Bisphosphonate-Related Osteonecrosis of the Jaw: Tip of the Iceberg

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Abstract: The World Health Organization predicts that people aged older than 65 years will comprise 20% of the world's population by 2030. One of the most commonly prescribed medications for the elderly are the bisphosphonates, which have been shown to significantly reduce debilitating and fatal fractures by preserving bone density and consequently saving governments billions of dollars annually. Despite rigorous testing, 190 million prescriptions worldwide and US$8000 million in revenue, there is a serious adverse effect called bisphosphonate-related osteonecrosis of the jaw, which is poorly described and difficult to treat. The difficulty is compounded by the inability of medical personnel to recognize and adequately refer these patients or take adequate precautions before instituting bisphosphonate therapy. A myriad of differentials and a lack of consensus on how to definitively treat these patients have made this new presentation a worrying precursor for millions of other consumers who will reach the 5-year oral half life of bisphosphonates, which is when they generally start to present. In this paper, we explore historical parallels and provide the most comprehensive review to date in the literature about the presentation, diagnosis, treatment, pathophysiology, oncogenic associations, and best practice guidelines. Legal action pursuant to bisphosphonate-related osteonecrosis of the jaw is underway on 3 continents, and we believe that every health care professional should become au fait with this condition for which our growing case series represents merely the tip of the iceberg.

Key Words: bisphosphonate, osteonecrosis, prophylaxis

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The World Health Organization estimates that people older than 65 years currently represent 12% of the global population, increasing by 800,000 per month and will comprise 20% of the world population by 2030.[1] The elderly are increasingly prescribed medications to alleviate morbidity and improve longevity, the most notable of which are the bisphosphonates (BPs).

Despite their use in osteoporotic prophylaxis, a poorly described or disclosed adverse effect is osteonecrosis of the jaw related to BP use. The American Association of Oral and Maxillofacial Surgeons (AAOMS), which has been at the forefront of identification, staging, grading, and prevention and treatment strategies,[2] has therefore defined and coined the term *bisphosphonate-related osteonecrosis of the jaw* (BRONJ), largely confined to the mandible, although the ear, the nose, and the maxilla are becoming more prevalent.[3] In our practice, BRONJ is becoming increasingly common, especially in the oral prophylaxis group. The lack of consensus on treatment by clinicians and the repeated failure of recognition prompted us to review the literature across multiple specialities involved in the presentation, diagnosis, and treatment of this phenomenon.

INCIDENCE

The sentinel case of BRONJ was described by Marx in 2003. Historically, BRONJ displays similarities with a phenomenon in the 19th century called "bis-phossy jaw" in matchmakers, prompting government at the time to draught legislation governing work-related pathological conditions pursuant to harmful practices such as chemical exposure.[1,4]

The most common cause of osteonecrosis of the mandible today is high-energy radiotherapy to the head and neck region, inducing apoptosis of proliferating progenitor osteoclasts and endothelial cells. Bisphosphonate intravenous (IV) use has largely been blamed for BRONJ, although many report a substantial increase in oral consumers.[5,6] Manufacturer data estimate the incidence of BRONJ with oral BPs at approximately 0.7/100,000 people per year exposed.[2] In a landmark paper with the largest cohort to date of 1086 patients receiving IV BPs, Wang et al[7] reported the incidence of BRONJ in patients with multiple myeloma, breast cancer, and prostatic cancer as 3.8%, 2.5%, and 2.9%, respectively, and a survey of medical claim reports has identified BRONJ as a serious contender for the number 1 cause for therapy-related jaw surgery.[8]

The International Myeloma Association also assessed the risk of BRONJ in myeloma and breast cancer patients receiving IV BPs in 2004. Cumulative incidence at 36 months showed 10% of IV zoledronic acid patients and 4% of IV pamidronate patients developed confirmed BRONJ or suspicious findings of bone erosion and spurs or exposed bone.[5,9] Other findings included increased risk in oncology patients with a recent history of either oral infection or dental extraction in the order of 2 and half times compared with controls (81% vs 33%) and significant morbidity secondary to nonhealing bone and soft tissue after maxillofacial surgery. Wessel et al[10] demonstrated a 30-fold increased risk and a significant association with obesity and smoking. An Australian review of all

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maxillofacial cases and adverse drug reactions reported to authorities found that osteoporotics had a 9 times higher risk of complication after extraction. Patients with malignant metastases needing treatment demonstrated a risk ratio of 6.[11] This emphasized the importance of dental intervention precipitating presentation and the explicit need for dental hygiene, informed consent, and alternative considerations. Compounding factors include age, race, and type of cancer. There is a 10% increased risk per decade, and whites are more affected than nonwhites. Furthermore, multiple myeloma has a particularly high risk, and no other known precipitators of oral cancer or other pathological conditions (eg, smoking, alcohol drinking, beetle nut chewing) seem to confer a higher risk.[12] The AAOMS has well-defined risk factors based on meta-analysis of all the available data and a defined criteria for BRONJ (Table 1).

THERAPEUTIC APPLICATIONS

One cannot deny the remarkable contribution that BPs have made to the morbidity and mortality of the elderly and infirmed. The Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly study of 7765 eligible patients demonstrated that once yearly, IV administration of zoledronic acid improved adherence with a 70% reduction in vertebral fractures and a 41% decrease in hip fractures in osteoporotic postmenopausal women.[13,14] Improved mineral density and a 25% reduction in other fractures were observed when given annual IV doses for 15 minutes, additionally ensuring correct administration.

Bisphosphonates currently treat osteoporosis, pathologic fractures, and malignant hypercalcemia associated with multiple myeloma or bone metastases from prostate and breast cancers.[15–17] They are less commonly used in Paget disease and osteogenesis imperfecta of childhood.[2] Cumulative data on BRONJ, however, have prompted calls for preventative action considering that more than 24 million prescriptions for BPs were issued in the United States alone and more than 190 million internationally by the end of 2007.[2,18,19] This equated to approximately US$8 billion in sales in 2007.[20]

MECHANISM OF ACTION

Bisphosphonates preferentially bind to sites of active bone resorption, exerting a direct effect on osteoclastic activity including cytoskeleton changes, decreased liposomal function, and inducing osteoclast apoptosis. Normal osteoclastic function ensures normal bone turnover, the abrogation of which results in the accumulation of nonvital osteoclasts, microfractures of the matrix, and bone necrosis.[4] Third-generation BPs are known to enhance proliferation of osteoblasts and osteoprogenitor cells and up-regulate the expression of bone morphogenic protein 2, collagen type 1, and osteocalcin. Zoledronate has, however, also been shown to inhibit endothelial proliferation and induce osteocytic apoptosis with a concomitant diminution of capillary formation. Pamidronate is also known to reduce circulating vascular endothelial and platelet-derived growth factors in vivo. Most presentations therefore accompany trauma where defective wound healing is a major cause of morbidity.[15,19,21,22]

Other described adverse effects include nephrotic syndrome, renal insufficiency, ophthalmic inflammation, upper gastrointestinal symptoms, hypocalcemia, myalgia, and, recently, atrial fibrillation.[23]

TABLE 1. Criteria Defining Established BRONJ[2]

Current or previous treatment with BPs
Exposed necrotic bone in the maxillofacial region that has been present for more than 8 consecutive weeks
No history of radiotherapy to the head and neck region

All 3 criteria are required. BPs = Bisphosphonates; BRONJ = bisphosphonate-related osteonecrosis of the jaw.

TABLE 2. Presenting Features of BRONJ[24]

Symptoms
Bone pain
Paraesthesia
Neuropathic pain
Loosening of teeth
Odontalgia
After extraction, persistently dry socket and persistence
Signs
Alveolar bone loss
Resorption
Changes in the trabecular pattern of the bones involved
Dense woven alveolar bone
Thickening/obscuring of the periodontal ligament
Inferior alveolar canal narrowing

BRONJ = Bisphosphonate-related osteonecrosis of the jaw.

PRESENTATION

Presentation varies (Table 2),[24] but there is often a radiograph/computed tomographic scan of mottled bone consistent with sequestrum formation in the affected area.[25] Patients present with heaviness or numbness in the jaw, pain, swelling, infection, lose teeth, exposed bone, and chronic nonhealing ulcers especially with a background of dental surgery[5,12] (Fig. 1).

Biopsies are typical with necrotic lacunae and infiltration of lymphocytes, histiocytes, macrophages, and neutrophils against a background of congested vasculature and reactive fibrosis in the

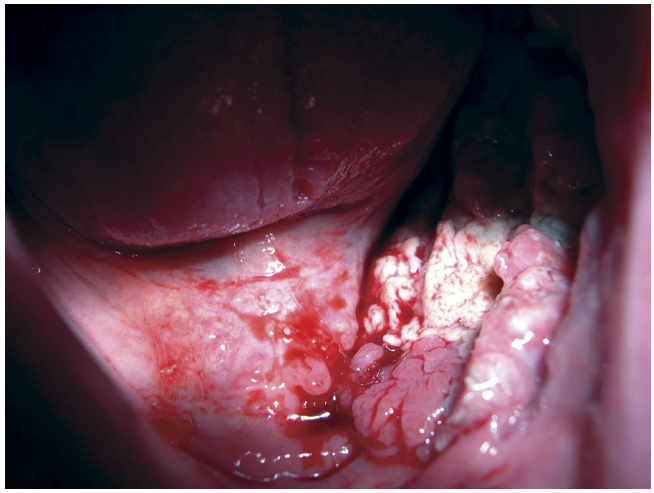


FIGURE 1. Open mouth, sublingual view. One of 20 patients with BRONJ showing chronic ulceration and bleeding of the body of the mandible.

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TABLE 3. Treatment Strategy for Initiating Treatment in Different Patients[2]

Initial IV BP Therapy	Asymptomatic Patients—IV BP Therapy	Asymptomatic Patients—Oral BP Therapy
Extensive dental workup	Ensure good oral hygiene	BRONJ may develop spontaneously or after trivial/minor trauma
Extraction/repair 21 d before	Monitoring is paramount	No increased risk of healing difficulties in these patients, although treatment for longer than 3 y does represent a noticeable cohort
Ensure complete healing	All nonessential dentoalveolar surgery avoided at all cost	
Exclude denture trauma		
Educate: local trauma and self care		

BP = Bisphosphonate; BRONJ = bisphosphonate-related osteonecrosis of the jaw; IV = intravenous.

TABLE 4. American Association of Oral and Maxillofacial Surgeons Guidelines for Patients Requiring Oral Surgery[2]

<3 y of Oral BP	<3 y of Oral BP and a Corticosteroid	>3 y of Oral BP With or Without Steroid Therapy	Patients With Established BRONJ
No delay in dentoalveolar surgery Informed consent if implant surgery is to be performed especially regarding the possible failure of said implant at a later date Recall regularly	Drug holiday from 3 mo before surgery if conditions permit and only recommenced a month after healing	Drug holiday from 3 mo before surgery if conditions permit and only recommenced a month after healing	These patients do not respond normally according to the principles of radio-osteonecrosis or osteomyelitis management. Surgical debridement is variably effective with establishment of healthy bleeding margins difficult due to pan-mandibular exposure to BPs. Debridement should be performed removing any tissue that may be causing a problem

BP = Bisphosphonates; BRONJ = bisphosphonate-related osteonecrosis of the jaw; IV = intravenous.

TABLE 5. American Association of Oral and Maxillofacial Surgeons Guidelines for Staging and Approach to Treatment of BRONJ[2]

Type 1 Patients	Type 2 Patients
At-risk patients in whom there is no evidence of exposed or necrotic bone despite being on IV or oral BPs	Stage 1: Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection—oral antimicrobial mouthwashes, for example, 0.12% chlorhexidine. No surgery is necessary, but the focus should rather be on finding the cause of the precipitating event, that is, ill-fitting dentures.
These patients do not require any treatment, and emphasis should be placed on prevention. This should involve extensive counseling about dental care and signs and symptoms to look for with BRONJ	Stage 2: Exposed/necrotic bone in patients who have pain and clinical evidence of infection; oral antimicrobial mouthwash and antibiotics (penicillins, quinolones, macrolides, metronidazole, and doxycycline) with a particular emphasis on actinomyces
	Stage 3: Exposed/necrotic bone in patients who have pain, infection, and 1 or more of the following sequelae: pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border. Surgical resection and debridement in these patients who are often symptomatic. Extraction of symptomatic teeth should also be undertaken because removal thereof is unlikely to have any effect on the already defunct bone.

BP = Bisphosphonates; BRONJ = bisphosphonate-related osteonecrosis of the jaw; IV = intravenous.

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TABLE 6. Cohort of Patients With BRONJ Within a Small Regional Health Service Hospital in Sydney, Australia

Patient	Sex	Age, y	BP	IV/Oral	Duration, y	Condition
B.K.	F	64	Alendronate/Fosamax	Oral	3	Osteoporosis
D.J.	M	80	Alendronate/Fosamax Alendronate/Fosamax	Oral	8	Osteoporosis Osteoporosis
L.H.	M	85	Alendronate/Fosamax	Oral	5	Osteoporosis
R.A.	F	54	Zometa/zoledronic acid	IV	0.5	Multiple myeloma
S.H.	F	62	Zometa/zoledronic acid	IV	2	Breast cancer
Y.L.	M	71	Zometa/zoledronic acid	IV	2	Osteoporosis Waldenström Macroglobulinemia
Y.T.	M	68	Alendronate/Fosamax	Oral	3	Osteoporosis

Abs = Antibiotics; BP = bisphosphonates; BRONJ = bisphosphonate-related osteonecrosis of the jaw; HT = hypothyroid; IDDM = insulin-dependent diabetes mellitus; IHD = ischemic heart disease; IV = intravenous; NIDDM = non-insulin-dependent diabetes mellitus.

deeper structures with associated gram-positive filamentous bacteria, invariably actinomyces. Normal areas abut necrotic territory, covered by hyperplastic squamous epithelium often misdiagnosed as osteomyelitis of unknown cause.[12,15] Bouquot et al[26] have therefore suggested a broader approach including periapical radiography, pulp vitality testing, and laser Doppler flow studies, accompanied by alternative diagnostic tools, such as technetium-99m–methylene diphosphonate scintigraphy and quantitative ultrasound.

Differential diagnoses in immunocompromised and elderly patients need to be considered. These include thromboembolic (thrombocytosis, altered rheology, and inflammation), infective (bacteria [actinomyces], viral [herpes zoster], spirochete [syphilis], fungal [zygomycosis and aspergillosis]), dysplastic/metaplastic (necrotizing sialometaplasia, squamous cell cancer, and ameloblastoma), environmental (chemical [phosphorus and beetle nut] and radiation [previous therapy]), traumatic (ill-fitting dentures and preexisting periodontal disease).[3] Commonly misdiagnosed conditions include alveolar osteitis, sinusitis, gingivitis/periodontitis, caries, periapical pathology, and temporomandibular joint disorders.[5,12]

PATHOPHYSIOLOGY

Antiangiogenic

Postulates for BRONJ focus on the inability of hypodynamic and hypovascular bone to meet an increased demand for repair and remodeling owing to physiologic stress, trauma, and infection in an environment prone to injury by brushing or extraction, which is often a haven for natural and opportunistic bacteria and fungi.[23] Compounding factors include antiangiogenic medications such as glucocorticoids, thalidomide, and bortezomib. Diabetes mellitus, mandibular irradiation, generalized vascular disease, and proliferative/inflammatory hyperviscosity also contribute in part.[9] Hewitt argues that BPs concentrate in the jaw because of the daily trauma associated with chewing and the constant remodeling around the periodontal ligament. She believes that it is the irreversible effect of BPs on osteoclasts that inhibits the paracrine loop originating within osteoclasts for osteoblasts that retards bone turnover, provides no incentive for angiogenesis, and results in avascular bone, with no support for an overlying multi-traumatized area.[23] Her belief is that the primary pathology is the antiangiogenic effect of the BPs that predisposes the area to the trauma. That trauma leads to exposure and consequent mishap, and she argues that BRONJ may be another form of avascular osteonecrosis accentuated by concomitant chemotherapy use called the bandwagon effect.[27,28]

Supporting the theory is the exceptionally long half-life of BPs. Pharmacological studies have shown that after taking 20-mg/d alendronate for 1 year, bone turnover did not return to normal levels until 5 years after treatment, compared with 2.5 to 5 mg/d when it reached the same level as the placebo in 1 year.[29] This may explain the presentation times for the alternatively treated patients where IV BP patients tend to present at approximately 18 months and, for those on oral medication, between 3 and 5 years after treatment. The insert in the packaging for oral alendronate (Fosamax) specifies a bone half-life of 10.9 years.[18]

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Medications		Risks	Site	Trigger	Smoker	Treatment	Status
Fluticasone		None	Mandible	Extraction	No	Chlorhexidine IV Abs Curettage Corticotomy/debride	Unresolved
Aspirin Omeprazole Metoclopramide Thyroxine Alprazolam	Insulin Temazepam Atorvastatin Sertraline	HT IDDM	Maxilla	Extraction	No	Chlorhexidine Recontour bone	Unresolved
Clopidogrel		HT/IHD	Maxilla	Extraction	No	Chlorhexidine Resection	Unresolved
Monopril Amlodipine Olanzapine OxyContin	Metoprolol Aspirin Thalidomide	IHD/HT	Maxilla	Extraction	No	Chlorhexidine Oral Abs	Unresolved
OxyContin Metoclopramide	Paracetamol	None	Maxilla	Extraction	Yes	Chlorhexidine Oral Abs	Unresolved
Warfarin Baraclude Ergocalciferol		Hepatitis B Waldenström Macroglobulinemia	Maxilla	Extraction	No	Chlorhexidine Oral Abs	Unresolved
Prednisone Ibuprofen Escitalopram	Metformin Clopidogrel Simvastatin	NIDDM HT Hyperlipidemia	Mandible	Extraction	No	Chlorhexidine Oral Abs	Unresolved

The question arises whether this phenomenon is directly due to the BPs, specifically the aminophosphates, or merely a coincidence in an already compromised patients receiving antiangiogenic chemotherapy, glucocorticosteroids, and estrogens, who are often anemic, thrombophilic, and hypofibrinolytic, all of which pose a serious threat to Virchow triad of equilibrium and hemostasis.[17]

Epithelial Toxicity

Alternatively, Reid et al[30] believe that the suppression of bone turnover should have no effect on the overlying epithelium and that the accumulating BPs are toxic to the overlying epithelium as seen in high-dose oral preparations where ulceration is common in the gastrointestinal tract. They argue that dental extraction releases toxic doses of the chemical into local epithelium and predisposes to bacterial and fungal superinfections. If doses of the BPs were to concentrate in bone, they argue that it should also do so in multiple other sites, yet only the mandible seems to exhibit this phenomenon despite other areas within the body that have much higher rates of bone turnover. Their hypothesis explains the difficulty in bone healing after curettage and resection with depressed epithelial response. The same effect has not been described in other nontissue toxic bone suppressors, and osteonecrosis has also been described in other areas with minimal integumentary cover such as the ear and the nose.[30] Considering the pharmacology of the BPs, they suggest that perhaps, geranylgeraniol and farnesol, which are known to reverse the epithelial toxic effects of BPs in vitro, should be used as treatment.

Polymicrobial Infection

The relatively new field of BioFilm theory questions whether there is a polymicrobial etiology that deserves closer attention and requires more extensive investigation. In a recent series of BRONJ patients, up to 15 species of bacteria and novel forms of yeast, spirochetes, and treponemes were identified, all confirmed by gene array and distinguishable from control specimens.[31] Some argue that the effect is due to the nitrogen content of the drugs in use, but even that has been disproved with cases now arising in non–nitrogen-containing variants of BPs.[32] The best hypothesis is probably that described by McMahon et al[33] and best approached as a problem that develops owing to "multiple hits" on an already compromised bone matrix.

Genetic Aberration

Genotoxic characteristics in translational mutagenic studies that specifically implicate nitrogen, phosphate, and superoxides in translocations, nondisjunction, DNA breakage, and messenger RNA aberrations are described. Chronic inflammation, a well-known precursor for the release of nitric oxide, when combined with superoxides, produces nitrosoperoxycarbonate, nitrous acid, nitric acid, and peroxynitrite within an ischemic environment due to oxidative stress and in the presence of carbon dioxide. All of these nitrogen species cause nitrosative DNA damage and mutation.

Bacteria, fungi, and viruses are often also seen within BRONJ samples. Nitric bacteria and fungi have been linked to oncogenic

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transformation, whereas human papilloma virus is well known to be a precursor for squamous metaplasia.[34,35]

The mutagenicity of phosphate and its derivatives has also been well documented since the 1970s, and it is within this context of nitrogen-containing BPs with a considerable half-life and a traumatized drug-induced ischemic, static, and nonreparative superoxide-producing environment that the pathophysiological mechanisms of cancer are also difficult to ignore.[27,36]

TREATMENT

In almost all of the articles reviewed, the consensus is that prevention is far better than an attempted cure.[2] In the largest multicentric analysis to date of treatment for patients with BRONJ, Abu-Id et al[37] highlight the international difficulty of treating the disorder, with poor results in all the centers assessed. Our experience is similar. Thorough dental screening and treatment should precede the initiation of BP therapy in patients with cancer in whom IV BPs are indicated and withdrawal of the drugs should be considered within the context of oral compromise in consultation with physicians.[5,9,38] Although small, the risk associated with oral BPs can also be magnified with the concomitant use of corticosteroids, and the accepted presentation time of 3 years may be noticeably shortened.[2] Meta-analysis by Van der Wyngaert et al[39] of the first 2 years of the literature showed that 73% of patients still have residual BRONJ after conservative and/or surgical management.

Marx et al,[40] in his review of 119 cases, maintained that oral antibiotics and chlorhexidine mouthwash reached resolution within 2 years. Another evaluation of 75 cases showed that after 18 months of conservative therapy, only 70% of cases resolved. A higher margin of 82% was reached when combined with surgery and Nd:YAG laser, but there are advocates for early surgical intervention.[41] Freiberger et al[42] recommended hyperbaric oxygen with 82% of patients regressing a stage with early treatment, but long-term follow-up showed that only 62% had stabilized and gone into remission probably because of continued BP therapy. Ozone exposure can exert a positive effect on bone defects by oxidative preconditioning, stimulating and/or reserving the endogenous antioxidant systems and blocking the xanthine/xanthine oxidase pathway for reactive oxygen species generation. Moreover, ozone can have a beneficial effect on the circulation of blood, increasing red blood cell concentration and hemoglobin rate, the diapedesis and the phagocytosis, and stimulating the reticulohistiocytes.[25]

Harper et al have described a novel form of therapy recommended for those with osteoporosis. They suggest anabolic parathyroid hormone, used in the treatment of postmenopausal osteoporosis, owing to its indirect effect on osteoclasts, by mobilizing osteoblasts. The recombinant form of the hormone has received Food and Drug Administration approval owing to its impressive effect on improved bone mass, restoration of bone architecture and increasing the bone diameter. Despite its catabolic and calcium mobilizing effects, intermittent low dose therapy has been shown to be effective in restoring and remodeling osseous microarchitecture even with a 6 months' delay. Parathyroid hormone is strictly prohibited in patients with cancerous osteolytic lesions, and the administration of 20 μg/d for up to 2 years has to be administered in conjunction with an endocrinologist using a definitive physiological bone profile.[18]

Developments in monoclonal antibodies such as denosumab, which may replace BPs in the future, are an exciting area of development.[20] Ma et al[43] have also provided in vivo murine evidence for the effective reversal of antiresorptive medication such as BPs when they were withdrawn.

Recommendations from the American Society of Clinical Oncology regarding multiple myeloma have emphasized considering withholding IV BP therapy in stable disease after 2 years to prevent BRONJ.[44] Similar recommendations by the International Society of Geriatric Oncology also advocate comprehensive oral review before commencement.[45]

Marx et al use a useful marker to determine whether there is indeed osteoclastic function before one is to commence therapy if a drug holiday was prescribed. C-terminal telopeptide (CTX) is a specific cross-linking peptide of type I collagen and is considered to be the best correlate of bone turnover. They measured morning serum levels of CTX and found that discontinuation of oral BP therapy caused a significant surge in the marker definitively linked to osteoclastic function. If the level is found to be less than 150 pg/mL, all dentoalveolar therapy should be deferred with an expected rise in CTX of 26 pg/mL per month of drug holiday. Furthermore, CTX may also be a potential marker to determine relative risk for developing BRONJ. They determined that the area of bone exposed is directly proportional to duration of oral therapy, that pain is a direct marker of super infection, and that alendronate was the worst culprit.[46] Similar recommendations were made by the International Society of Geriatric Oncology about the N-terminal telopeptide and its response to BPs.[45]

Prevention therefore seems to be the consensus among all experts and has lead to a drive by the Food and Drug Administration to label all BPs as potential osteonecrosis-inducing medication, which has also been extended to the oral form.[2,5]

There is little consensus, however, on how to treat patients in whom BRONJ has been diagnosed but who need to continue IV BP therapy. Recommendations from the Mayo Clinic suggest that complications are more commonly seen in those patients on zoledronic acid than those on pamidronate. They emphasized the need for prevention, good oral hygiene, limited dental work, and referral to an experienced oral and maxillofacial surgeon should surgery be required. They also suggest omission of IV BP treatment 1 month before surgery.[47]

Treatment strategy recommendations from the AAOMS exist for several subtypes of patients who are due to have IV therapy (Table 3).

Obstacles facing clinicians include the lack of research available to make sound decisions. Many of the guidelines in the literature are largely based on task force cumulative clinical experience (level 4). The best guidelines for patients on oral BPs who need dental surgery are from the AAOMS who have stratified the approach (Table 4). The AAOMS has also devised a staging protocol to maximize unification of protocols and ensuring uniform approach to the problem of patients who have or are at significant risk of developing established BRONJ (Table 5). Discontinuation of BPs, whether they be oral or IV, has been associated with gradual healing. Their discontinuation should be considered according to individual demands and in consultation with relevant team members.[2]

Surgical treatment is very poorly described, and various papers address issues relating to lesions similar to BRONJ such as osteoradionecrosis of the jaw, using microsurgical free fibula flap approaches.[48] Bisphosphonate-related osteonecrosis of the jaw cases differ owing to the lack of recipient site response that lacks osteoblastic and osteoclastic functions. On occasion, a patient may present with significant risk of pathologic fracture or orocutaneous fistula, and there is extensive exposure of the bone. Engroff and Kim[49] describe a series of vascularized free fibula grafts to treat BRONJ with great success. They point out that BRONJ exclusively affects the bone and does not involve the local soft tissue as it does in osteoradionecrosis. They emphasize that once local soft tissue infection is controlled and if there is healthy bone, any graft will heal. Furthermore, their observations concerning the effect of BPs on osteoclastic function and not osteoblastic function add weight to their argument for early reconstruction. They maintain that demarcation of the area between devitalized and healthy bone

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is easily recognized intraoperatively and often does not match radiographs and that it is the ineffective debridement beyond the radiographically described area that accounts for poor healing in other case series.[49,50] Alternative methods described advocate debridement back to vascularized bone using a scalpel and periosteal release/buccal (local) flaps to cover the defect with great success at 1 month.[51]

Despite years of interest and seminal publications addressing research, assessment, and treatment of BRONJ, there are very few comprehensive reviews addressing issues for all team members involved in treating these patients. Our experience of treatment difficulty has been similar to that described within the literature (Table 6). Considering the exponential increase in prevalence as we reach the 5-year oral exposure of BPs and current medicolegal implications on 3 continents, we believe that all disciplines including craniofacial, maxillofacial, and plastic and reconstructive surgeries; oncology; and hematology should be made aware of the current recommended guidelines for treating BRONJ; a significant emerging problem illustrated by our patients who probably represented merely the tip of the iceberg.

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