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Systematic Review: Bisphosphonates and Osteonecrosis of the Jaws

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Osteonecrosis of the jaws is a recently described adverse side effect of bisphosphonate therapy. Patients with multiple myeloma and metastatic carcinoma to the skeleton who are receiving intravenous, nitrogen-containing bisphosphonates are at greatest risk for osteonecrosis of the jaws; these patients represent 94% of published cases. The mandible is more commonly affected than the maxilla (2:1 ratio), and 60% of cases are preceded by a dental surgical procedure. Oversuppression of bone turnover is probably the primary mechanism for the development of this condition, although there may be contributing comorbid factors. All sites of potential jaw infection should be eliminated before bisphosphonate therapy is initiated in these patients to reduce the necessity of subsequent dentoalveolar surgery. Conservative débridement of necrotic bone, pain control, infection management, use of antimicrobial oral rinses, and withdrawal of bisphosphonates are preferable to aggressive surgical measures for treating this condition. The degree of risk for osteonecrosis in patients taking oral bisphosphonates, such as alendronate, for osteoporosis is uncertain and warrants careful monitoring.

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Bisphosphonates are used to treat osteoporosis, Paget disease of bone and other metabolic bone diseases, multiple myeloma, and skeletal events associated with metastatic neoplasms. Their primary mechanism of action is inhibition of osteoclastic resorption of bone. Within the past 2 years, an increasing body of literature has suggested that bisphosphonate use, especially intravenous preparations, may be associated with osteonecrosis of the jaws. We briefly review the action of bisphosphonates, outline the clinical manifestations of bisphosphonate-associated osteonecrosis of the jaws, summarize current treatment strategies, discuss possible mechanisms of etiopathogenesis, and suggest avenues of research.

Methods

We performed MEDLINE and PubMed searches of English- and foreign-language literature (1966 to 31 January 2006) using the following Medical Subject Headings (MeSH) and terms: *osteonecrosis, avascular necrosis, phosphorous necrosis, bisphosphonates,* and *diphosphonates*. We then crossed the same terms with the terms *jaw diseases, myeloma, breast cancer,* and *metastatic cancer*. Other references were obtained from citations from retrieved articles. Similar terms were used to search abstracts from meetings of the American Society of Clinical Oncology.

We specifically reviewed all case reports and case series of patients with bisphosphonate-associated osteonecrosis of the jaws. We included any report that provided acceptable documentation of disease and use of bisphosphonates, regardless of whether it included information on the sex of patients, the site of the lesions, and the bisphosphonate used. Several authors published more than 1 paper describing patients with osteonecrosis. Through direct communication with these authors, we confirmed that some of the same patients were included in multiple reports. When this occurred, we used and cited data only from the larger, more recent publication.

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Actions of Bisphosphonates

Bisphosphonates are powerful inhibitors of osteoclastic activity. They are analogues of inorganic pyrophosphates with low intestinal absorption, are excreted through the kidneys without metabolic alteration, and have a high affinity for hydroxyapatite crystals (1, 2). Because they are incorporated into the skeleton without being degraded, they are remarkably persistent drugs; the estimated half-life for alendronate is up to 12 years (3). Alendronate, risedronate, pamidronate, zoledronic acid, and ibandronate, which are called aminobisphosphonates, have much higher potency because they contain nitrogen in a side chain (**Table 1**).

The nonaminobisphosphonates are metabolized by osteoclasts to inactive nonhydrolyzable adenosine triphosphate analogues that are directly cytotoxic to the cell and induce apoptosis (1, 2). The newer aminobisphosphonates have 2 actions (4): induction of another adenosine triphosphate analogue that induces apoptosis, and inhibition of farnesyl diphosphonate synthase, which is part of the mevalonate pathway of cholesterol synthesis. Such inhibition results in dysregulation of intracellular transport, cytoskeletal organization, and cell proliferation, leading to inhibition of osteoclast function. In addition, aminobisphosphonates reduce recruitment of osteoclasts and induce osteoblasts to produce an osteoclast-inhibiting factor (5, 6).

Aminobisphosphonates exert several antitumor effects, including induction of tumor cell apoptosis, inhibition of tumor cell adhesion to the extracellular matrix, and inhibition of tumor invasion (4, 7). Bisphosphonates also have

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antiangiogenesis properties (8, 9) and can activate γδ T cells (10, 11). The use of bisphosphonates in patients with multiple myeloma and metastatic cancer to the bones, such as breast, prostate, lung, and renal cell carcinomas, has resulted in a statistically significant reduction in skeletal complications, including pathologic fractures, spinal cord compression, hypercalcemia of malignant disease, and the need for subsequent radiotherapy or surgery to bone (12–14). Intravenous bisphosphonates have improved bioavailability and do not produce gastrointestinal side effects, resulting in better patient adherence. They have become standard therapy in the management of patients with multiple myeloma and metastatic cancer.

Potential Adverse Effects of Bisphosphonate Actions

In normal bone homeostasis, osteoclastic resorption is tightly linked to osteoblastic bone deposition and both functions are essential for repair of physiologic microdamage. Prolonged use of bisphosphonates may suppress bone turnover to the point that such microdamage persists and accumulates (15). The result is hypodynamic bone with decreased biomechanical competence. Although osteoblastic function is also reduced during bisphosphonate therapy, continued mineralization yields a hard, brittle bone with an osteopetrotic appearance and an increased risk for fracture (16–18). Thus, some experts caution that the benefits of prolonged use of bisphosphonates must be carefully weighed against the potential negative effects of oversuppression of bone metabolism (1, 19, 20). Other experts argue that although long-term use of bisphosphonates may retard fracture healing or slow callus remodeling, it may not affect bone mineralization or mechanical properties (21, 22).

Oral Complications of Bisphosphonate Therapy

Although oral bisphosphonates may cause oral mucosal lesions (purportedly arising from direct contact injury) (23, 24), we focus our review on bisphosphonate-associated osteonecrosis of the jaw. **Table 2** summarizes 368 reported cases of bisphosphonate-associated osteonecrosis of the jaw (25–54). Reported cases manifested as exposure of portions of the bone of the mandible only (65%), maxilla only (26%), or both (9%). Approximately one third of lesions were painless (27), and there was a slight female predilection in a ratio of 3:2 among all reported cases. Multifocal or bilateral involvement was slightly more common in the maxilla than in the mandible (31% vs. 23%). Most lesions were on the posterior lingual mandible near the mylohyoid ridge. Of importance, 60% of cases occurred after a tooth extraction or other dentoalveolar surgery and the remaining cases occurred spontaneously. The latter cases often involved patients wearing dentures, a possible source of local trauma. Marx and colleagues (27) reported that 39% of cases that occurred spontaneously were located on bony exostoses that were easily traumatized. There is 1 case report of dental implant failure associated with bisphosphonate use (55).

Most patients (94%) were treated with intravenous bisphosphonates (primarily pamidronate and zoledronic acid), and most patients (85%) had multiple myeloma or metastatic breast cancer (**Table 3**). The remaining patients

Table 1. **Bisphosphonate Formulations***

Generic Name	Brand Name	Manufacturer and Location	Dosage Forms	Nitrogen-Containing	FDA Approval Date
Etidronate disodium	Didronel	Procter & Gamble Pharmaceuticals, Cincinnati, Ohio	200- and 400-mg tablets	No	1 September 1977
Clodronate disodium	Bonefos (Canada)	Schering AG, Berlin, Germany	400- and 800-mg tablets; 60 mg/mL ampule†	No	Not approved
Tiludronate disodium	Skelid	Sanofi-Synthelabo Inc., New York, New York	200-mg tablet	No; sulfur moiety	7 March 1997
Alendronate sodium	Fosamax	Merck & Co. Inc., Whitehouse Station, New Jersey	5-, 10-, 35-, 40-, and 70-mg tablets; 70 mg/75 mL oral solution	Yes	29 September 1995
Alendronate sodium plus vitamin D_3	Fosamax plus D	Merck & Co. Inc., Whitehouse Station, New Jersey	70-mg and 2800-U cholecalciferol tablet	Yes	7 April 2005
Pamidronate disodium	Aredia	Novartis Pharmaceuticals, East Hanover, New Jersey	30-, 60-, and 90-mg vials†	Yes	31 October 1991
Risedronate sodium	Actonel	Procter & Gamble Pharmaceuticals, Cincinnati, Ohio	5-, 30-, and 35-mg tablets	Yes	27 March 1998
Risedronate sodium plus calcium	Actonel with calcium	Procter & Gamble Pharmaceuticals, Cincinnati, Ohio	35-mg and 500-mg calcium tablets	Yes	12 August 2005
Zoledronic acid	Zometa	Novartis Pharmaceuticals, East Hanover, New Jersey	4-mg vial†	Yes	20 August 2001
Ibandronate sodium	Boniva	Roche Laboratories Inc., Nutley, New Jersey	2.5-mg tablet 150-mg tablet 3 mg/3 mL†	Yes	16 May 2003 24 March 2005 6 January 2006

* This table shows the most common brand names. Generic forms, other names, and other doses may be available outside the United States. Clodronate is included because of its common use in Canada and Europe. FDA = Food and Drug Administration.
† Drug is administered intravenously.

Table 2. **Reports of Cases of Bisphosphonate-Associated Osteonecrosis of the Jaws***

Study, Year (Reference)	Patients, *n*	Sex, *n*		Primary Diagnosis	Sites	Previous Surgical Procedure, *n* (%)	Medications
		Male	Female				
Ruggiero et al., 2004 (25)	63	18	45	Myeloma (*n* = 29) Breast cancer (*n* = 21) Prostate cancer (*n* = 3) Lung cancer (*n* = 1) Uterine leiomyosarcoma (*n* = 1) Leukemia (*n* = 1) Osteoporosis (*n* = 7)	Mandible (*n* = 39) Maxilla (*n* = 23) Both (*n* = 1)	54 (86)	Pamidronate (*n* = 34) Zoledronic acid (*n* = 9) Pamidronate and zoledronic acid (*n* = 13) Alendronate (*n* = 5) Risedronate (*n* = 1) Alendronate and zoledronic acid (*n* = 1)
Estilo et al., 2004 (26)	13	4	9	Breast cancer (*n* = 9) Myeloma (*n* = 4)	Mandible (*n* = 6) Maxilla (*n* = 5) Both (*n* = 2)	9 (69)	Intravenous forms, not specified
Marx et al., 2005 (27)	119	NS	NS	Myeloma (*n* = 62) Breast cancer (*n* = 50) Prostate cancer (*n* = 4) Osteoporosis (*n* = 3)	Mandible (*n* = 81) Maxilla (*n* = 33) Both (*n* = 5)	55 (46)	Zoledronic acid (*n* = 48) Pamidronate and zoledronic acid (*n* = 36) Pamidronate (*n* = 32) Alendronate (*n* = 3)
Migliorati et al., 2005 (28)	18	4	14	Breast cancer (*n* = 10) Myeloma (*n* = 3) Prostate cancer (*n* = 2) Ovarian cancer (*n* = 1) Ovarian/breast cancer (*n* = 1) Osteoporosis (*n* = 1)	Mandible (*n* = 8) Maxilla (*n* = 2) Both (*n* = 1) Unknown (*n* = 7)	6 (33)	Zoledronic acid (*n* = 8) Pamidronate and zoledronic acid (*n* = 6) Pamidronate (*n* = 3) Alendronate (*n* = 1)
Purcell and Boyd, 2005 (29)	13	7	6	Breast cancer (*n* = 5) Prostate cancer (*n* = 4) Myeloma (*n* = 3) Osteoporosis (*n* = 1)	Mandible (*n* = 4) Maxilla (*n* = 2) Unknown (*n* = 7)	5 (38)	Zoledronic acid (*n* = 9) Pamidronate (*n* = 2) Pamidronate and zoledronic acid (*n* = 1) Alendronate (*n* = 1)
Bagan et al., 2006 (30)	20	5	15	Breast cancer (*n* = 10) Myeloma (*n* = 9) Prostate cancer (*n* = 1)	Mandible (*n* = 11) Maxilla (*n* = 1) Both (*n* = 8)	11 (55)	Zoledronic acid (*n* = 9) Pamidronate and zoledronic acid (*n* = 6) Pamidronate (*n* = 5)
Pires et al., 2005 (31)	12	9	3	Breast cancer (*n* = 6) Myeloma (*n* = 4) Prostate cancer (*n* = 1) Lung cancer (*n* = 1)	Mandible (*n* = 8) Maxilla (*n* = 3) Both (*n* = 1)	8 (67)	Pamidronate and zoledronic acid (*n* = 5) Pamidronate (*n* = 4) Zoledronic acid (*n* = 3)
Bamias et al., 2006 (32)	17	10	7	Myeloma (*n* = 11) Prostate cancer (*n* = 3) Breast cancer (*n* = 2) Other neoplasm (*n* = 1)	Mandible (*n* = 14) Maxilla (*n* = 3)	13 (76)	Pamidronate and zoledronic acid (*n* = 9) Zoledronic acid (*n* = 7) Zoledronic acid and ibanronate (*n* = 1)
Melo and Obeid, 2005 (33)	11	7	4	Breast cancer (*n* = 3) Myeloma (*n* = 7) Lung cancer (*n* = 1)	Mandible (*n* = 8) Maxilla (*n* = 2) Both (*n* = 1)	9 (82)	Zoledronic acid (*n* = 4) Pamidronate (*n* = 4) Pamidronate and zoledronic acid (*n* = 3)
Zarychanski et al., 2006 (34)	12	7	5	Myeloma (*n* = 10) Breast cancer (*n* = 1) Renal cancer (*n* = 1)	Mandible (*n* = 10) Maxilla (*n* = 1) Both (*n* = 1)	7 (58)	Pamidronate (*n* = 12)
Summary of studies with fewer than 10 patients (35–54)†	70	38	23	Myeloma (*n* = 29) Breast cancer (*n* = 26) Prostate cancer (*n* = 5) Paget disease (*n* = 3) Osteoporosis (*n* = 3) Lung cancer (*n* = 2) Lymphoma (*n* = 1) Mesothelioma (*n* = 1)	Mandible (*n* = 30) Maxilla (*n* = 14) Both (*n* = 9) Not assigned (*n* = 17)	44 (63)	Zoledronic acid (*n* = 27) Pamidronate and zoledronic acid (*n* = 21) Pamidronate (*n* =14) Alendronate (*n* = 5) Alendronate and zoledronic acid (*n* = 1) Pamidronate, zoledronic acid, and alendronate (*n* = 1) Oral ibandronate (*n* = 1)

* NS = not stated.
† Sex was not reported for 9 patients in these studies.

were taking oral bisphosphonates for osteoporosis or Paget disease of bone (25, 27–29, 40, 50, 51).

Clinically, intraoral lesions appear as areas of exposed yellow-white, hard bone with smooth or ragged borders (**Figures 1** and **2**). Extraoral or intraoral sinus tracts may be present (**Figure 3**). Painful ulcers may develop in soft tissues that impinge on the ragged bony margins.

Results of radiographic evaluation may be negative in early cases. Although some investigators have noted subtle changes, such as widening of the periodontal ligament,

Table 3. **Primary Diagnoses and Types of Bisphosphonates in Reported Cases of Osteonecrosis of the Jaws**

Variable	Patients, *n* (%)*
Primary diagnosis	
Multiple myeloma	171 (46.5)
Metastatic breast cancer	143 (38.8)
Metastatic prostate cancer	23 (6.2)
Osteoporosis	15 (4.1)
Other metastatic disease†	13 (3.5)
Paget disease of bone	3 (0.8)
Total	368 (100)
Bisphosphonate medications	
Zoledronic acid	124 (35)
Pamidronate	110 (31)
Pamidronate and zoledronic acid	100 (28)
Oral alendronate	15 (4.2)
Alendronate and zoledronic acid	2 (0.6)
Oral risedronate	1 (0.3)
Oral ibandronate	1 (0.3)
Ibandronate and zoledronic acid	1 (0.3)
Pamidronate, zoledronic acid, and alendronate	1 (0.3)
Total	355 (100)
Intravenous bisphosphonates, not specified	13
Patients with osteoporosis	15
Receiving alendronate	13 (87)‡
Receiving risedronate	1 (7)§
Receiving alendronate and zoledronic acid	1 (7)§

* Percentages may not sum to 100% because of rounding.
† Five patients had lung tumors. Other diseases were leiomyosarcoma, leukemia, ovarian/breast cancer, ovarian cancer, renal cancer, lymphoma, mesothelioma, and "other."
‡ Nine of 11 cases were in the mandible, and 2 of 11 cases were in the maxilla. The remaining 2 cases were not specified.
§ All cases were in the mandible.

these findings are indistinguishable from chronic periodontal infection, a predisposing factor for osteonecrosis (27). Advanced cases show a moth-eaten, poorly defined radiolucency, with or without radio-opaque sequestra. In 1 series, 5 of 63 patients developed pathologic jaw fractures (25). Cultures of exposed bone may identify *Actinomyces* species, but care must be taken to distinguish between a true suppurative infection and mere surface colonization by *Actinomyces*, because such organisms are a common component of dental plaque.

Patients with bisphosphonate-associated osteonecrosis may present similarly to those with osteoradionecrosis of the jaws. Osteoradionecrosis is a complication of radiotherapy. It is thought to result from osteocyte and microvascular damage after the jaws are exposed to ionizing radiation and also frequently occurs after tooth extraction (56). Osteoradionecrosis, however, infrequently involves the maxilla (<5% of cases) and is more common in men than in women (57, 58).

Risk Factors and Etiopathogenesis

The most important predisposing factors for the development of bisphosphonate-associated osteonecrosis of the jaws are the type and total dose of bisphosphonate and history of trauma, dental surgery, or dental infection. Ninety-four percent of patients with osteonecrosis received pamidronate or zoledronic acid. The doses for oncologic indications are often up to 12 times higher than those used for osteoporosis (13, 59). Of interest, clodronate, a non-aminobisphosphonate, has not been implicated in the development of osteonecrosis (60). The risk for osteonecrosis of the jaws is substantially higher for patients taking zoledronic acid and increases over time, probably because of the long half-life of these drugs. Although oral lesions may develop after as few as 4 months of bisphosphonate therapy, the median duration of drug use ranged from 22 to 39 months (32, 38, 48) and the mean ranged from 9 to 14 months (27, 33). The cumulative hazard was 1% within the first year and 21% at 3 years of treatment with zoledronic acid. In contrast, it was 0% in the first year and 4% in the third year for patients receiving pamidronate alone or with subsequent zoledronic acid (32). Another study showed that 10% of 211 patients receiving zoledronic acid developed osteonecrosis compared with 4% of 413 patients receiving pamidronate (61).

A few cases have been reported in patients taking alendronate (10 mg/d) for osteoporosis (25, 27–29, 50, 51). One patient had taken alendronate for only 2 years (27). The concern is that with more women aging and taking bisphosphonates for longer periods of time, more cases of osteonecrosis may develop even in patients receiving alendronate or ibandronate therapy.

Trauma to oral tori is also associated with osteonecrosis (27) (**Figure 2**). Furthermore, 60% of patients had some form of dentoalveolar surgery resulting in nonhealing of the surgical site and necrosis of bone. Because most dentoalveolar surgeries are performed to treat dental infection, the contribution of each to the development of osteo-

Figure 1. **Osteonecrosis of the right mandible after tooth extraction in a patient taking zoledronic acid for metastatic breast cancer.**

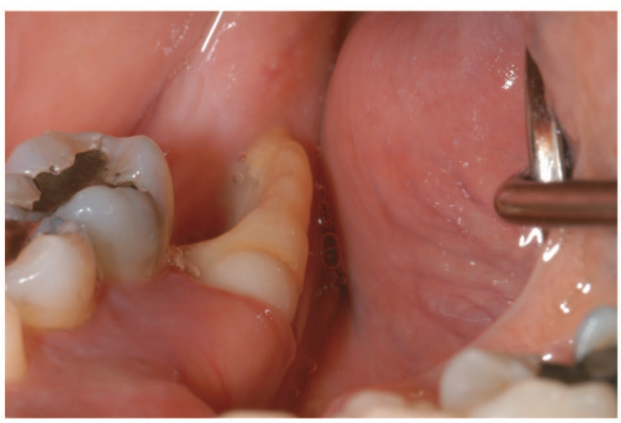
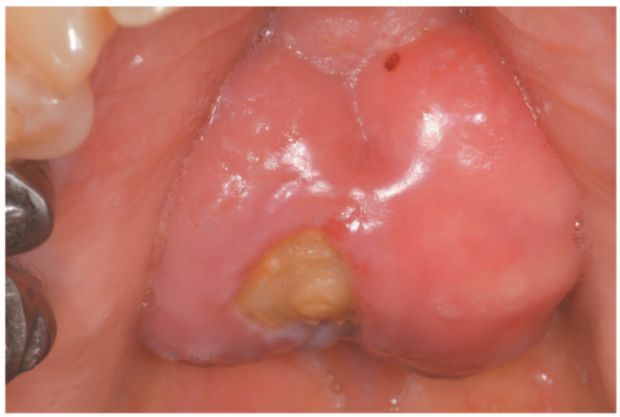


Figure 2. **Osteonecrosis of the palatal torus in a patient with osteoporosis taking alendronate.**



necrosis is unclear, although it is likely that together they compound the problem.

Patients with myeloma tend to be prothrombotic and are often treated with other antiangiogenic agents, such as glucocorticoids, thalidomide, and the new proteasome inhibitors, such as bortezomib, in addition to bisphosphonates (62, 63). Although neither corticosteroids nor thalidomide has been shown to be associated with additional risk for osteonecrosis of the jaws, prospective studies are needed to more fully address this issue (32, 61). The impact of local factors, such as smoking, and of underlying medical conditions, such as diabetes or peripheral vascular diseases, remains to be determined.

Susceptibility of the Jaws to Osteonecrosis

The question often asked is "Why the jaws?" First, the jaw bones are separated from a trauma-intense and microbiologically diverse oral environment by thin mucosa and periosteum. The fragility of this barrier is reflected by the condition known as *lingual mandibular sequestration*, which occurs in healthy adults yet resembles mild cases of bisphosphonate-associated osteonecrosis of the jaws (64). In this condition, 1- to 3-mm slivers of bone are sequestrated in the area of the protuberant mylohyoid ridge with spontaneous resolution. It is thought that minor trauma causes local damage to the thin mucosa and underlying periosteum, leading to bone necrosis. Because the posterior lingual mandible is also a frequent site for osteonecrosis, it seems probable that the hypodynamic bone in patients receiving bisphosphonate therapy may turn this typically innocuous process into chronic bone exposure. Trauma to the periosteum may also serve to initiate osteonecrosis in patients wearing dentures or dental prostheses or in patients with prominent exostoses.

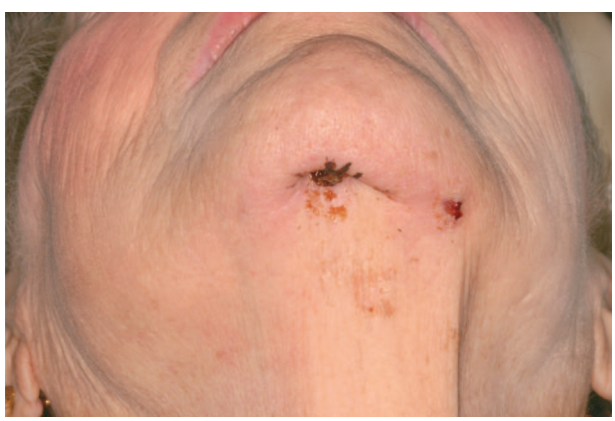
Second, teeth are readily infected by bacteria that cause caries and periodontal disease, 2 common infectious diseases. Because the teeth are separated from bone by no more than 2 mm of periodontal connective tissue, such infections have easy access to the underlying bone. A case of osteonecrosis in the ear of a patient taking zoledronic acid for multiple myeloma was reported recently (44). The lesion occurred after removal of exostoses in the external auditory canal, and the patient had concurrent osteonecrosis of the maxilla.

We suggest that bisphosphonate-associated osteonecrosis of the jaws results from marked suppression of bone metabolism that results in accumulation of physiologic microdamage in the jawbones, compromising biomechanical properties. Trauma and infection increase demand for osseous repair that exceeds the capacity of the hypodynamic bone, resulting in localized bone necrosis. The antiangiogenic property of bisphosphonates and other medications and the presence of other comorbid factors may promote the risk for or persistence and progression of this condition.

Prevalence of Bisphosphonate-Associated Osteonecrosis of the Jaws

A Web-based survey conducted by the International Myeloma Foundation resulted in 1203 respondents, 904 with myeloma and 299 with breast cancer. Seven percent and 4% of patients with myeloma and breast cancer, respectively, reported osteonecrosis, and 6% and 8% of patients with myeloma and breast cancer, respectively, reported lesions suspicious for osteonecrosis (61). In a single-center study of 252 patients who had received intravenous bisphosphonates since January 1997, 10% of 111 patients with myeloma and 3% of 46 patients with breast cancer developed osteonecrosis (32). In another study of 124 patients with myeloma or breast cancer who were treated with intravenous bisphosphonates in a dental clinic in a cancer center, 4 and 9 patients with myeloma and breast

Figure 3. **Extraoral fistula in a patient with intraoral osteonecrosis.**



Key Summary Points

Osteonecrosis of the jaws is strongly associated with the use of aminobisphosphonates, and the mechanism of disease is probably severe suppression of bone turnover.

Ninety-four percent of patients are treated with zoledronic acid or pamidronate or both; 85% of affected patients have multiple myeloma or metastatic breast cancer, and 4% have osteoporosis.

The prevalence of osteonecrosis in patients with cancer is 6% to 10% and the prevalence in those taking alendronate for osteoporosis is unknown; osteonecrosis seems to be time- and dose-dependent because of the long half-life of aminobisphosphonates.

More than half of all cases (60%) occur after dentoalveolar surgery (such as tooth extraction) to treat infections, and the remaining 40% are probably related to infection, denture trauma, or other physical trauma.

Preventive strategies include removing all foci of dental infection before starting bisphosphonate therapy.

Treatment is directed toward control of pain and infection and careful local débridement of dead bone, but not wide excision of lesions.

cancer, respectively, developed osteonecrosis (prevalence of 10%) (26).

Management Recommendations

Treatment protocols have been outlined, but trials and outcomes of treatment and long-term follow-up data are not yet available (25, 27, 28, 65). In June 2004, an expert panel outlined recommendations for the management of bisphosphonate-associated osteonecrosis of the jaws (66). Because there are no randomized clinical trials that assess management strategies, we propose the following guidelines based on published literature, our own experience, and the experience of our colleagues.

We group patients who are either receiving bisphosphonate therapy or about to begin therapy into the following 3 broad categories: group 1, patients about to begin aminobisphosphonate therapy; group 2, patients without osteonecrosis of the jaws who are receiving aminobisphosphonate therapy; and group 3, patients with osteonecrosis of the jaws. Patients with osteoporosis who are taking oral preparations, such as alendronate, and are at lower risk than those receiving intravenous preparations are included in group 1. We note that the risks associated with oral ibandronate, recently approved for the treatment of osteoporosis, are unknown.

Patient management before initiation of therapy with aminobisphosphonates is targeted at eliminating active sites of infections to minimize future infections and the need for future dentoalveolar surgery, such as tooth extractions, to treat such infections. Similar protocols have been established for patients preparing for allogeneic stem-cell transplantation and those about to receive radiation to the head and neck (67, 68).

Recommendations for group 1, patients about to begin intravenous bisphosphonate therapy, are outlined in **Table 4**. It is probably not necessary to delay initiation of bisphosphonate therapy if dental treatment can be completed within 1 to 2 months. With drug use between 3 and 6 months, patients in group 2 (those receiving intravenous aminobisphosphonates who do not have signs of osteonecrosis of the jaws) should be evaluated on a case-by-case basis. Those who have been receiving intravenous bisphosphonate therapy for oncologic indications for more than 6 months are at risk for this condition. In group 3, patients with osteonecrosis of the jaws, there are anecdotal reports of the use of acrylic stents (with or without soft liners) to cover areas of exposed bone, protect adjacent soft tissues, and improve comfort. However, there is a risk that the stent may act as a fomite and that additional trauma may be caused by the stent itself.

Reduction of pain and regression or even resolution of lesions of osteonecrosis have been observed in patients treated with antibiotics and mouth rinses, withdrawal of bisphosphonates, and removal of loose sequestra (31, 45, 48). Extensive resection has not consistently resulted in wound closure and may lead to worsening or progression of disease (25, 27). However, even for patients with multiple myeloma who are potential candidates for hematopoietic stem-cell transplantation or continued chemotherapy, asymptomatic osteonecrosis may not necessarily pose a substantial risk for increased morbidity if there is no evidence of active infection, as characterized clinically by pain and suppuration. Hyperbaric oxygen therapy, given to a few patients, has only infrequently shown clinical efficacy (25, 27, 28, 32, 33, 36, 69).

Discontinuation of Bisphosphonate Therapy

Currently, there is no published evidence to support or oppose discontinuation of bisphosphonate therapy once osteonecrosis develops or before required dental surgery. Because of the long half-life of bisphosphonates, recovery of normal osteoclast function and bone turnover after drug withdrawal may be too gradual for this measure to have clinical significance. It is also unclear what effect, if any, discontinuation of such therapy would have on overall morbidity and mortality among patients with cancer.

Nevertheless, patients may benefit from bisphosphonate withdrawal. There have been anecdotal reports of healing and complete resolution of existing sites of osteonecrosis after several months of therapy cessation. The re-

Table 4. **Management Recommendations***

Patient Category	Treatment Recommendations
Group 1: patients about to begin aminobisphosphonate therapy	Treat active oral infections, eliminate sites at high risk for infection (partially impacted wisdom teeth, nonrestorable teeth, or teeth with substantial periodontal bone loss) Encourage routine dental care Perform biannual oral examination and dental cleaning Minimize periodontal inflammation Provide routine restorative care of carious teeth Provide endodontic therapy of nonsalvageable teeth
Group 2: patients without osteonecrosis of the jaws who are receiving intravenous aminobisphosphonate therapy	Less than 3 months of drug therapy Same as above for group 1 More than 3 months of drug therapy Seek conservative alternatives to surgical procedures (endodontic therapy with or without decoronation, scaling, and débridement) with appropriate local and systemic antibiotics Perform extractions and other surgery using minimal bone manipulation with appropriate local and systemic antibiotics; follow up to ensure healing
Group 3: patients with osteonecrosis of the jaws	Same as above for group 2 with more than 3 months of drug therapy Consider additional imaging studies, such as computed tomography scans Perform conservative removal of dead bone as necessary with minimal trauma to adjacent hard and soft tissues Prescribe oral rinses (0.12% chlorhexidine rinse, hydrogen peroxide) Prescribe systemic antibiotic therapy (monotherapy or combination therapy with β-lactam, tetracycline, macrolide, metronidazole, and/or clindamycin) Prescribe systemic analgesics as indicated Prescribe a soft acrylic stent Suggest discontinuation of bisphosphonate therapy until osteonecrosis heals or underlying disease progresses

* Patients receiving or scheduled to begin bisphosphonate therapy should receive a comprehensive dental examination and panoramic and intraoral radiographs. Patients should be made aware of osteonecrosis, including its signs, symptoms, and sequelae.

moval of the antiangiogenic effects of the drug on the soft tissues and periosteum may play a role in healing. For this reason, discontinuation of oral bisphosphonate therapy for several weeks before and after dentoalveolar surgery may be warranted. Until data from clinical trials are available, the optimal timing and duration of such a drug holiday are somewhat arbitrary and must be weighed against the risks posed by not taking medication. If the patient's underlying systemic disease is stable, bisphosphonates can be withdrawn until the area of osteonecrosis heals or until clinical variables indicate disease progression.

Research Avenues

Clinical trials are urgently needed to address many issues. Can alternative dosing schedules reduce the incidence of osteonecrosis while maintaining the enormous benefits of these drugs? For example, once the patient's condition is stabilized, perhaps lower-potency, nonaminobisphosphonates can be substituted in a maintenance role (60, 70). Monitoring bone turnover markers may help clinicians avoid oversuppression (71). A staging system can be developed, possibly including serologic and imaging data, that more accurately determines disease severity; this could then be used to guide treatment. Establishing criteria for the diagnosis of early changes that precede or predict bone exposures would also be desirable.

Prospective studies are also needed to more precisely determine what additional risk factors, if any, may predispose the patient to the development of osteonecrosis of the jaws. Such variables as age, sex, medications, preexisting medical conditions, and individual genetic variations need to be examined. Finally, clinical trials should be done to determine the most effective treatment protocols for patients with this condition.

Conclusion

Osteonecrosis of the jaws is a newly recognized condition reported in patients treated with bisphosphonates, in particular potent aminobisphosphonates. Most cases have developed in patients with multiple myeloma or metastatic cancer, but the condition has also been identified in patients with osteoporosis. This article reviews the findings in 368 cases, suggests treatment strategies, and outlines research avenues that may help us better understand and treat this condition.

Note added in proof: An article describing this condition in 22 patients was recently published in the *Journal of Clinical Oncology*: Badros A, Weikel D, Salama A, Goloubeva O, Schneider A, Rapoport A, et al. Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. J Clin Oncol. 2006;24:945-52. [PMID: 16484704].

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