexamethasone before dental extractions mimic bisphosphonate-related osteonecrosis in cancer patients. *Oral Oncol* 2009;45:164–172. [PubMed: 18715819]
43. Pratt G, Goodyear O, Moss P. Immunodeficiency and immunotherapy in multiple myeloma. *Br J Haematol* 2007;138:563–579. [PubMed: 17686051]
- 44* *. Kikuri T, Kim I, Yamaza T, et al. Cell-based immunotherapy with mesenchymal stem cells cures bisphosphonate-related osteonecrosis of the jaw-like disease in mice. *J Bone Miner Res*. 2010 [Epub ahead of print]. This study reported the development of ONJ-like lesions following tooth extractions in mice that were under a combination therapy of bisphosphonate and dexamethasone. In such mice the adaptive regulatory T cells (Tregs) were suppressed. When those rats received the systemic infusion of mesenchymal stem cells, Tregs were restored and ONJ-like lesions were healed.
45. Hokugo A, Christensen R, Chung E, et al. Increased prevalence of bisphosphonate-related osteonecrosis of the jaw with vitamin D deficiency in rats. *J Bone Miner Res*. 2010 [Epub ahead of print].
46. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266–281. [PubMed: 17634462]
47. Kobayashi Y, Hiraga T, Ueda A, et al. Zoledronic acid delays wound healing of the tooth extraction socket, inhibits oral epithelial cell migration, and promotes proliferation and adhesion to hydroxyapatite of oral bacteria, without causing osteonecrosis of the jaw, in mice. *J Bone Miner Metab* 2010;28:165–175. [PubMed: 19882100]
48. Hikita H, Miyazawa K, Tabuchi M, et al. Bisphosphonate administration prior to tooth extraction delays initial healing of the extraction socket in rats. *J Bone Miner Metab* 2009;27:663–672. [PubMed: 19436946]
49. Cackowski FC, Anderson JL, Patrene KD, et al. Osteoclasts are important for bone angiogenesis. *Blood* 2010;115:140–149. [PubMed: 19887675]
50. Hirbe AC, Roelofs AJ, Floyd DH, et al. The bisphosphonate zoledronic acid decreases tumor growth in bone in mice with defective osteoclasts. *Bone* 2009;44:908–916. [PubMed: 19442620]
51. Mantovani A, Sica A. Macrophages, innate immunity and cancer: balance, tolerance, and diversity. *Curr Opin Immunol*. 2010
52. Lesclous P, Abi Najm S, Carrel JP, et al. Bisphosphonate-associated osteonecrosis of the jaw: a key role of inflammation? *Bone* 2009;45:843–852. [PubMed: 19631301]
53. Sedghizadeh PP, Kumar SK, Gorur A, et al. Microbial biofilms in osteomyelitis of the jaw and osteonecrosis of the jaw secondary to bisphosphonate therapy. *J Am Dent Assoc* 2009;140:1259–1265. [PubMed: 19797556]
54. Cardaropoli G, Araujo M, Lindhe J. Dynamics of bone tissue formation in tooth extraction sites. An experimental study in dogs. *J Clin Periodontol* 2003 Sep;30(9):809–18. [PubMed: 12956657]
55. Griffith JF, Yeung DKW, Antonio GE, et al. Vertebral marrow fat content and diffusion and perfusion indexes in women with varying bone density: MR Evaluation. *Radiology* 2006;241:831–838. [PubMed: 17053202]

Table 1

Potential mechanisms affecting the risk of ONJ

<ul style="list-style-type: none">• Oversuppression of bone turnover• Immune dysfunction• Suppressed angiogenesis

Table 2Clinical trials in patients with metastatic bone disease assessing ONJ <http://www.clinicaltrials.gov/ct>

Clinicaltrials.gov identifier	Title (running title)	Sponsor	Comments
NCT00462098	Randomized Controlled Trial of Hyperbaric Oxygen in Patients Who Have Taken Bisphosphonates	Duke University	This study is currently recruiting participants
NCT00874211	Zoledronic Acid in Treating Patients With Metastatic Breast Cancer, Metastatic Prostate Cancer, or Multiple Myeloma With Bone Involvement	Southwest Oncology Group	This study is currently recruiting participants
NCT00869206	Long Term Efficacy and Safety of Zoledronic Acid Treatment in Patients With Bone Metastases	Cancer and Leukemia Group B	This study is currently recruiting participants
NCT00320710	Efficacy and Safety of Zoledronic Acid (Every 4 Weeks vs. Every 12 Weeks) in Patients With Documented Bone Metastases From Bone Cancer	Novartis	This study is currently recruiting participants
NCT00375427	Safety and Efficacy of Zoledronic Acid in Patients With Breast Cancer With Metastatic Bone Lesions	Novartis	This study is currently recruiting participants
NCT00434447	Long Term Efficacy and Safety of Zoledronic Acid Treatment in Patients With Bone Metastases	Long Term Efficacy and Safety of Zoledronic Acid Treatment in Patients With Bone Metastases	This study is ongoing, but not recruiting participants
NCT00601068	Proposal For The Development Of A Well Defined Database For Patients With Oral Bisphosphonate-Related Osteonecrosis	University of Florida, Merck	This study is ongoing, but not recruiting participants
NCT00592982	Bisphosphonate-Associated Jaw Osteonecrosis and PET Imaging	University of Arkansas	This study is ongoing, but not recruiting participants