IBMS BoneKEy. 2011 April;8(4):205-210
http://www.bonekey-ibms.org/cgi/content/full/ibmske;8/4/205
doi: 10.1138/20110508

COMMENTARIES

Bisphosphonates in Periodontitis: Friend or Foe?

Serge Ferrari[1], Nicolas Bonnet[1] and Philippe Lesclous[2]

[1]Division of Bone Diseases, Geneva University Hospital and Faculty of Medicine, Geneva, Switzerland
[2]Faculté de Chirurgie Dentaire, Université Paris Descartes, Montrouge, France

Commentary on: Aghaloo TL, Kang B, Sung EC, Shoff M, Ronconi M, Gotcher JE, Bezouglaia O, Dry SM, Tetradis S. Periodontal disease and bisphosphonates induce osteonecrosis of the jaws in the rat. *J Bone Miner Res*. 2011 Feb 23. [Epub ahead of print]

Periodontal disease (PD) refers to the common inflammatory disorders of tissues surrounding and supporting the teeth: inflammation of the gingival tissue leading to gingivitis, and of the periodontal ligament and alveolar bone leading to periodontitis. PD is caused by pathogenic local microflora, as opposed to invasion by pathogenic microorganisms. Consecutive inflammation that extends deep into the tissues causes loss of supporting connective tissue and alveolar bone, resulting in loosening of the teeth in susceptible hosts (1). Periodontitis is a common problem as it is estimated that 48.2% of the U.S. population aged ≥ 30 years is affected, with up to 20% of subjects showing severe attachment loss in the NHANES III survey (2). Moreover, PD has been associated with osteoporosis (3-5). A few small but controlled, sometimes randomized, studies have suggested that bisphosphonates (BPs), particularly alendronate and risedronate, may reduce the radiological and/or clinical signs of PD, including alveolar bone loss, gingival index and bleeding (6-8). A larger, 2-year, randomized controlled trial of weekly alendronate (70 mg) in 355 men and women showed no significant effect of alendronate on alveolar bone loss (alveolar crestal height) overall, but a preservation in a subgroup of subjects with low mandibular bone mineral density (BMD) at baseline (9). Moreover, only 30 teeth were lost in the alendronate group, vs. 52 in the placebo group. The rate of overall and specifically oral/dental adverse events did not differ between treated and placebo groups. Osteonecrosis of the jaw (ONJ) did not occur, which is not surprising considering the limited number of relatively low risk subjects, *i.e.*, not cancer patients, included in this study. On another side, patients with a history of inflammatory dental diseases, *i.e.*, PD and dental abscesses, may be at increased risk for developing ONJ when receiving BPs (10). The clinical benefits of BPs in periodontitis are supported by a number of experimental data in animals, which are summarized below. In this context, a recent experimental model published by Aghaloo *et al*. (11) showing bone lesions consistent with ONJ in rats receiving zoledronate raises questions regarding the benefit/risk of BP administration in periodontitis.

Experimental Periodontitis

The rice rat was the first model, reported in the mid-fifties, to investigate the development of PD (12-15). In 1981, Gotcher and Jee reported the detailed mandibular bone histology of the rice rat administered a high sucrose diet for 18 weeks (16). Their work demonstrated an early and heavy infiltration of the epithelium by inflammatory cells (PMNs and lymphocytes), followed by a marked increase of osteoclasts and loss of alveolar bone. This inflammation results from an

infectious gingivitis by enterococci, as previously shown by the periodontal response to antibiotic therapy (13). Some animals showed a total destruction of the periodontium and only small spicules (fragments) of alveolar bone were left at 18 weeks, in which the bone surface appeared "quiescent" whereas other bone spicules contained some osteoclasts. In addition, there were large vascular spaces and a marked proliferation of fibroblasts, while the overall number of osteoblasts was unchanged at any time point (16). This experiment demonstrated, therefore, that severe periodontitis, that is, local infection and inflammation, could lead to the destruction of alveolar bone with the appearance of small necrotic bone remnants.

In parallel, these authors treated a group of rice rats with clodronate, an early generation non-nitrogen-containing BP, at doses from 0.1 to 10 mg/kg/d for up to 18 weeks (17). The amount of alveolar bone was increased by the higher doses of clodronate, and the vascular spaces were reduced. Osteoblast numbers were also reduced in the treated animals. Trabeculae of alveolar bone lined with epithelial cells and heavily infiltrated by PMNs were observed protruding into the oral cavity. Portions of alveolar crestal bone exposed to the oral cavity and devoid of bone cells as well as scalopped spicules were also observed. The authors concluded that the main effect of clodronate in this experiment was to increase bone mass in the interdental alveolar space, but also that inhibition of bone remodeling delayed the removal of necrotic bone remnants.

Similarly, in a rat model in which inflammatory periodontitis was created by placing an elastic ring around the neck of the right mandibular first molar, short term (7 days) injections of risedronate (0.8 to 3.2 μmol/kg/d) prevented the resorption of alveolar bone and the loss of bone mineral content in a dose-dependent manner (18). The authors reported the presence of large, "frustrated" osteoclasts detached from the bone surface, but no differences in the degree of inflammation compared to controls, nor the presence of necrotic bone. It is unclear whether or not the investigators looked specifically for exposed bone in the oral cavity. Effects of alendronate on the preservation of alveolar bone were also shown in a cynomolgus monkey periodontitis model after both tooth ligature and bacterial inoculations (21;22).

In beagle dogs in which naturally-occurring periodontitis was exacerbated by silk ligature of the study teeth, oral alendronate (3 mg/kg/d) for 6 months preserved jaw bone mass compared to placebo (as evaluated by digital image analysis of oral radiographs), and had no effect on clinical parameters of gingival inflammation or plaque (19). Moreover, intramuscular pamidronate (0.6 mg/kg every 3 days for 3 months) inhibited alveolar bone resorption in experimentally-induced peri-implantitis in beagle dogs (20). In contrast, after administering a "clinical dose" (0.2 mg/kg/d) or a high dose (1 mg/kg/d) of alendronate for 3 years, Allen and Burr noted areas of necrotic alveolar bone, as assessed by the absence of basic fuchsin staining, in 3 and 4, respectively, out of 12 dogs in each treatment group, vs. none in the control group (23). The absence of staining in this case represents a disruption of the canalicular network, *i.e.*, an indirect sign of osteocyte apoptosis. The authors found no sign of avascular necrosis, as vessels were always present, and no animals with exposed bone in the oral cavity. As concluded properly by the authors, the areas of dead bone matrix are not necessarily caused by the BP, but could be explained by naturally dead (old) bone remaining rather than being removed since bone remodeling is low with BP treatment. To support the latter conclusion, areas of dead bone were also found in the ribs (24). Moreover, in a separate study with zoledronic acid (0.06 mg/kg/month) for 6 months, no animals showed evidence of necrosis based on fuchsin staining (24). However, at this early six-month time point, on lactate dehydrogenase staining the number of necrotic osteocytes was higher in the zoledronic acid group than in either the alendronate or control groups.

The rat model recently published by Aghaloo *et al*. also induced severe PD by wire ligature placement around the crown of the

right maxillary first molar (11). Consistent with the other studies, ligature placement induced significant alveolar bone loss, which was attenuated by zoledronic acid treatment (66 μg/kg three times per week for 3 weeks prior to intraoral procedures). Zoledronate also significantly reduced the distance between the cementoenamel junction (CEJ) and the alveolar bone crest (ABC). However, osteonecrosis was observed associated with ligature-induced periodontitis in 47% of the zoledronate group and 5% of controls. This was seen as sequestration and extensive periosteal alveolar bone on μCT in the ligated site of BP-treated animals. Histologic examination confirmed these findings, including observation of necrotic bone with diffuse loss of osteocytes (of which apoptosis was increased as evaluated by TUNEL) and empty lacunae, rimming of the necrotic bone by squamous epithelium and inflammation, and exposure to the oral cavity in 21% vs. 0% of zoledronate and control groups, respectively. The authors propose a mechanism by which non-resorbed alveolar bone under the effects of BPs remains in the vicinity of the inflammatory and infected nidus, in which a toxic environment of osteonecrosis can develop.

A mouse genetic model of PD has been reported recently, *i.e*., the periostin-deficient mouse (25-27). Periostin is an extracellular matrix protein, synthesized by osteoblasts/osteocytes, that is linked to type I collagen in the periodontal ligament, where it regulates fibrillogenesis and consequently the biomechanical properties of fibrous connective tissues around the tooth. Its expression is increased in the periodontal ligament upon mechanical loading and is essential for the integrity and function of this ligament during occlusal loading. Periostin-deficient mice show severe alterations in tooth (incisor) eruption, resulting from a failure to digest collagen fibers in the shear zone of the periodontal ligament (26;27). As a consequence, the enamel and dentin of the incisors are compressed and disorganized, and these mice develop severe periodontitis, with loss of alveolar bone. The severity of periodontitis, however, can be moderated with age and a soft diet. These mice also have osteopenia and a reduced response to mechanical loading (28), thereby representing a unique model of osteoporosis and PD, as often seen in aging humans. Repeated administration of high-dose zoledronate (100 μg/kg/week, equivalent to 6-times the monthly dose in cancer patients, *i.e*., 4 mg) for 3 months in periostin-deficient mice improved basal BV/TV in the mandible and trabecular BV/TV in long bones, without significant changes in alveolar BV/TV nor in the distance between enamel-cement and alveolar bone (DEA), an index of apparent bone in the oral cavity (29). Moreover, histological analysis based on standard HE and toluidine blue stainings provided no signs of worsening inflammation nor necrotic bone in the zoledronate group, despite some increase in the number of empty osteocytic lacunae.

Discussion

The rat experiment reported by Aghaloo *et al*. is the first to indicate that BP administration in periodontitis could lead specifically to ONJ. Through infection and inflammation, severe periodontitis causes alveolar bone loss and can also lead to bone matrix necrosis. In the presence of infectious/inflammatory sockets and in the absence of bone remodeling, necrotic bone remnants could therefore develop and persist, eventually protruding into the oral cavity. This was suggested from the early studies with clodronate in the rice rat, and is consistent with the interpretation of their own data by Aghaloo *et al*. Nevertheless, it remains unclear why these rats developed lesions compatible with ONJ, *i.e*., exposed bone in the oral cavity, while in the mouse genetic periodontitis model (periostin-deficient mice), as well as in beagle dogs, this was not the case. Besides obvious species and sex differences, contrasting results could be explained by the higher cumulative dose of zoledronate administered over a short period of time in the Aghaloo *et al*. study, which is equivalent to the human monthly 4-mg dose given 9 times over the course of 3 weeks in these rats. It could also be due to the aggressive periodontitis induced by the tooth wire ligature, whereas inflammation does not appear to be so severe with cotton or silk

ligature generally used in the recent periodontal literature (30), as well as in the periostin-deficient mouse.

Thus far, the animal models showing necrotic bone lesions compatible with ONJ upon BP administration were based on multiple and traumatic molar tooth extractions, causing tooth fragments and tissue ulcerations in the jaw (31;32). In some experiments, high-dose dexamethasone was administered concomitantly (32). The limitations of the Sonis *et al*. study (32) have been commented upon previously in *BoneKEy* (33) and there is no proof thus far that BPs, or any anti-resorptive, directly cause bone necrosis in the mandible/maxilla in humans (34). Utilizing pharmacological agents at clinically-relevant doses and dosing schedules will be important to strengthen the validity of the models. Equally important will be to perform time-dependent dynamic histomorphometry analyses of the mandibular/maxillar bones in order to evaluate the relationship between bone remodeling and the development, or persistence, of osteonecrotic fragments.

Conflict of Interest: Dr. Ferrari reports that he receives research support from Amgen and Merck Sharp & Dohme, and is an advisory committee member and lectures occasionally at conference symposia for Amgen, Merck Sharp & Dohme, Eli Lilly, Servier, and Novartis. Dr. Bonnet and Dr. Lesclous: none reported.

Peer Review: This article has been peer-reviewed.

References

1. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. *Lancet*. 2005 Nov 19;366(9499):1809-20.

2. Albandar JM, Brunelle JA, Kingman A. Destructive periodontal disease in adults 30 years of age and older in the United States, 1988-1994. *J Periodontol*. 1999 Jan;70(1):13-29.

3. Al Habashneh R, Alchalabi H, Khader YS, Hazza'a AM, Odat Z, Johnson GK. Association between periodontal disease and osteoporosis in postmenopausal women in Jordan. *J Periodontol*. 2010 Nov;81(11):1613-21.

4. Gomes-Filho IS, de S Passos J, Cruz SS, Vianna MI, de MM Cerqueira E, Oliveira DC, dos Santos CA, Coelho JM, Sampaio FP, Freitas CO, de Oliveira NF. The association between postmenopausal osteoporosis and periodontal disease. *J Periodontol*. 2007 Sep;78(9):1731-40.

5. Van Dyke TE, Sheilesh D. Risk factors for periodontitis. *J Int Acad Periodontol*. 2005 Jan;7(1):3-7.

6. El-Shinnawi UM, El-Tantawy SI. The effect of alendronate sodium on alveolar bone loss in periodontitis (clinical trial). *J Int Acad Periodontol*. 2003 Jan;5(1):5-10.

7. Lane N, Armitage GC, Loomer P, Hsieh S, Majumdar S, Wang HY, Jeffcoat M, Munoz T. Bisphosphonate therapy improves the outcome of conventional periodontal treatment: results of a 12-month, randomized, placebo-controlled study. *J Periodontol*. 2005 Jul;76(7):1113-1122.

8. Rocha ML, Malacara JM, Sánchez-Marin FJ, Vazquez de la Torre CJ, Fajardo ME. Effect of alendronate on periodontal disease in postmenopausal women: a randomized placebo-controlled trial. *J Periodontol*. 2004 Dec;75(12):1579-85.

9. Jeffcoat MK, Cizza G, Shih WJ, Genco R, Lombardi A. Efficacy of bisphosphonates for the control of alveolar bone loss in periodontitis. *J Int Acad Periodontol*. 2007 Jul;9(3):70-6.

10. Hoff AO, Toth BB, Altundag K, Johnson MM, Warneke CL, Hu M, Nooka A, Sayegh G, Guarneri V, Desrouleaux K, Cui J, Adamus A, Gagel RF, Hortobagyi GN. Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. *J Bone Miner Res*. 2008 Jun;23(6):826-36.

11. Aghaloo TL, Kang B, Sung EC, Shoff M, Ronconi M, Gotcher JE, Bezouglaia O, Dry SM, Tetradis S. Periodontal disease

and bisphosphonates induce osteonecrosis of the jaws in the rat. *J Bone Miner Res*. 2011 Feb 23. [Epub ahead of print]

12. Auskaps AM, Gupta OP, Shaw JH. Periodontal disease in the rice rat. III. Survey of dietary influences. *J Nutr*. 1957 Nov 10;63(3):325-43.

13. Gupta OP, Auskaps AM, Shaw JH. Periodontal disease in the rice rat. IV. The effects of antibiotics on the incidence of periodontal lesions. *Oral Surg Oral Med Oral Pathol*. 1957 Nov;10(11):1169-75.

14. Gupta OP, Shaw JH. [Periodontal disease in the rice rat. II. Methods for the evaluation of the extent of periodontal disease]. *Oral Surg Oral Med Oral Pathol*. 1956 Jul;9(7):727-35.

15. Gupta OP, Shaw JH. [Periodontal disease in the rice rat. I. Anatomic and histopathologic findings]. *Oral Surg Oral Med Oral Pathol*. 1956 Jun;9(6):592-603.

16. Gotcher JE, Jee WS. The progress of the periodontal syndrome in the rice rat. I. Morphometric and autoradiographic studies. *J Periodontal Res*. 1981 May;16(3):275-91.

17. Gotcher JE, Jee WS. The progress of the periodontal syndrome in the rice cat. II. The effects of a diphosphonate on the periodontium. *J Periodontal Res*. 1981 Jul;16(4):441-55.

18. Shoji K, Horiuchi H, Shinoda H. Inhibitory effects of a bisphosphonate (risedronate) on experimental periodontitis in rats. *J Periodontal Res*. 1995 Jul;30(4):277-84.

19. Reddy MS, Weatherford TW 3rd, Smith CA, West BD, Jeffcoat MK, Jacks TM. Alendronate treatment of naturally-occurring periodontitis in beagle dogs. *J Periodontol*. 1995 Mar;66(3):211-7.

20. Shibutani T, Inuduka A, Horiki I, Luan Q, Iwayama Y. Bisphosphonate inhibits alveolar bone resorption in experimentally-induced peri-implantitis in dogs. *Clin Oral Implants Res*. 2001 Apr;12(2):109-14.

21. Brunsvold MA, Chaves ES, Kornman KS, Aufdemorte TB, Wood R. Effects of a bisphosphonate on experimental periodontitis in monkeys. *J Periodontol*. 1992 Oct;63(10):825-30.

22. Weinreb M, Quartuccio H, Seedor JG, Aufdemorte TB, Brunsvold M, Chaves E, Kornman KS, Rodan GA. Histomorphometrical analysis of the effects of the bisphosphonate alendronate on bone loss caused by experimental periodontitis in monkeys. *J Periodontal Res*. 1994 Jan;29(1):35-40.

23. Allen MR, Burr DB. Mandible matrix necrosis in beagle dogs after 3 years of daily oral bisphosphonate treatment. *J Oral Maxillofac Surg*. 2008 May;66(5):987-94.

24. Burr DB, Allen MR. Mandibular necrosis in beagle dogs treated with bisphosphonates. *Orthod Craniofac Res*. 2009 Aug;12(3):221-8.

25. Ma D, Zhang R, Sun Y, Rios HF, Haruyama N, Han X, Kulkarni AB, Qin C, Feng JQ. A novel role of periostin in postnatal tooth formation and mineralization. *J Biol Chem*. 2011 Feb 11;286(6):4302-9.

26. Rios H, Koushik SV, Wang H, Wang J, Zhou HM, Lindsley A, Rogers R, Chen Z, Maeda M, Kruzynska-Frejtag A, Feng JQ, Conway SJ. periostin null mice exhibit dwarfism, incisor enamel defects, and an early-onset periodontal disease-like phenotype. *Mol Cell Biol*. 2005 Dec;25(24):11131-44.

27. Rios HF, Ma D, Xie Y, Giannobile WV, Bonewald LF, Conway SJ, Feng JQ. Periostin is essential for the integrity and function of the periodontal ligament during occlusal loading in mice. *J Periodontol*. 2008 Aug;79(8):1480-90.

28. Bonnet N, Standley KN, Bianchi EN, Stadelmann V, Foti M, Conway SJ, Ferrari SL. The matricellular protein periostin is required for sost inhibition and the anabolic response to mechanical loading and physical activity. *J Biol Chem*. 2009 Dec 18;284(51):35939-50.

29. Bonnet N, Lesclous P, Ferrari S. Frequent administration of high-dose zoledronate safely prevents ovariectomy-induced loss of jaw alveolar bone in a genetic mouse model of osteoporosis and periodontal disease. *J Bone Min Res*. 2010;25(Suppl 1). [Abstract]

30. Oz HS, Puleo DA. Animal models for periodontal disease. *J Biomed Biotechnol*. 2011;2011:754857.

31. Maahs MP, Azambuja AA, Campos MM, Salum FG, Cherubini K. Association between bisphosphonates and jaw osteonecrosis: A study in Wistar rats. *Head Neck*. 2011 Feb;33(2):199-207.

32. Sonis ST, Watkins BA, Lyng GD, Lerman MA, Anderson KC. 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 Feb;45(2):164-72.

33. Allen MR. Does rat + bisphosphonate + exposed bone = an animal model of ONJ? *IBMS BoneKEy*. 2009 Jun;6(6):227-31. [Full Text]

34. Allen MR, Ruggiero SL. Osteonecrosis of the jaw: recent clinical and preclinical advances. *IBMS BoneKEy*. 2011 Mar;8(3):141-53. [Abstract] [Full Text]