Guidelines for the diagnosis of bisphosphonate-related osteonecrosis of the jaw (BRONJ)

Salvatore L. Ruggiero

Assistant Professor
Department of Oral and Maxillofacial Surgery
Stony Brook School of Dental Medicine
Attending
Long Island Jewish Medical Center
Division of Oral and Maxillofacial Surgery
New Hyde Park, New York, USA

Address for correspondence:
Salvatore L. Ruggiero, DMD, MD
New York Center for Orthognathic and Maxillofacial Surgery
2001 Marcus Ave, Suite N10
Lake Success, NY 11042, USA
Fax +1 516-775-0892
E-mail: drruggiero@nycoms.com

Summary

Bisphosphonates are a class of agents used to treat osteoporosis and malignant bone metastases. Despite these benefits, osteonecrosis of the jaws has recently emerged as a significant complication in a subset of patients receiving these drugs. Based on a growing number of case reports and institutional reviews, bisphosphonate therapy may cause exposed and necrotic bone that is isolated to the jaw. This complication usually presents following simple dentoalveolar surgery and can cause a significant adverse effect on the quality of life for most patients. The pathogenesis for this complication appears to be related to the profound inhibition of osteoclast function and bone remodeling. This report will review the clinical signs and symptoms and risks associated with this new complication and provide a guideline for establishing a stage-specific diagnosis of BRONJ.

KEY WORDS: bisphosphonate-related osteonecrosis of the jaw, BRONJ, bisphosphonate associated osteonecrosis of the jaw, bisphosphonate, osteonecrosis of the jaw.

Introduction

Bisphosphonates are a class of agents used to treat osteoporosis and the complications associated with malignant bone metastases. Their use has dramatically increased over the past few years as new indications for their use have arisen. Bisphosphonate therapy has made a significant impact in the palliation of cancer morbidity. Their role in decreasing osteoclast-mediated lysis of bone in disease secondary to multiple myeloma, breast cancer and other solid tumors has been well established in clinical trials (1, 2). The efficacy of intravenous bisphosphonates in reducing bone pain, hypercalcemia and skeletal complications has been extensively documented in patients with advanced breast cancer and multiple myeloma (3-8). Thus bisphosphonates are frequently administered to patients with osteolytic metastases, especially if there is risk for significant morbidity.

Based on clinical practice guidelines established by the American Society of Clinical Oncology, the use of bisphosphonates is considered the standard of care for treatment of: 1) moderate to severe hypercalcemia associated with malignancy; and 2) metastatic osteolytic lesions associated with breast cancer and multiple myeloma in conjunction with antineoplastic chemotherapeutic agents (9, 10).

As potent suppressors of osteoclast activity, bisphosphonates slow the remodeling process and increase bone mineral density thereby reducing the risk of fracture in women with osteopenia and osteoporosis (11, 12). All bisphosphonates currently approved for osteoporosis treatment have been shown to significantly reduce the risk of osteoporotic fractures. Alendronate has been shown to prevent bone loss at the spine and hip in menopausal women and reduce fractures at these sites by approximately 50% (13-15). In a large prospective trial, risedronate produced a 30% reduction in hip fractures (16, 17). Due to their proven clinical efficacy, bisphosphonates are considered first-line therapy in the treatment of osteoporosis and are the most widely prescribed antiresorptive agent.

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

Since 2003 numerous reports have been published highlighting the adverse effect profile of this class of agents including the development of osteonecrosis of the jaw in patients treated with bisphosphonates (18-31). Although the exact mechanism of bisphosphonate-induced osteonecrosis of the jaw (BRONJ) has not yet been determined, several hypotheses have been proposed. In most cases the pathogenesis of this process is consistent with a defect in jawbone physiologic remodeling or wound healing. The profound inhibition of osteoclast function can also inhibit normal bone turnover to an extent that local micro damage from normal mechanical loading or injury (tooth extraction) cannot be repaired. Alternatively, the antiangiogenic properties of bisphosphonates may affect the local bone blood supply contributing to the apparent ischemic changes noted in the affected patients' jawbones. Since only a minority of bisphosphonate users develop bone necrosis, it is also possible that individual genetic variations in drug metabolism or skeletal homeostasis may confer susceptibility or resistance to developing BRONJ.

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

Several retrospective clinical studies have identified potential risk factors associated with the development of BRONJ (32-40). These include a history of dentoalveolar trauma, duration of bisphosphonate exposure and the type of bisphosphonate. In the majority of BRONJ cases reported to date, recent dentoalveolar trauma was the most prevalent and consistent risk factor (24, 38, 39). Patients with a history of inflammatory dental disease, e.g., periodontal and dental abscesses, are at a seven-fold increased risk for developing BRONJ (41). This underscores the importance of maintaining good oral health and avoiding extractions in this population. The duration of bisphosphonate therapy also appears to be related to the likelihood of developing necrosis with longer treatment regimens associated with a greater risk of developing disease (38, 41). In addition, the more potent intravenous bisphosphonates, such as pamidronate and especially zolendronate, appear to be significantly more problematic as compared with the oral bisphosphonate medications. Initially, BRONJ was seen only with the use of the more potent intravenous forms of the drug, however, their have been reports of osteonecrosis in patients on the less potent oral forms (20, 24, 42). This alarming finding may have significant implications as the number of patients on oral bisphosphonates increases. Though found in both sexes, the literature reports more cases of BRONJ in females than males which is likely a reflection of the large number of cases reported in breast cancer patients. With postmenopausal osteoporosis as an indication for bisphosphonate use, a large percentage of the female population may also be at risk for developing BRONJ. Patients receiving oral bisphosphonate therapy for osteoporosis that develop BRONJ have typically been exposed to these agents for a longer period of time (greater than 3 years) or were also exposed to steroid therapy (43).

Current incidence data for BRONJ are limited to retrospective studies with limited sample sizes. The current difficulty in establishing exact incidence data is due to several factors which include a non-standardized definition and inconsistencies in case recognition and reporting. With that understanding, the estimate of cumulative incidence of BRONJ in patients receiving intravenous bisphosphonates for malignant disease ranges from 0.8%-12% (43). For those patients exposed to oral bisphosphonates, the incidence appears to be significantly less (43).

In 2005 the Food and Drug Administration responded to the growing number of BRONJ cases by issuing broad drug class warning of this complication for all bisphosphonates.

This has also prompted a change in clinical practice. With the benefit of bisphosphonate therapy beyond 5 years coming into question for patients with low to moderate risk of an osteoporotic fracture (44, 45) and the growing concern about long-term suppression of bone turnover (46, 47), some clinicians have emphasized the importance of a drug holiday. Bisphosphonate treatment algorithms for the oncology patient have been modified in some institutions as well. In a consensus statement from the Mayo Clinic, the use of bisphosphonates in the treatment of multiple myeloma was modified to limit the exposure of intravenous bisphosphonates and minimize the potential for developing BRONJ (48). The efficacy of these new treatment strategies in decreasing the incidence of BRONJ remains to be determined. In the patient group receiving oral bisphosphonates, the benefit will be especially difficult to establish given the low incidence of BRONJ.

Clinical presentation

A universally accepted term for this new condition has yet to be established and this has resulted in some degree of confusion. This complication has been referred to in the literature by several acronyms including BRONJ (bisphosphonate-related os-teonecrosis of the jaw), BRON (bisphosphonate-related osteonecrosis), BON (bisphosphonate osteonecrosis), BAONJ (bisphosphonate-associated osteonecrosis of the jaw) and simply ONJ (osteonecrosis of the jaw). Based on the pattern of association between bisphosphonate therapy and jaw necrosis that has been established in numerous retrospective clinical case studies, the American Association of Oral and Maxillofacial Surgeons (AAOMS) has decided to adopt the term BRONJ for this entity.

Standardization of diagnostic criteria for this new clinical entity is important in order to facilitate future clinical and epidemiological research. In addition, a uniform definition for BRONJ will serve to distinguish this new clinical entity from other delayed intraoral healing conditions. Various organizations have proposed clinical definitions for BRONJ, all of which are analogous to each other. The AAOMS established a working definition for BRONJ that is fairly concise and specific (43). Patients may be considered to have BRONJ if all of the following three characteristics are present: 1. Current or previous treatment with a bisphosphonate; 2. Exposed, necrotic bone in the maxillofacial region that has persisted for more than eight weeks; and 3. No history of radiation therapy to the jaws.

The American Society of Bone and Mineral Research (ASBMR) will make a recommendation for a provisional case definition for *confirmed* and *suspected* cases of bisphosphonate-associated osteonecrosis. A *confirmed case* is characterized by an area of exposed bone in the maxillofacial region which did not heal within 8 weeks in a patient who is or was exposed to a bisphosphonate and did not have radiation therapy to the craniofacial region. A *suspected case* was defined as an area of exposed bone in the maxillofacial region that was present for less than 8 weeks in a patient who is or was exposed to a bisphosphonate and did not have radiation therapy to the craniofacial region. It is assumed that suspected cases are followed to determine if they eventually meet the definition of a confirmed case. The differential diagnosis of BRONJ should exclude other common clinical conditions which may include but are not limited to alveolar osteitis, sinusitis, gingivitis/periodontitis, caries, periapical pathology and temporomandibular joint disorders.

The patient history and clinical examination are the most sensitive diagnostic tools for this condition. Areas of exposed and necrotic bone may remain asymptomatic for weeks, months or years and may result in pain or exposed maxillary or mandibular bone. These lesions are most frequently symptomatic when surrounding tissues become inflamed or there is clinical evidence of exposed bone. Signs and symptoms that may occur before the development of clinically detectable osteonecrosis include pain, tooth mobility, mucosal swelling, erythema, and ulceration. These may occur spontaneously or more commonly at the site of prior dentoalveolar surgery (Fig. 1). Most case series have described this complication at regions of previous dental surgery (i.e. extraction sites) however exposed bone has also been reported in patients with no history of trauma or in edentulous regions of the jaw (Fig. 2). Intraoral and extraoral fistula may develop when necrotic jaw bone becomes secondarily infected (Fig. 3). Some patients may also present with complaints of altered sensation in the affected area as the neurovascular bundle becomes compressed from the inflamed surrounding bone. Chronic maxillary sinusitis secondary to osteonecrosis with or without an oral-antral fistula can be the presenting symptom in patients with maxillary bone involvement (Fig. 4).

It has been observed that lesions are found more commonly in the mandible than the maxilla (2:1 ratio) and more commonly in areas with thin mucosa overlying bony prominences such as tori, bony exostoses, and the mylohyoid ridge (20, 24, 27). The size of the affected area can be variable and range from a non-

Figure 1 - A non-healing extraction site in a patient with a history of intravenous bisphosphonate exposure.

Figure 3 - Extra-oral draining fistula at the submental region of the jaw in a patient with stage 3 BRONJ.

Figure 2 - An area of exposed, necrotic bone that appeared spontaneously (i.e. no history of trauma) on the medial aspect of the mandible.
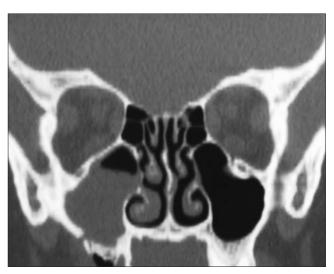

Figure 4 - Coronal CT of the right maxillary sinus demonstrating necrosis of the maxillary alveolar ridge and sinusitis.

healing extraction site to exposure and necrosis of the entire jaw (Fig. 5). The area of exposed bone is typically surrounded by inflamed erythematous soft tissue. Purulent discharge at the site of the exposed bone will be present when these sites become secondarily infected.

Radiographic changes are typically not evident until there is significant bone involvement or demineralization. Therefore, panoramic and periapical radiographs may not reveal significant changes in the early stages of osteonecrosis. Little or no ossification at a previous extraction site may represent an early radiographic sign. Early or late radiographic changes may mimic classic periapical pathology, osteomyelitis, or in cancer patients raise the suspicion of primary (myeloma) or metastatic bone disease. If there is a strong clinical suspicion of metastatic disease within the jaw and the diagnosis of such will alter clinical treatment decisions, then a bone biopsy should be considered. Otherwise, bone biopsies in these patients who have been exposed to intravenous bisphosphonate therapy should not be performed given the potential for creating a non-healing bone wound. When there is extensive bone

Figure 5 - Resected right hemi-mandible in a patient with stage 3 BRONJ. Note the extensive amount of necrosis throughout the ramus and body region of the mandible.

involvement, regions of mottled bone or sequestrum similar to that of diffuse osteomyelitis are noted (Fig. 6). Widening of the periodontal ligament space may also be noted radiographically. After prolonged exposure to the intravenous bisphosphonates, osteosclerosis of the bone may be noted radiographically, especially osteosclerotic lamina dura. In more advanced stages of BRONJ, the osteolytic changes can extend to the inferior border of the mandible and result in a pathologic fracture (Fig. 7).

Computerized tomography scans can provide more accurate 3-dimensional information about the extent of the necrosis and is often useful for planning surgical debridement procedures. However it has not proved helpful with early identification of this process in asymptomatic individuals. Magnetic resonance imaging (MRI) has the ability to detect marrow edema which may be an early sign of bone ischemia and necrosis but it is associated with a high rate of false positive results. Radionucleotide bone scans are the most sensitive modality for detecting changes in

Figure 6 - Panoramic radiograph demonstrating a region of osteolysis at the right mandibular angle region.

Figure 7 - Panoramic radiograph demonstrating a pathologic fracture of the right parasymphysis region of the mandible in a patient with metastatic breast and stage 3 BRONJ.

bone vascularity and may be helpful if vascular changes prove to be part of the early phase of BRONJ. In general, all imaging modalities have proved helpful in determining the extent of the existing necrotic process but have yet to demonstrate any efficacy in assessing patients at risk for BRONJ.

The microscopic examination of debrided specimens of exposed bone will typically reveal necrotic bone with associated bacterial debris and granulation tissue.

Microbial cultures from areas of exposed bone will usually isolate normal oral microbes and therefore are not always helpful. However in cases where there is extensive soft tissue involvement, microbial culture data may define co-morbid oral infections and facilitate the selection of an appropriate antibiotic regimen.

Staging

The presentation and symptomatology of BRONJ can vary in patients despite similar disease processes, bisphosphonate dosage regimens and treatment duration. A clinical staging system (Tab. I) has been developed in order to more accurately categorize patients with BRONJ, direct rational treatment guidelines and collect data to assess the prognosis in patients who have used either intravenous (IV) or oral bisphosphonates (27, 43). In a broad sense, patients can be categorized into those at risk and those with established disease. Patients who are considered "at risk" by the AAOMS criteria have no evidence of exposed or necrotic bone but have been exposed to either IV or oral bisphosphonates. The potency of the bisphosphonate used, the duration of exposure and dental surgery appear to be the main determinates in assessing the risk of developing BRONJ.

Patients with stage 1 disease have exposed bone but are asymptomatic. There is no evidence significant adjacent or regional soft tissue inflammatory swelling or infection. It is possible that patients may have symptoms of pain prior to the development of radiographic changes suspicious for osteonecrosis or clinical evidence of exposed bone. Stage 2 disease is characterized by exposed bone with associated pain, adjacent or regional soft tissue inflammatory swelling or secondary infection. Patients with stage 3 disease have exposed bone associated with pain, adjacent or regional soft tissue inflammatory swelling or secondary infection. Patients with pathologic fracture, extra-oral fistula or radiographic evidence of osteolysis extending to the inferior border are also considered stage 3. The likelihood of a patient with stage 1 or 2 progressing to a more advanced stage has not been determined but will certainly be dependant on several variables, not the least of which is the duration of bisphosphonate exposure and whether the patient is still receiving bisphosphonate therapy.

In broad terms, managing patients with BRONJ can be very challenging since most surgical and medical interventions do not eradicate this process. In fact, except for those patients

Table I - Clinical staging of BRONJ.

At risk category	No apparent exposed/necrotic bone in patients who have been treated with either oral or intravenous bisphosphonates
Stage 1	Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage
Stage 3	Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border

with stage 3 disease who require surgical resections for palliation, most surgical interventions have resulted in an increase in the area of exposed bone. It is important for patients and clinicians to realize that a cure may not be a realistic expectation. The goal of treatment for patients at risk of developing BRONJ or who have active disease is to preserve the quality of life by controlling pain, managing infection and preventing the development of new areas of necrosis. This has to be balanced with the oncologic management of the patient with osteolytic metastases.

The BRONJ treatment algorithms that have been published are either a consensus of expert opinions or based on case series data (27, 24, 27, 43). These management strategies have varied according to the risk of developing BRONJ or the stage of disease. Nonetheless, the main emphasis at this time is to minimize the risk of developing BRONJ. Although a small percentage of patients receiving bisphosphonates develop osteonecrosis of the jaw spontaneously, the majority of affected patients experience this complication following simple dentoalveolar surgery (i.e. extraction, dental implant placement or apical surgery). Therefore, treatment strategies that optimize dental health have been the main directive in managing patients who will receive or are receiving bisphosphonate therapy. Consideration has also been given to those patients who are about to initiate bisphosphonate therapy and therefore assume a level of risk at a future point in time. Their degree of risk will certainly depend on the type of bisphosphonate and the duration of exposure. For those patients with established BRONJ, treatment is basically directed by the symptoms. Patients with stage 1 disease are by definition asymptomatic and therefore require no intervention other than periodic oral rinses and close clinical follow up. Otherwise, patient with symptomatic disease (stages 2 and 3) will require antibiotic therapy and/or surgical debridement. All patients with established BRONJ are likely at high risk of developing BRONJ at any future site of dentoalveolar surgery and therefore should educated on the benefits of prophylactic dental care and avoid extractions.

Conclusion

Despite the strong clinical correlation between jaw necrosis and bisphosphonate therapy, a definitive casual relationship has yet to be established. Retrospective studies have established an association but prospective clinical trials and basic science research are needed to elucidate the pathogenesis of this process and to more accurately define the clinical and perhaps genetic risk factors. The efficacy of these agents in treating and preventing the significant skeletal complications associated with osteoporosis and bone metastases has had a major positive impact for patients. A more complete understanding of BRONJ will allow clinicians to predict who will benefit most from bisphosphonate therapy and to make more accurate judgments about risk, prognosis, treatment selection, and outcome.

References

1. Hortobagyi GN, Theriualt RL, Lipton A, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. J Clin Oncol. 1998;16:2038.
2. van Holten-Verzantvoort ATM, Kroon HM, Bijvoet OLM, et al. Palliative pamidronate treatment in patients with bone metastases from breast cancer. J Clin Oncol. 1993;11:491-8.
3. Berensen JR, Lichtenstein A, Porter L, et al. Long term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. J Clin Oncol. 1998;16:593.
4. Hortobagyi GN, Theriualt RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastasis. N Engl J Med. 1996;335:1785-92.
5. Berensen JR, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. N Engl J Med. 1996;334:448-93.
6. Theriualt RL, Lipton A, Hortobagyi ON, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic lesions: a randomized placebo-controlled trial. J Clin Oncol. 1999; 17:846.
7. Michaelson MD, Smith MR. Bisphosphonates for the treatment and prevention of bone metastases. J Clin Oncol. 2005;23:8219-8224.
8. Conte P, Coleman R. Bisphosphonates in the treatment of skeletal metastases. Semin Oncol. 2004;31:59-63.
9. Hillner BE, Ingle JN, Berenson JR, et al. American Society of Clinical Oncology guideline on the role of bisphosphonates in breast cancer. J Clin Oncol. 2000;18:1378-91.
10. Berenson JR, Hillner BE, Kyle RA, et al. American Society of Clinical Oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma. J Clin Oncol. 2002;20:3719-36.
11. Chestnut C, Majumdar S, Gardner J. Assessment of bone quality, quantity and turnover with multiple methodologies at multiple skeletal sites. Adv Exp Med Biol. 2001;496:95-7.
12. Guyatt GH, Cranney A, Griffith L. Summary of meta-analysis of therapies for postmenopausal osteoporosis and the relationship between bone density and fractures. Endocrinol Metab Clin North Am. 2002;31:659-79.
13. Black DM, Cummings SR, Karpf DB, et al. Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet. 1996;348:1535-41.
14. Hosking D, Chilvers CED, Christiansen C, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. Early Postmenopausal Intervention Cohort Suty Group. N Engl J Med. 1998;338:485-92.
15. Ravn P, Bidstrup M, Wasnick RD, et al. Alendronate and estrogen-progestin in the long-term prevention of bone loss: four-year results from the early postmenopausal intervention cohort study randomized, controlled trial. Ann Intern Med. 1999;131:935-42.
16. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. N Engl J Med. 2001; 344:333-40.
17. Miller P, Roux C, McClung M, et al. Risedronate reduces hip fractures in patients with low femoral neck bone mineral density [abstract]. Arthritis Rheum. 1999;42(Suppl 9):S287.
18. Mehrotra B, Fantasia J, Nissel-Horowitz S, et al. Osteonecrosis of the maxilla: an unusual complication of prolonged bisphosphonate therapy. A case report. [Abstract 3194] Proceedings Am Soc Clin Oncol. 2003;22:795.
19. Rosenberg TJ, Ruggiero SL. Osteonecrosis of the jaws associated with the use of bisphosphonates. [Abstract] J Oral Maxillofac Surg. 2003; 61(suppl 1:)60.
20. Ruggiero SL, Mehrotra B, Rosenberg TJ, et al. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg. 2004;62:527-34.
21. Greenberg MS. Intravenous bisphosphonates and osteonecrosis. [Editorial] Oral Surg Oral Med Oral Pathol Oral Radiol Endond. 2004; 93:259-60.
22. Vannucchi AM, Ficarra G, Antonioli E, et al. Osteonecrosis of the jaw associated with zoledronate therapy in a patient with multiple myeloma. Br Hematol. 2005;128:738.
23. Migliorati CA, Schubert MM, Petersen DE, et al. Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone. An emerging oral complication of supportive cancer therapy. Cancer. 2005;104:83-93.
24. Marx RE, Sawatari Y, Fortin M, et al. Bisphosphonate-induced exposed bone (Osteonecrosis\Osteopetrosis) of the jaws: Risk factors, recognition, prevention and treatment. JOMS. 2005;63:1567-1575.
25. Mehrotra B, Ruggiero SL. Bisphosphonate related osteonecrosis (BRON) of the jaw: single institutional update. Blood. 2005;106: Abstract #291

26. Melo MD, Obeid G. Osteonecrosis of the jaws in patients with a history of receiving bisphosphonate therapy. JADA. 136:1675-1681.

27. Ruggiero SL, Fantasia J, Carlson E. Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management: Oral Surg Oral Med Oral Path Oral Rad Endod. 2006 Oct;102(4):433-441.

28. Van Poznak C, Ward, B. Osteonecrosis of the jaw. Current Opinion Orthopaedics. 2006;17:1-7.

29. Gibbs SD, O'Grady J, Seymour JF, et al. Bisphosphonate-induced osteonecrosis of the jaws requires early detection and intervention. MJA. 2005;183:549-550.

30. Purcell PM, Boyd IW. Bisphosphonates and osteonecrosis of the jaw. MJA. 2005;182:417-418.

31. Bilezikian JP. Osteonecrosis of the jaw- Do bisphosphonates pose a risk? N Engl J Med. 2006;355:2278-2281.

32. Migliorati CA, Casiglia J, Epstein J, et al. Managing the care of patients with bisphosphonate-associated osteonecrosis. JADA. 2005; 136:1658-68.

33. Dimopoulos M, Kastritis E, Moulopoulos LA, et al. The incidence of osteonecrosis of the jaw in patients with multiple myeloma who receive bisphosphonates depends on the type of bisphosphonate. Blood. 2005;106:Abstract #637

34. Tosi P, Zamagni E, Cangini D, et al. Bisphosphonates and osteonecrosis of the jaws: incidence in a homogeneous series of patients with newly diagnosed multiple myeloma treated with zolendronic acid. Blood. 2005;106:Abstract #3461

35. Pozzi S, Marcheselli R, Sacchi S, et al. Analysis of frequency and risk factors for developing bisphosphonate associated necrosis of the jaw. Blood. 2005;106:Abstract #5057.

36. Gallucci C, Agrillo A, Iannetti G, et al. Possible role of ozone therapy in the treatment of osteonecrosis of the jaw in multiple myeloma patients. Blood. 2005;106:Abstract # 3460.

37. Cafro AM, Barbarano LA, Andriani A, et al. Osteonecrosis of the jaw associated with chronic bisphosphonate therapy: an Italian experience. Blood. 2005;106:Abstract #5152.

38. Badros A, Weikel D, Salama A, et al. Ostonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. J Clin Oncol. 2006;24:945-952.

39. Durie BGM, Katz M, Crowley J. Osteonecrosis of the jaw and bisphosphonates. [Letter] N Engl J Med. 2005;353:99.

40. Woo SB, Hellstein JW, Kalmar JR. Narrative review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med. 2006 May 16;144(10):753-61. Review. Erratum in: Ann Intern Med. 2006 Aug 1;145(3):235.

41. Hoff AO, Toth BB, Altundag K, et al. Osteonecrosis of the jaw in patients receiving intravenous bisphosphonate therapy. J Clin Oncol. 2006 ASCO Annual Meeting Proceedings (post meeting edition). 2006;24:8528. Available at: http://meeting.jco.org/cgi/content/abstract/24/18_suppl/8528

42. Cheng A, Mavrokokki A, Carter G, et al. The dental implications of bisphosphonates and bone disease. Aust Dent J Med Suppl. 2005; 50:4.

43. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. http://www.aaoms.org/docs/position_papers/osteonecrosis.pdf. Accessed january 2007.

44. Odvina CV, Zerwekh JE, Sudhaker R, et al. Severely suppressed bone turnover: a potential complication of Alendronate therapy. J Clin Endocrinol Metab. 2005;90:1294-1301.

45. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment. The Fracture Intervention Trial Long-term Extension (FLEX): A randomized trial. JAMA. 2006;296:2927-2938.

46. Ott SM. Long-term safety of bisphosphonates (Editorial). J Clin Endocrinol Metab. 2005;90:1897-99.

47. Colon-Emeric CS. Ten vs five years of bisphosphonate treatment for postmenopausal osteoporosis. Enough of a good thing (Editorial). JAMA. 2006;296:2968-2969.

48. Lacy MQ, Dispenzieri A, Gertz MA, et al. Mayo clinic consensus statement for the use of bisphosphonates in multiple myeloma. Mayo Clin Proc. 2006;81:1047-53.