INTRODUCTION

Bisphosphonates belong to a class of drugs referred to as Anti-Resorptive medications. Although they are the standard treatment of choice for skeletal problems such as osteoporosis, other bone disorders and certain forms of malignancy, the use of anti-resorptive therapy has been implicated in the aetiology of osteonecrosis of the jaw which is a painful and debilitating condition. The pathogenesis of antiresorptive agent-induced osteonecrosis of the jaws (ARONJ) is poorly understood. There are no established risk assessment methods to predict the level of developing ARONJ and no predictability of disease resolution. In addition, there is no consensus regarding the definitive standard of care for this disease. Dentists and other health care providers must be aware of the potential adverse effects of these medications when providing dental treatment including implants.

In 2009, the ADI invited Professor Jon B. Suzuki to produce a white paper on “Bisphosphonates”. In view of continuous new scientific clinical research findings, we have invited Professors Jon B. Suzuki, DDS PHD MBA and Cameron Y. S. Lee DMD MD PHD to update the current information in a new paper titled, “ADI White Paper on Anti-Resorptive Therapy and Osteonecrosis of the Jaws (ARONJ) for the Dental Practitioner” (see full text paper). Please also refer to Professors Suzuki & Lee’s C.V. link.

The ADI Review Group has produced the following two short guidelines: “Dental Management of Patients Receiving Anti-Resorptive Treatment” and “The Diagnosis and Management of Patients with ARONJ”. The documents are based on the best available current scientific literature and expert opinion as presented in Professor Suzuki and Lee’s white paper (2012) which should be helpful when making decisions on how to manage dental patients on anti-resorptive therapy. It is highly recommended that the clinician read the full text White Paper 2012 to develop a complete understanding of the disease. The current guidelines replace the previous ADI guidance published in 2009.

Cemal Ucer, June 2012
ADI President

The ADI Review Group:
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ABSTRACT

The benefits of antiresorptive therapy (formally referred to as bisphosphonates) for patients diagnosed with a malignancy or osteoporosis are immense and have proven to be the cornerstone in the medical management of these patients. They have a high tolerability profile and good efficacy. However, antiresorptive therapy is not without adverse side effects. For the dental practitioner, there has been an increase in the number of reported cases of antiresorptive agent-induced osteneocrosis of the jaws (ARONJ) since 2003.

This disease remains poorly understood as the pathogenesis remains to be fully elucidated. At present, there are no established risk assessment methods to predict the level of developing ARONJ and no predictability of disease resolution. Also, no definitive standard of care has been established for ARONJ, as well as no definitive consensus guidelines (Marx et al, 2007; Ruggiero et al, 2009; Hellstein et al, 2011). Dentists and other health care providers must be aware of the potential adverse side effects of these medications.

This objective of this white paper is to assist the dental clinician in their professional clinical judgment in management of the patient prescribed antiresorptive agents or is diagnosed with ARONJ. We review the current literature of the pathogenesis and pathophysiology of ARONJ and the contemporary prevention, treatment strategies and recommended guidelines for the dental clinician when treating the patient on antiresorptive agents or diagnosed with ARONJ. This information is based on the current scientific, medical and dental literature and expert opinion, including the personal opinion of the two authors of this white paper. This white paper is an update of the 2009 Association of Dental Implantology White Paper (Suzuki, 2009).

PREFACE

The Association of Dental Implantology invited Professors Jon B. Suzuki and Cameron Y.S. Lee to update the 2009 White Paper on management of the dental patient receiving intravenous or oral antiresorptive agents. Dr. Suzuki is a leading expert on this subject, and his vast experience has included being named Chairperson of the United States Food and Drug Administration (USFDA). Dr. Cameron Y. S. Lee is known for his clinical research in oral, maxillofacial and reconstructive surgery and has a special interest in ARONJ and has published several articles with Dr. Suzuki regarding the surgical and non-surgical management of ARONJ.
SCOPE OF THE PROBLEM

At present, there are no published studies that have accurately determined the true incidence of developing antiresorptive agent-induced osteonecrosis of the jaws (ARONJ). This is due to the fact that most reports are retrospective studies and case reports. Most cases of ONJ are associated with long term therapy with antiresorptive agents and administration of the intravenous agents Zoledronic acid (Zometa; Novartis Pharmaceuticals Co; East Hanover, NJ) and Pamidronate (Aredia; Novartis Pharmaceuticals Co; East Hanover, NJ). It is believed that ONJ is both a time-dependent and dose dependent disease process (Marx et al, 2005; Migliorati et al, 2006; Marx et al, 2007). The incidence of ARONJ for patients taking the intravenous form of this medication is estimated at 2% to 18% (Bamias et al, 2005; Wang et al, 2007). For patients taking the oral form of antiresorptive agents, Merck and Co, estimate the risk as 0.7 cases per 100,000 person years of exposure (Merck & Co, 2008). The American Association of Oral and Maxillofacial Surgeons position paper on antiresorptive agent related ONJ estimate the incidence of ONJ cases for patients taking the oral form as 0.01 to 0.04 % (AAOMS Advisory Task Force, 2007; 2009). In an Australian study, Mavrokokki et al (2007), presented their epidemiological data and estimate the incidence of ONJ in osteoporotic patients taking the oral form of antiresorptive agents as 1 in 2,260 to 8,470 patients (0.01 to 0.04 %). If dental extractions were completed, the frequency was calculated as 1 in 296 to 1,130 cases (0.09 to 0.34 %). Sedghizadeh et al (2009) at the University of Southern California School of Dentistry identified 208 patients taking Alendronate. The average age of all participants was 73 years. Risk factors for developing ONJ were no different from other previously published studies. Of the 208 patients, 9 patients were being actively treated for ONJ. Their findings represent a 4% incidence (1 in 23 patients) of developing ONJ with oral antiresorptive agents. All cases of ONJ were associated with simple extractions of teeth and denture trauma. The results of this institutional study has significance as it represents a higher risk of developing ONJ compared to other studies reported in the literature.

The purpose of this 2012 White Paper is to assist the dental clinician in arriving at treatment decisions when managing the patient prescribed antiresorptive agents by their physician. The authors of this white paper believe that the entire dental community must have a better understanding of this world-wide problem that has impacted dental medicine. To fully comprehend the negative impact on the oral health of patients, dental clinicians must also understand the pathogenesis and pathophysiology of osteoporosis in addition to being familiar with the antiresorptive agents that contribute to ARONJ.

As antiresorptive agents have known adverse side effects, the medical and dental communities are working together to prevent and treat ARONJ. For all stakeholders, especially the patient, the primary goal is the prevention of ARONJ. Therefore, if a physician has indicated to an individual that they will initiate antiresorptive therapy, it is important for the patient and their dentist to be informed of this medical decision. It is extremely important that during the discussion of the patient’s health history, the clinician always inquire about a positive history of malignancy, osteoporosis or osteopenia.

The preceding information defines the challenges faced by the dental and medical communities and their patients. The following sections in this white paper are recommendations that will assist the clinician in their professional judgment in managing this problem.
OSTEOPOROSIS

Osteoporosis is a common metabolic skeletal disorder characterized by disruption of osseous architecture, loss of bone mass and increased skeletal fragility leading to skeletal fractures (Genant et al, 1999; Cummings & Melton, 2002). Measuring bone mineral density by Dual Energy X-Ray Aborptiometry (DXA) Scan, the World Health Organization and the National Institutes of Health consensus conference defines osteoporosis as a bone mineral density that is 2.5 Standard Deviations (SD) or more below the normal mean value for young adults (T score of -2.5 or lower). In the United States, over 10 million Americans are diagnosed with osteoporosis, while over 33 million are diagnosed with osteopenia (Jamal et al, 2005). It is estimated that 47% of women and 22% of men 50 years of age and older will experience an osteoporotic fracture in their lifetime (Larsen et al, 2004; Boonen et al, 2006). Both conditions increase the risk of skeletal fracture, most commonly the arm, hip, pelvis and vertebral bodies. The clinical significance is the risk of skeletal fractures, with increased disability, morbidity and mortality (Cummings & Melton, 2002). Annually, there are greater than 1.5 million skeletal fractures in the United States (Gabriel et al, 2002). Therefore, the prevention and management of osteoporosis is of extreme importance.

Many factors contribute to the risk of osteoporosis, such as menopausal status, age, obesity, smoking, coexisting diseases, medications such as glucocorticoids, estrogen and an existing family history of osteoporosis (Hirschhorn & Gennari, 2008; Wade & Suzuki, 2007). Of the different types of skeletal fractures, hip fractures are associated with the highest morbidity and mortality (Cooper et al, 1993). Decreased estrogen levels have been identified as the main cause of osteoporosis and a major risk factor for skeletal fractures (Guyatt, 2002). Glucocorticoid therapy is the most common secondary cause of osteoporosis (Angeli, 2006; Canalis et al, 2007).

Composition of Bone and Bone Strength

The composition of bone consists of type I cross-linked collagen in a triple helix configuration supported by calcium hydroxyapatite crystals (Currey, 1969; Seeman, 1997; Banse et al, 2002). Increases in bone mineral density will resist bone deformation allowing bone to be loaded. Bone must also be elastic and able to resorb deformation under load (Viguet-Carrin, et al, 2006). If bone becomes brittle and too stiff, energy absorbed by bone during loading will result in fracture of bone (Garnero et al, 2002).

The life cycle of bone is a process that undergoes modeling (construction) and remodeling (reconstruction) that results in the formation of new mineralized bone (Seeman & Delmas, 2006; Canalis, et al 2997). The process (Figure 1) occurs in bone multicellular units (BMU) made up of osteoblasts and osteoclasts (Parfitt, 2001). Osteoblasts are of mesenchymal origin, while osteoclasts are multinucleated cells of hematopoietic lineage (Wlodarski, 1990; Canalis, 2005).
Osteoblasts are responsible for synthesis of the bone matrix that supports osteoclast formation, survival and function (Taichman & Emerson, 1988; Takahashi et al, 1988). During the remodeling phase osteocytic apoptosis results in loss of bone strength before bone resorption (O’Brien et al, 2004; Seeman & Delmas, 2006). This could be attributed to advancing age, hormone replacement therapy with estrogen and glucocorticoid therapy (Taylor, 1997; O’Brien et al, 2004).

By signals that are not yet completely understood at the molecular cellular level, the bone resorbing osteoclasts are directed to bone sites that have become a bone remodeling unit (Canalis, 2007). At these sites, osteoclasts resorb bone by an acidification process on the bone surface (Teitelbaum, 2000). This leads to a zone of dissolution of the hydroxyapatite mineral matrix (Figure 2). Secretion of enzymes digest the organic portion of bone that results in resorption lacunae that will eventually be filled in with new mineralized bone by the attraction of osteoblasts directed to the area (Teitelbaum, 2000; Tolar & Teitelbaum, 2004). These cellular mechanisms of bone modeling and remodeling are responsible for the human skeleton’s bone strength and repair of microdamage.

In postmenopausal women with osteoporosis, the remodeling rate is high as BMU are in the process of excavating resorption bone cavities (Seeman & Delmas, 2006). With the addition of antiresorptive agents, this cell damaging activity is disrupted (Delmas, 2000; Borah, et al, 2004; Seeman & Delmas, 2006). Formation of new BMU is decreased and new bone formed undergoes mineralization. The deposition and increased bone mineral density of newly formed bone reduces bone porosity, microdamage and decreases the incidence of skeletal fracture (Seeman & Delmas, 2006).

Pathophysiology of Osteoporosis

The RANK (receptor activator of nuclear factor kappa beta) receptor has been identified as a key molecule located on osteoclasts in the regulation of bone remodeling (Lacey et al, 1998).

To further understand the mechanism of bone destruction, much interest has focused on the cytokine RANKL (receptor activator of nuclear factor kappa B ligand) that belongs to the tumor necrosis factor (TNF) family of ligands and receptors (Martin, 2004). Therefore, the RANKL-RANK signaling pathway plays a pivotal role in the regulation of bone metabolism and is a key mediator of osteoclast differentiation, function and bone resorption (Yasuda et al, 1998; Burgess et al, 1999). In healthy non-osteoporotic bone, osteoblasts and T cells express RANKL on their cell surfaces that results in the differentiation and activation of osteoclasts (Martin, 2004).

RANKL activates osteoclastogenesis when it binds to the receptor RANK on osteoclast precursor cells. This signaling pathway is crucial in the osteoblast-osteoclast axis of healthy bone metabolism (Figure 3). In healthy bone metabolism, bone is first resorbed by osteoclasts and then remodeled with osteoblastic activity that leads to maturation of bone (Seeman & Delmas, 2006).
Several cytokines and hormones involved in regulation of the immune system and calcium homeostasis are known to enter the bone microenvironment that results in the over expression and release of RANKL from osteoblasts (Boyle et al, 2003; Roodman, 2004). Among these substances are parathyroid hormone (PTH), prolactin, prostaglandin E2, interleukin-1, interleukin-6, and corticosteroids. When there is an increase in RANKL signaling, this leads to the formation of osteoclasts and their activation leading to bone resorption, skeletal fractures and other skeletal-related events (Boyle et al, 2003; Roodman, 2004). The bone resorbing activity of RANKL is suppressed by the decoy antagonist modulator, osteoprotegerin (OPG) produced by osteoblasts (Lacey et al, 1998; Boyle et al, 2003; Tolar et al, 2004; Schneewis et al, 2005; Whyte, 2006). OPG interferes with differentiation of osteoclasts precursors by interacting with RANKL. Pharmacologic inhibition of RANKL is an effective treatment strategy for osteoporosis (McClung et al, 2006). In animal models, binding of OPG to RANKL prevents activation of the osteoclast RANK receptor and inhibition of RANKL activity and bone resorption (Zhang et al, 2001). In the rat model, OPG injected into bone resulted in a reduction of osteoclasts on the surfaces of bone and an increase in bone mineral density (Capparelli et al, 2003). Therefore, the RANKL-RANK pathway and the natural decoy receptor, OPG are major regulators of osteoclastic bone activity responsible for bone resorption (Kearns et al, 2008).

Decreased levels of estrogen leads to an increase in bone marrow stromal cells and an increase in RANKL and their binding affinity to the osteoclast receptor, RANK. This activity leads to the formation of osteoclasts and bone resorption activity (Hirschhorn & Gennari, 2008). With advancing age and menopause, bone loss is exacerbated, as well as bone fragility and the risk of skeletal fracture (Kearns et al, 2008).

Diagnosis of Osteoporosis

The National Osteoporosis Foundation (2002), the American Association of Clinical Endocrinologists (2003) and the United States Preventive Services Task Force (USPSTF) all recommend that women 65 years and older obtain a measurement of bone mineral density (Hodgson et al, 2003). This recommendation is based on the observation that women over the age of 65 have an increased risk of skeletal fracture associated with decreased levels of bone mineral density (Raisz, 2005). This guideline is also recommended for men who have a history of skeletal fractures. Postmenopausal women under the age of 65 years may be screened for low bone mineral density based on a history of existing risk factors for osteoporosis and osteopenia.

The diagnosis of osteoporosis is made when bone mineral density (BMD) measurements with the use of Dual Energy X-Ray Aboorptiometry (DXA) Scan of the lumbar spine (L1 to L4) or the hip, including the femoral neck fulfills the World Health Organizations (WHO) criteria of a T score less than -2.5 (Genant et al, 1999; Leib et al, 2004). The T score is the standard deviation change in BMD from the theoretical bone mass of a Caucasian woman in their mid-20s to the current BMD. Although the relative risk for fracture is higher in the osteoporotic population of patients, there are many more females who experience skeletal fractures with low bone mass, or osteopenia (DXA T score of -1.0 to -2.5) instead of osteoporosis (Schuit et al, 2004).
ANTIRESORPTIVE AGENTS

Antiresorptive agents are a pharmacologic class of synthetic analogs of inorganic pyrophosphate that has an affinity for calcium (Rogers et al, 1997; Greenberg, 2004). Intravenous agents are used in the treatment of various malignant and benign metabolic conditions (Table 1), such as hypercalcemia of malignancy; Paget’s disease of bone; multiple myeloma; and metastases from distant sites such as breast, thyroid, prostate glands and lung. The oral form of antiresorptive agents is indicated in the management of osteoporosis; fibrous dysplasia and most recently, osteogenesis imperfecta in the pediatric population (Greenberg, 2004; Rausch & Glorieux, 2004).

Oral antiresorptive agents are considered the standard of care for the prevention and treatment of women with postmenopausal osteoporosis and are the most widely used medications for this skeletal disorder (Rosen, 2005; Black et al, 2007; Khosla, 2009; Favus, 2010). Orally administered antiresorptive agents (Table 2) approved by the United States Food and Drug Administration (FDA) include the following: Alendronate sodium (Fosamax; Merck & Co., Inc.; Whitehouse Stations, NJ); Risedronate sodium (Actonel, Warner Chilcot, Dublin) and Ibandronate sodium (Boniva, Roche Group, South San Francisco). Each of the medications differ in their binding affinity to bone, potency and duration (Genant et al, 1999; Jamal et al, 2005).

Antiresorptive agents decrease bone resorption and skeletal fracture (Figure 4) by chemically binding to calcium hydroxyapatite in the mineral phase of bone, thereby inhibiting the function and survival of osteoclasts and stimulating osteoclastic apoptosis which are engulfed by bone marrow phagocytes (Sato et al, 1991; McClung, 2003; Russell et al, 2008). They deposit in three compartments of the body: the serum, the cortical bone surface and the deeper medullary bone. Antiresorptive agents are attracted to areas of bone remodeling, where osteoclast activity is high and concentrating in the lacunae of the osteoclast. Therefore, the osteoclastic cell is the main target for antiresorptive agents and affects osteoclast recruitment, differentiation and function. This mechanism of action disrupts the activity of the enzyme, farnesyl pyrophosphate synthase (Luckman et al, 1998; Fisher et al, 1999). Inhibition of enzyme activity prevents osteoclasts from binding to the surfaces of bone which prevents bone resorption and increases bone mineral density (Bergstrom et al, 2000).

A regimen consisting of a once a year intravenous infusion of Zoledronic acid (Zometa, Novartis Pharmaceuticals) appears to be an alternative to the use of weekly oral antiresorptive therapy (Black et al, 2007). During a 3-year period, an annual infusion of 5 mg of Zoledronic acid significantly reduced the risk of fracture at all major osteoporotic anatomic sites, especially vertebral and hip fractures. Once per year infusion of Zoledronic acid may be more appealing to the osteoporotic patient, as strict adherence to a weekly regimen of oral dosing for 12 months can be challenging and lead to non-compliance (Cramer et al, 2005; Recker et al, 2005; Downey et al, 2006).
Adverse Effects of Antiresorptive Agents

Reported adverse affects associated with oral antiresorptive therapy reported include the following: erosive esophagitis, esophageal ulceration, varices, and bleeding, heart burn, chest pain, hoarseness and vocal cord irritation (Ribeiro et al, 1998; Watts & Diab, 2010). Known ocular complication reported include conjunctivitis, anterior uveitis and scleritis (Fraunfelder, 2003). Use of oral antiresorptive agents and esophageal cancer has been reported in the literature, but are inconclusive (Shane, 2010).

Case reports of atypical femoral fracture have been reported with bisphosphonate therapy (Neer, 1995; Black et al, 2010; Shane et al, 2010). Epidemiologic studies and case reports have demonstrated a relationship between long-term antiresorptive therapy and atypical femoral fractures. Although the exact cause is not known, it is speculated that atypical femoral fractures and antiresorptive agents are the result of marked bone suppression and bone micro cracks that leads to fatigue fractures (Neer, 1995).

In the dental community, antiresorptive-associated osteonecrosis of the jaw (ARONJ) due to long-term oral antiresorptive therapy has been well documented. Since the first reports by Marx (2003) in 2003 who described 36 patients with ONJ while receiving intravenous antiresorptive agents and Ruggiero et al (2004) who presented an additional 63 cases in 2004, multiple reports of antiresorptive agent-induced osteonecrosis of the jaws (ARONJ) have appeared in the medical and dental literature, including oral ARONJ (Jeffcoat, 2006; Nase & Suzuki, 2006; Lee et al, 2007; Nase & Suzuki, 2006). Development of soft and hard tissue lesions is usually due to an inciting event, such as tooth extraction, bone grafting of the jaws in preparation for dental implants, and implant surgery (Marx, 2003; Ruggiero et al, 2004; Marx et al, 2007). However, spontaneous cases of ONJ have been reported (Marx et al, 2007). In these instances, thin overlying soft tissues are easily perforated, such as the gingival tissue overlying a palatal torus or the mucosa of the posterior lingual mandible.

Reports of antiresorptive osteonecrosis of the jaw (ARONJ) have been reported in patients with cancer treated with multiple doses of intravenous Zoledronic acid (Erichsen et al, 2011; Lewiecki, 2011). To our knowledge, there have been no reports in the English literature of this occurring with the once-yearly infusion of this medication for the management of osteoporosis (Khosla, 2009).

Pathogenesis of Antiresorptive Agent-Induced ONJ

We believe that the pathogenesis of ARONJ is multifactorial, as several hypotheses have been presented in the literature to explain the pathogenesis of ARONJ. Marx (2003) hypothesized that bone turnover is effectively inhibited, since the primary action of antiresorptive agents is the inhibition of osteoclastic-mediated bone resorption. As nitrogen containing bisphosphonates concentrate in bone hydroxyapatite, the major toxic effect is cellular apoptosis of osteoclasts. Therefore, coupling of osteoclastic and osteoblastic activity is disrupted, resulting in suppression of bone turnover. A second theory is that ONJ is due to the antiangiogenic effects of antiresorptive agents that affects vascularization, inhibits angiogenesis and ultimately, delays wound healing (Migliorati et al 2005; Allegra et al 2007; Ziebart et al 20110).
Several authors (Landesberg et al, 2008; Kyrgidis & Luczak, 2009, Kyrgidis et al, 2009; Agis et al in 2010) hypothesize that oral epithelial cells are exposed to localized increased toxic concentrations of antiresorptive agents following trauma resulting in compromised epithelial wound healing, jaw exposure and development of ONJ. Kyrgidis and colleagues (2009) published their hypothesis that antiresorptive agents inhibit cell to cell signaling that impairs not only osteoblasts and osteoclasts, but fibroblasts and keratinocytes as well. This mechanism would result in defective mucosal wound healing and allows for oral flora to come into contact with the jaws.

Otto et al (2010) theorize that local tissue acidosis in the jaw due to antiresorptive agents may elicit the onset of osteonecrosis. The two most recent hypotheses believe that ARONJ is due to ineffective remodeling of bone that results in a central zone of brittle, poorly vascularized bone that undergoes necrosis (Subramanian et al, 2011). This is due to compromised osteoblastic function that increases the chances of developing ARONJ. Osteoclast inhibition with normal osteoblastic function does not result in pathology. Wehrhan and their colleagues (2011) believe that angiogenesis is impaired in the mucoperiosteal tissues, but vascularization is not compromised. However, the overall result is poor regeneration and vessel remodeling when neovascularization is required. Both of these latest studies specifically suggest that the underlying pathogenesis could be impaired angiogenesis and cellular remodeling.

All of the above theories attempt to explain the pathogenesis of ARONJ. However, they fail to explain why nitrogen containing bisphosphonates result in osteonecrosis of the jaws, but not other parts of the skeletal bones. To our knowledge, the only sites affected by antiresorptive agents are the jaw bones and the external acoustic meatus (EAM), as both are derivative of the first pharyngeal arch. There are no studies that demonstrate that bisphosphonates selectively accumulate in the jawbones compared to other parts of the skeleton and provide a direct causal relationship between osteonecrosis of the jaws and antiresorptive therapy (Bilezikian, 2006; Silverman & Landesberg, 2009; Otto et al, 2010;)

**COMORBIDITIES**

**Medical Comorbidities**

The most significant comorbidity for the patient diagnosed with a malignancy is the impact it has on human nutrition and the immune system (Marx et al, 2005). Other reported systemic risk factors and comorbidities include immunosuppressive therapy, use of steroids, medications with antiangiogenic activity, corticosteroid medications, use of tobacco, diabetes mellitus and hypertension (Marx et al 2005; 2007; Ruggiero, 2009).

**Dental Comorbidities**

Dental conditions (Ruggiero et al 2004; Marx et al, 2005; Marx et al 2007; Wade & Suzuki, 2007) that increase the risk of developing ARONJ include periodontal disease, dental decay, intraosseous infections of the jaws, failed endodontic treatment, tooth extractions, tori removal and pressure necrosis from removable partial dentures. Dentoalveolar surgery increases the risk of developing ARONJ and may include the following: extraction of teeth, dental implant surgery, periapical surgery and periodontal surgery involving osseous tissues.
Classification of ARONJ

We adhere to the classification of the American Association of Oral and Maxillofacial Surgeons (AAOMS) to define ARONJ that consist of four stages (0-4) (Table 3). The diagnosis of ARONJ is based on the following characteristics: A history of antiresorptive therapy; exposed jaw bone for 8 weeks or greater; no history of radiation therapy where the jaw bones were in the field of radiation. This clinical staging system has been established to define the severity of ARONJ and guide the clinician in the management of this surgical problem. Please see Table 3 for a more detailed description of the four stages.

Clinical Features of ARONJ

The clinical presentation and severity of ARONJ will vary between patients. It may include any of the following (Marx, 2003; Ruggiero et al, 2004; Marx et al, 2005; Melo & Obeid, 2005; Ruggiero et al, 2006; Marx et al, 2007; Ruggiero, 2009; Ruggiero, 2010): vague pain or no pain with non-specific clinical findings of sensitivity of the jaw and teeth; no healing or delayed wound healing, such as with an extraction site; exposure of necrotic bone (Figure 5) with or without pain; mobility of teeth; neurosensory changes of the lip; foul taste in the oral cavity; inflammation of the surrounding soft tissues; purulent discharge, the presence of fistulous tracts and pathologic fracture of the jaw (Figure 6).

It is important to realize that diagnosis of this condition can be delayed, as radiographic findings are not detected early in the course of the disease process (Stage 0). As the disease progresses through the various stages, detectable radiographic findings may appear indicative of antiresorptive alveolar bone toxicity as described below.

Radiographic Signs of ARONJ

In the early stages of ARONJ, there may be little to no obvious changes to the bony architecture of the jaws in periapical, panoramic radiographs and even CT scans. As ONJ toxicity of the alveolar bone progresses over time and with the development of exposed bone and the presence of microorganisms, an increase in bone mineral density indicative of antiresorptive toxicity may be observed. Sclerosis of the lamina dura around the roots of the teeth and widening of the periodontal ligament space (Figure 7) are other radiographic signs of antiresorptive toxicity to the alveolar bone. In advanced cases of ARONJ, osteolysis, sequestration of bone and pathologic fracture has all been observed.
ACTINOMYCES AND OSTEONECROSIS OF THE JAWS

A review of published cases identified multiple bacterial species in ARONJ patients, especially the genus Actinomyces (Hellstein & Marek, 2005; Marx et al, 2005; Hansen et al, 2006; Lee et al, 2007; Sedghizadeh et al, 2008; Mawardi et al, 2009; Naik & Russo, 2009; Thumbigere et al, 2009; Wongchuensoontorn et al, 2009; Lee et al, 2011.) Other commonly cultured microbial pathogens identified include the following: Streptococcus, Staphylococcus, treponemes, Bacteroides, Actinobacillus, Moraxella, and Eikenella corrodens (Schuster, 1987; Hellstein & Marek, 2005; Lee et al, 2007; K Sedghizadeh et al, 2008; Allen & Burr, 2009; Kaplan et al, 2009; Mawardi et al, 2009; Naik & Russo, 2009; Thumbigere-Math et al, 2009). It is postulated that these microorganisms exert a synergistic effect in the pathogenesis of disease, secreting bacterial enzymes, such as collagenases and hyaluronidases that are tissue destructive and promote extension of the lesion to other areas of the head and neck (Schuster, 1987; Sedghizadeh et al, 2008; Mawardi et al, 2009). Currently, it is not known if the infection of the jaws and overlying soft tissues is a primary or secondary event in ARONJ (Hansen et al, 2006; Lee et al, 2008, Allen & Burr, 2009; Thumbigere-Math, et al, 2009; Lee et al, 2011).

The difficulty is in determining if actinomyces represents free-floating microbial bacteria, referred to as planktonic bacteria on the hard and soft tissues, or is a true infection made up of a bacterial biofilm. The detection of biofilm communities in osteonecrotic specimens has recently been described in patients diagnosed with ARONJ (Sedghizadeh et al, 2008). In the past decade, we have been able to develop a better understanding of the pathogenesis of infections from new molecular and cellular techniques used in the study of the host-pathogen interaction. There is much evidence that ARONJ could be due to infections from biofilms and is a likely contributor to the pathogenesis of ARONJ.

Biofilms are three-dimensional, densely structured communities of bacterial cells enclosed in a polymeric matrix that protects them from other organisms, phagocytosis, antibiotics and antiseptics. These bacterial communities are able to communicate with each other through cell to cell signaling, a phenomenon called quorum sensing and allow for the flow of nutrients and waste (Donlan & Costerton, 2002; Vuong et al, 2003). Biofilms are difficult to eradicate and it has been suggested that they could be present in all chronic wounds (Costerton et al, 1999; Lewis 2001; Cowan, 2010; Stotts, 2012). The Center for Disease Control and Prevention estimates that 60-80% of infections caused by bacteria is due to biofilms and is the cause periodontitis, endocarditis, urinary tract infections and other chronic infections (Donlan & Costerton, 2002; James et al, 2008; Wolcott et al, 2009). Growth of biofilms may increase the microbial resistance to standard antibiotic therapy.

Although actinomyces is a normal inhabitant of the oral cavity, it is the author’s clinical experience, as well of others (Hellstein & Marek, 2005; Biasotto et al, 2006; Lee et al, 2007; Sedghizadeh et al, 2008; Naik & Russo, 2009; Lee et al, 2011; Suzuki & DeLisle, 1984) that this microbial pathogen is an opportunistic bacterium directly involved in the pathology of the hard and soft tissues of the maxillofacial region and oral cavity in the ARONJ patient (Figure 8). It has been demonstrated in human and animal studies that biofilms can lead to osteomyelitis (Parsek & Singh, 2003). The potential for biofilms to cause chronic, debilitating infections, including ARONJ leaves little doubt that biofilms may
be involved in the pathogenesis (Sedghizadeh et al, 2008; Sedghizadeh et al, 2009). The presence of actinomyces should not be neglected, as a plausible hypothesis is that actinomyces plays a critical role in the pathogenesis of antiresorptive-associated osteonecrosis of the jaws (Kaplan et al, 2009; Naik & Russo, 2009; Lee et al, 2007; Sedghizadeh et al, 2008; Curi et al, 2011; Lee et al, 2011).

With ARONJ, it is theorized that pathogenicity is due to various bacteria gaining direct entry into the jaw bones from surgical procedures that violate overlying gingival or mucosal tissues of the mandible and maxilla (Schuster, 1987; Ruggiero et al, 2004; Marx et al, 2005; Marx et al, 2007). The most common entry site to the jaw bones is the alveolus during extraction of teeth (Marx et al, 2005; Marx et al, 2007). Actinomyces is a chronic infection characterized by both granulomatous and suppurative infection intra- and extraorally, invading both soft and hard tissues of the oral cavity and maxillofacial region (Schuster, 1987; Nagler et al, 1997; Brooks et al, 2001; Russo et al, 2010). The infection is capable of advancing across anatomic boundaries, resulting in the formation of pyogenic lesions (Schuster, 1987). These lesions are often associated with fistulous tracts that may contain granules, composed of micro colonies of the pathogen embedded in the soft tissues of the jaws. There are four clinical types of human actinomycosis that are categorized based on anatomic site of pathology: cervicofacial, cutaneous, thoracic and abdominal (Brooks et al, 2001; Russo, 2010). For the dentist, the area of interest is the cervicofacial region that may involve the soft tissues of the oral cavity, jaw bones, sinuses and face (Schuster, 1987; Nagler et al, 1997). With cervicofacial actinomycosis involving ARONJ, onset can be insidious or slow forming. Actinomycosis initially presents as a soft tissue swelling that fails to resolve in the peri- and submandibular regions of the neck. Often, there is no pain reported by the patient, unless there is a secondary infection. The persistent swelling is firm, and the skin in the affected area is dark red to purple in color. With progression of the cervicofacial variant, the infection becomes fluctuant and does not follow the usual fascial planes of the head and neck (Schuster 1987). With chronic inflammation, the skin is perforated with suppuration of pus from draining orocutaneous fistulas (Figure 9). The pus from draining fistulas may contain yellow granules, known as “sulfur granules,” that are colonies of filamentous bacteria (Schuster 1987; Brooks et al, 2001; Russo 2010). With progression of infection, disease may extend to other tissues of the maxillofacial region, including the jaw bones and lymph nodes of the head and neck (Schuster 1987). Irrespective of anatomic site, actinomycosis is usually initiated by mechanical trauma that allows these endogenous microbial pathogens entry into the mucosa barrier and ultimately, the jaw bones.

MANAGEMENT STRATEGIES FOR PATIENTS PRESCRIBED ANTIRESORPTIVE AGENTS OR DIAGNOSIED WITH OSTEONECROSIS OF THE JAWS

The objective of treatment is to cure the infection, prevent recurrence of the infection and to create a pain-free jaw for the patient. This can best be accomplished by creating a multidisciplinary team consisting of the patient’s dentist, an oral and maxillofacial surgeon, an infectious disease specialist and if needed, a microbiologist. It is the authors experience that the use of antimicrobial agents alone without surgical intervention fails in the majority of cases.
Based on the current literature and our clinical experience with both oral and intravenous ARONJ, we recommend the following: For the patient who is prescribed oral antiresorptive agents by their physician, no deviation in routine dental treatment is necessary. The dental clinician should always present the recommended treatment plan and all alternatives that may decrease the patient’s level of risk of developing ARONJ. In addition, a complete discussion of the benefits versus risks of dental treatment is recommended if any surgical procedure that involves the jawbones is treatment planned. All discussions should be completely documented in the patient’s chart that the patient acknowledged that such discussion occurred. Most important, informed consent must be obtained from each patient before initiating treatment. The following information should be presented to each patient during the consultation and examination visit:

1. There is a low risk of developing ONJ when taking antiresorptive agents. At best, estimates of such risk are approximately 0.1 % (Hellstein et al, 2011).

2. There are no predictable laboratory diagnostic methods to predict the level of risk of developing ARONJ prior to initiating procedures that involve the jawbones, such as the serum CTX test (Bagan et al, 2008; Lehrer et al, 2008, Lee & Suzuki, 2010).

3. It is not recommended to discontinue antiresorptive therapy prior to initiating invasive surgical procedures that involves the jawbones, referred to as a “drug holiday”. It is uncertain if there is any benefit to discontinue antiresorptive therapy when considering the risk of skeletal related events (SRE), such as hip and vertebral fractures, spinal cord compression and hypercalcemia of malignancy (Papapoulos & Cremers, 2007; Van den Wyngaert, et al, 2009; Lee & Suzuki, 2010; Nicolatou-Galitis, 2011; Wilde et al, 2011). It has been shown that orally administered antiresorptive agents used in the management of osteoporosis can reduce vertebral and non-vertebral fractures by 50%. Consultation with the patient’s physician is advised if there are any issues about initiating a drug holiday.

4. Patients with oral pathology, such as caries, periodontal disease, endodontic lesions and osseous pathology should be treatment planned. The benefits of antiresorptive therapy outweigh the risk of developing ARONJ for the patient taking oral antiresorptive agents.

5. Patients with oral pathology that extends beyond the dental clinicians level of surgical management and experience should be referred to the appropriate specialist, such as periapical pathology, odontogenic infections with sinus tracks, advanced periodontal disease that involves the cortical and medullary bone that could initiate ONJ.

Conservative Non-Surgical and Surgical Intervention

The management of ARONJ remains controversial as the exact pathophysiology remains unknown. To date, there is no consensus regarding the non-surgical and surgical management as how best to manage this disease (Marx et al, 2007; Bedogni et al, 2007; Magopoulous et al, 2007, Ruggiero et al, 2009; Hellstein et al, 2011). In addition, there are no prospective studies comparing the various surgical treatments of ARONJ.
Treatment of ARONJ is difficult and most management strategies depend on the stage of ARONJ (Table 3). Most recommendations do emphasize conservative, non-surgical management with antimicrobial therapy, oral antimicrobial rinses and analgesics to control pain. In some instances, minor localized surgical debridement of sinus tracts and devitalized bone and soft tissues are recommended for Stage 1 and Stage 2 (Cheng et al, 2005; Ruggiero et al, 2006; Lam et al, 2007; Weitzman et al, 2007; Ruggiero et al, 2009; Ruggiero et al, 2010). The goal is to improve or maintain the quality of patient life; management of pain; controlling the progression of osteonecrosis; managing complications of this dreaded disease; and controlling the progression of disease (Migliorati, et al, 2005; Ruggiero et al, 2006; Ruggiero, et al, 2006; Estilo et al, 2008; La Verde, 2008; Dimopoulos et al, 2009; Ripamonti et al, 2009 Dickinson, et al, 2009; Ruggiero et al, 2009; Moretti et al, 2011). But, conservative treatment does not always resolve the disease and its progression.

In cases of advanced ONJ or cases that have proven to be refractory to conservative treatment, a more surgical aggressive approach that includes surgical resection of all infected and necrotic bone is indicated to permit wound healing in the form of primary closure of soft tissues (Abu-Id et al, 2008; Pautke et al, 2009; Carlson & Basile, 2009; Stockmann et al, 2010; Curi et al, 2011; Wilde et al, 2011; Nase & Suzuki, 2006). The mainstay of surgical management involves debridement, sequestrectomy and in some instances, resection (Stage 3) for patients that are clinically symptomatic with evidence of necrotic bone sequestrae; pathologic fracture; and purulent drainage in the maxillofacial region or area of exposed bone. It must be emphasized that throughout the entire course of treatment, oral hygiene education and continued patient observation are important in preventing and controlling the progression of ARONJ.

Based on our surgical experience and that of others (Abu-Id et al, 2008; Carlson et al, 2009; O’Ryan et al, 2009; Scoletta et al, 2010; Stockmann et al, 2010; Curi et al, 2011; Pautke et al, 2011; Wilde et al, 2011), surgical intervention should be considered early in the course of management of the ARONJ. It has been demonstrated that conservative management in many advanced cases (Stage 2 and 3) results in only a 50% resolution defined as closure of the oral mucosa and remains refractory to conservative treatment (Hoff, et al, 2008; O’Ryan et al, 2009; Filleul, et al, 2010; Pautke et al, 2011). Surgical intervention may result in a more definitive treatment and resolution of ARONJ despite the fact that most published articles support non-surgical conservative management of ARONJ and recommend surgical intervention for only advanced stages, or when conservative treatment is refractory.

Delaying appropriate treatment in the form of surgical intervention may result in increased complications of bone and soft tissue, progressive spread of osteonecrosis, infection and pathologic fracture (Figure 10 A and B). In some instances, a delay in appropriate treatment could result in a partial loss of the jaw that will later require reconstructive surgery. Most important, the patient continues to experience a poor quality of life, remains debilitated and in pain. This is especially with the patient on intravenous antiresorptive agents for treatment of a malignant condition, as most of these patients experience more severe cases of ARONJ. Several authors has reported positive treatment outcomes in greater that 80 % of cases when surgical intervention was initiated (Wutz et al, 2008; Carlson & Basile, 2009; Markose et al, 2009; Stanton & Balasanian; 2009; Wilde et al, 2010; Williamson, 2010). Successful treatment outcome is considered when there is no longer any clinical signs and symptoms of the following: exposed bone; infection; purulent discharge; minimal to no pain and imaging studies such as plain radiography or CT scans that demonstrate healing of osseous tissues.
Antibiotic Therapy

It is the consensus that all patients with ARONJ should be placed on a course of antibiotic therapy ([Cheng et al, 2005; Marx et al, 2005; Marx et al, 2007; Migliorati, et al, 2005; Ruggiero et al, 2006; Ruggiero, et al, 2006; Estilo et al, 2008; La Verde, 2008; Dimopoulos et al, 2009; Ripamonti et al, 2009; Ruggiero et al, 2009; Dickinson, et al, 2009; Ruggiero et al, 2009; Moretti et al, 2011; Nase & Suzuki, 2006]. The ideal antimicrobial agent should have bactericidal activity against surface adhering, slow growing biofilm pathogens (Widmer et al, 1999; Costerton et al, 1999; Anderl et al, 2003). However, the optimal antimicrobial regimen and the duration remain incompletely defined. Most common microorganisms identified in hard and soft tissue specimens, such as actinomyces, eikenella and moraxella are sensitive to the penicillin class of antibiotics. Penicillin VK 500 mg four times per day is the recommended regimen. For the patient that is allergic to penicillin, zithromycin (Zithromax) 250 mg/day and doxycycline (Vibramycin) 100 mg twice per day are suitable alternatives. In addition, quinolones, such as ciprofloxacin 500 mg twice per day and levofloxacin (Levaquin) 500 mg/day are effective agents because of their bioavailability, antimicrobial activity and tolerability in patients with bone infections. All of these antibiotic regimens should be prescribed for a period of two or more weeks. Metronidazole (Flagyl) 500 mg/ three times per day may also be added to the above antibiotics for cases that have proven to be refractory to treatment. In aggressive cases of infection and maxillofacial cellulitis that may result in admission to the hospital, intravenous antibiotic therapy is indicated and may include ampicillin 1,000 mg with clavulonate 500 mg (Unasyn 1.5 GM, Pfizer, New York) every 6 hours.

As actinomyces is part of a biofilm community and is directly involved in the pathogenesis of ARONJ, it has been suggested that short duration and high doses of antibiotics may only temporarily weaken the biofilm community. This accepted standard high-dose antibiotic regimen may even permit the microbial community to regenerate and gain resistance to antibiotic therapy (Marshall & Marshall, 2004). This could be due to the bacteria’s slow or reduced growth rate in a biofilm community compared to free-floating planktonic surface bacteria, incomplete delivery of nutrient substrates, such as glucose and oxygen, inhibition of antimicrobial efficacy due to biofilm substances and poor penetration of antibiotics into the biofilm (Ceri et al, 1999; Donlan & Costerton, 2002; Anderl et al, 2003).

To avoid this paradoxical reaction of biofilm resistance with standard high doses of antibiotics, effectively targeting biofilms requires a specific long term, low dose regimen of antibiotics to destroy the biofilm community. Biofilms may be difficult to destroy because of protection from the host immune system and persisters, which are microbial cells that have survived the initial round of high dose antibiotic treatment (del Pozo & Patel, 2007). If not eradicated, persister cells allow the biofilm community to survive and propagate, while developing antibiotic resistance (Lewis, 2001; Lewis, 2007). Therefore, targeting and exposing biofilms with low doses of antibiotics for a longer time period has proven to be more effective compared to standard short term high dose antibiotic treatment (Fu et al, 2010; Lee et al, 2011).

There are no controlled trials evaluating the choice or duration of antibiotic therapy for actinomycosis (Schuster, 1987; Brooks et al, 2001; Naik & Russo, 2009). Current recommendations include both high dose and prolonged duration antibiotic therapy (Brooks et al, 2001; Hansen et al, 2007; Gomez-Font et

Since acquiring sufficient clinical experience (Lee et al, 2011) treating this specific type of bone pathology, we suggest a standard regimen of oral antibiotics for at least 3-6 months. This empirical recommendation is dependent on the initial size and response of the infection to antibiotic therapy. Our current treatment regimen is penicillin VK at a dose of 1 gram 3-4 times per day. If patients are under age 65, probenicid, 500 mg 3-4 times per day is added to decrease antibiotic renal clearance. For patients that are allergic to penicillin, an alternative pharmacologic regimen may include doxycycline 100 mg twice daily; erythromycin 500 mg or clindamycin 300 mg four times per day. If orocutaneous fistulas are present, we recommend extending antibiotic therapy until complete healing is observed.

**ADJUNCTIVE THERAPY IN ARONJ**

**Cellular Based Therapy**

Cellular based therapy, such as platelet rich plasma (PRP) may have some positive benefit in the management of ARONJ (Adornato et al, 2007; Curi et al, 2007; Lee et al, 2008; Curi et al, 2011). Platelet rich plasma is an autologous source of growth factors sequestered from the patient’s own blood. The platelets are concentrated by gradient density centrifugation from the blood. Cellular based technology produces high levels of human platelets that contain several different types of growth factors that can be applied to the surgical site to enhance hard and soft tissue wound healing (Marx et al, 1998, Marx 2001; Lee et al, 2008; Curi et al, 2011) in the ARONJ patient. Such biologic growth mediators have been shown to stimulate bone regeneration and soft tissue healing by promoting angiogenesis and increased VEGF levels.

Platelet rich plasma contains 4-6 times the normal level of growth factors compared with peripheral blood. Normal human platelet counts are in the range 150 000 u/L to 350 000 u/L. The average platelet count is in the range of 200 000 u/L. Specifically defined, PRP is a platelet concentration with a least 1,000,000 u/L in a 5 mL volume of plasma (Marx et al, 1998; Marx 2001). Activated platelets will release the contents of the alpha secretory granules that contain growth factors, such as PDGF, TGF-b, VEGF, EGF and insulin-like growth factor. These growth factors will recruit undifferentiated mesenchymal stem cells to the site of injury and stimulate wound healing and mitosis of these cells (Marx et al, 1998, Marx 2001; Barry & Murphy, 2004). Since 2006, PRP is part of our surgical protocol in the management of ARONJ and the results have been impressive (Figure 11 A and B) especially for cases that have proven to be refractory to both conservative and surgical treatment.
Teriparatide

Most recently, several reports have documented the positive effects of a drug called, teriparatide (Forteo, Eli Lily & Co; Indianapolis, IN) that resulted in resolution of ARONJ. Teriparatide is a synthetic peptide similar to human parathyroid hormone. It is administered subcutaneously on a daily basis can be prescribed over a 24 month period. Therapy with the medication promotes anabolic bone deposition. Subramanian et al (2011) believe that this anabolic drug actively promotes bone remodeling as it enhances osteoblastic function by inhibition of osteoblast apoptosis. In their hypothesis, they theorize that compromised osteoblastic function increases the susceptibility of patients to developing ARONJ. Treatment with teriparatide is also known to promote the expression of RANKL in preosteoblasts. This action enhances osteoclastic activity by osteoblasts by increasing crosstalk between the two cell types. An increase in the number of osteoclast from the hematopoietic system could possibly overcome the toxic effects of antiresorptive therapy on osteoclasts.

However, like antiresorptive agents, teriparatide is not without adverse side effects (Sikon & Batur, 2010). In addition to reports of postural hypotension, hypercalcemia, leg cramps and joint pain, osteosarcoma has been reported in rats and humans.

SPECIFIC DENTAL TREATMENT AND RECOMMENDATIONS

The following recommendations are based on the current guidelines proposed by the advisory committee of the American Dental Association Council on Scientific Affairs (Hellstein et al, 2011), published data and on our experience and that of our colleagues.

Restorative and Prosthetic Dental Procedures. There are no contraindications to performing routine dental procedures on the patient taking antiresorptive agents. The clinician must avoid using any dental devices that increase the risk of ulcerating or creating abrasions of the gingival or mucosa that could lead to exposed bone.

Endodontic Procedures. Routine endodontic procedures are not a contraindication for the patient on antiresorptive agents. The clinician must be careful not to instrument the canal of the tooth beyond the apex and out into the bone. There are no contraindications for surgical endodontic procedures. Primary soft tissue wound closure is advised, if possible. Use of prophylactic antibiotics and chlorhexidine oral rinses twice per day is recommended.

Periodontal Disease. Active periodontal disease should be treatment planned and managed appropriately. Patients prescribed antiresorptive agents are not a contraindication to non-surgical and surgical periodontal procedures. As stated previously, a complete discussion with the patient regarding the benefits versus risks of developing ARONJ, which includes verbal and written informed consent is mandatory. To our knowledge, there are no published studies in the literature that have discussed the risk of developing ARONJ after such procedures of guided tissue regeneration and bone grafting.
Implant Treatment. It is the authors’ opinion that the risk of developing ARONJ in the dental implant patient is low. It is advised that all clinicians discuss the overall success rates of dental implant treatment of the maxilla and mandible. We have observed no differences in the implant failure rate in both groups of patients. In a study by Fugazzatto et al (2007), no cases of post-operative ARONJ were observed in 61 implant patients. In this cohort of subjects, the average duration of antiresorptive therapy was 3.3 years. In a retrospective study by Grant and colleagues (2008), 468 dental implants were placed in 115 patients. The implant success rate was 99.6%. No reports of ARONJ occurred.

Oral and Maxillofacial Surgery. As stated previously, informed consent is mandatory. In addition to discussing the treatment plan, alternative options of treatment must be presented, which includes endodontic therapy, versus extraction of the tooth and use of fixed or removable partial dentures. If possible, extraction of teeth should be performed prior to initiation of antiresorptive therapy, especially for the patient diagnosed with a malignancy.

Conservative surgical technique is recommended. Primary soft tissue wound closure should be attempted, but is not absolute. It has been our experience that when primary wound closure is not possible, secondary intention by granulation of soft tissue has been observed that eventually resulted in closure of the wound and exposed bone.

To enhance wound closure and avoid post-operative infection and ARONJ, use of antibiotic coverage for about seven days after surgery is highly recommended. In addition, use of chlorhexidine oral rinses twice daily is recommended for a period of 4-6 weeks. In a study by Lodi et al (2010), use of prophylactic antibiotics and chlorhexidine oral rinses may reduce the risk of developing ARONJ after oral surgical procedures.

Orthodontic Procedures. For the patient taking antiresorptive agents, orthodontic treatment is not a contraindication. However, there have been reports of difficulty with tooth movement in patients on antiresorptive therapy. This could potentially become a concern for the adult enrolled in orthodontic treatment. In the United States, 20% of patients undergoing orthodontic treatment is an adult. Therefore, it is recommended that during the consultation procedure, the issue of inhibited tooth movement that could prolong treatment time should be presented.

Author Recommendations on Specific Issues of ARONJ

Predicting risk of developing ARONJ with serum bone markers, such as the C-terminal telopeptide (CTX) is not recommended. Several studies have questioned the validity of the CTX test in predicting the level of risk of developing ARONJ after oral surgical procedures (Bagan et al, 2008; Lehrer et al, 2008, Kunchur et al, 2009; Lee & Suzuki, 2010). The authors of this white paper conducted a study of 163 patients, in which 54 patients completed the CTX test prior to surgery. The results demonstrated that there was no correlation between the results of the CTX test and the ability to accurately predict the level of risk (low, medium, high) of developing ARONJ after oral surgery (Lee & Suzuki, 2010). Therefore, it is the opinion of the authors, and others, that the use of this serum bone marker in predicting the risk of developing ARONJ after surgical procedures involving the jaws is not recommended.
In position papers developed by most dental specialties, including the American Association of Oral and Maxillofacial Surgeons (2007; 2009), hard and soft tissue biopsy procedures are not routinely recommended. However, it is the authors’ opinion that identification of the microbial pathogens is of extreme importance for selection of the appropriate antibiotic regimen. Recently, there has been much interest and speculation that microbial pathogens, such as Actinomyces are directly involved in the pathogenesis of ARONJ and not just a free-floating planktonic organism that is routinely observed in histopathologic specimens (Kaplan et al, 2009; Naik & Russo, 2009; Lee et al, 2007; Sedghizadeh et al, 2008; Curi et al, 2011; Lee et al, 2011). As part of our specific protocol in managing the ARONJ patient, low dose and long-term oral antibiotic therapy is instituted when Actinomyces organisms have been identified in the soft or hard tissue biopsy specimen.

Routine biopsy should also be considered in every suspected case of ARONJ to rule-out occult malignancy. One of the authors of this white paper (CYSL) recently was involved in a case where a 90 year old Asian female with a negative history for malignancy was being treated for periodontal disease by her periodontist for three months (Figure 12). When the condition did not improve, the patient was referred for oral and maxillofacial surgery consultation with the clinical diagnosis of ARONJ due to long-term Alendronate therapy. Before instituting our surgical treatment protocol, a soft tissue biopsy procedure was performed that demonstrated lymphoma of the lingual gingival tissues (Figure 13 A and B). Therefore, we are of the opinion that biopsy is warranted to avoid a misdiagnosis of occult malignancy and to facilitate appropriate timely management.

Author Specific Management Protocol of the ARONJ Patient

In our specific management protocol for the ARONJ patient, treatment consists of routine hard or soft tissue biopsy; use of platelet rich plasma (PRP); surgical intervention that consists of debridement of sinus tracts, resection of non-vital hard and soft tissues of the jaws with or without sequestrectomy; and a prolonged course of oral antibiotic therapy. In cases that have proven difficult to effectively manage, especially the patient on the intravenous formulary hyperbaric oxygen (HBO) therapy may be considered. In a study consisting of 40 patients by Freiberger et al (2007) at Duke University Medical Center, 40 sessions of HBO therapy resulted in remission or improvement in 62.5 % of patients.

From past clinical experience, we have observed several cases of exposed jaw bone that did eventually heal without surgical intervention and cessation of bisphophonate therapy. As bisphophonates have a long half life, we do not have a set duration for a “drug holiday”. This is despite the fact that the AAOMS position paper recommends a 3 month drug holiday prior to treatment for patients taking the oral formulation of bisphosphonates for greater than three years (Ruggiero et al, 2009).

Conclusions. Many questions remain unanswered regarding the pathogenesis and pathophysiology of ARONJ. Clinical observations and the few studies available have provided some answers and form the basis of this white paper. There is no question that the benefits of timely recognition and appropriate management are immense. Information obtained from the scientific literature suggests that clinicians will continue to see more cases of ARONJ in their clinical practice. Therefore, acute attention to the information presented in this white paper, such as education for all stakeholders in the mechanisms of osteoporosis, ONJ and management strategies set forth in this paper cannot be over emphasized.
Lastly, this white paper does not represent the standard of care in managing the patient taking antiresorptive agents, or is diagnosed with ARONJ. Rather, the recommendations are based on the contemporary scientific literature, expert opinion, and the authors’ clinical experience. All of this information should be used to assist the dental clinician in their clinical professional judgment in managing the patient on antiresorptive agents or diagnosed with ARONJ.

REFERENCES


Wolcott RD, Kennedy JP, Dowd SE et al. Regular debridement is the main tool for maintaining a healthy wound bed in most chronic wounds. J Wound Care. 2009; 18_54-56.


Table 1. Parental Antiresorptive Agents

<table>
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<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Dosage</th>
<th>Indications</th>
</tr>
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<tbody>
<tr>
<td>Bonefos</td>
<td>Clodronate disodium</td>
<td>60 mg/mL; 1,500 mg single dose</td>
<td>Paget disease of bone; hypercalcemia of malignancy; multiple myeloma; parathyroid carcinoma</td>
</tr>
<tr>
<td>Boniva</td>
<td>Ibandronate sodium</td>
<td>3 mg/3 mL single dose</td>
<td>Treat osteoporosis in postmenopausal women</td>
</tr>
<tr>
<td>Prolia</td>
<td>Denosumab</td>
<td>60 mg SQ injection every 6 months</td>
<td>Treat postmenopausal women at high risk for SRE</td>
</tr>
<tr>
<td>Reclast (USA); Aclasta (Europe)</td>
<td>Zoledronic acid</td>
<td>5mg/100 mL infuse solution</td>
<td>Treat and prevent osteoporosis in postmenopausal women; increase BMD in men with osteoporosis; Paget disease of bone; treat and prevent glucocorticoid-induced osteoporosis</td>
</tr>
<tr>
<td>Zometa</td>
<td>Zoledronic acid</td>
<td>5mg/5mL every months</td>
<td>Hypercalcemia of malignancy; complications of MM and bone metastases.</td>
</tr>
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SRE: Skeletal related events; BMD: Bone mineral density; MM: Multiple myeloma; SQ: Subcutaneous
<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
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<th>Indications</th>
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<tr>
<td>Actonel</td>
<td>Risedronate sodium</td>
<td>5 mg/day; or 35 mg per week</td>
<td>Prevent and manage osteoporosis in postmenopausal women, and men with osteoporosis; Paget disease of bone</td>
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<td>Atelvia</td>
<td>Risedronate sodium</td>
<td>35mg tablet once weekly</td>
<td>Treatment of osteoporosis in postmenopausal women.</td>
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<td>Bonefos</td>
<td>Clodronate disodium</td>
<td>400mg capsules (Canada); 800mg capsules (Europe)</td>
<td>Prevent and manage osteoporosis in postmenopausal women; hypercalcemia and osteolysis from malignancy; reduce bone metastasis in primary breast cancer</td>
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<td>Boniva</td>
<td>Ibandronate sodium</td>
<td>2.5mg/day, or 150mg per month</td>
<td>Prevent and treat osteoporosis in postmenopausal women</td>
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<td>Didronel</td>
<td>Etidronate disodium</td>
<td>400mg tablet</td>
<td>Paget disease of bone; hypercalcemia of malignancy; heterotopic ossification</td>
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<td>Fosamax</td>
<td>Alendronate sodium</td>
<td>10mg/day, or 70mg per week</td>
<td>Prevent and treat osteoporosis in postmenopausal women; increase BMD in men with osteoporosis; Paget disease of bone</td>
</tr>
<tr>
<td>Fosamax Plus D</td>
<td>Alendronate sodium</td>
<td>70mg tablet; 70mg oral solution</td>
<td>Treat osteoporosis in post-menopausal women; increase BMD in men with osteoporosis.</td>
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<tr>
<td>Alendronate</td>
<td>Alendronate sodium</td>
<td>10mg/day, or 70mg per week</td>
<td>Prevent and treat osteoporosis in postmenopausal women; increase BMD in men with osteoporosis; Paget disease of bone</td>
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<td>Skelid</td>
<td>Tiludronate disodium</td>
<td>240 mg tablets</td>
<td>Paget disease of bone.</td>
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Staging of ARONJ:

<table>
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<th>Stage</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Non-specific clinical findings and symptoms. Sinus tracts may be present, but no exposed bone. Pain may be present, but no obvious etiology.</td>
<td>Conservative management. Use of analgesics and antibiotics</td>
</tr>
<tr>
<td>1</td>
<td>Asymptomatic. Exposed and necrotic bone. No evidence of infection.</td>
<td>Stage 0 treatment strategy, chlorhexidine mouth rinse, close monitoring of patient.</td>
</tr>
<tr>
<td>2</td>
<td>Exposed necrotic bone with clinical signs of infection, with or without purulent discharge.</td>
<td>Stage 1 treatment strategy, debridement of jaws, sequestrectomy.</td>
</tr>
<tr>
<td>3</td>
<td>Exposed necrotic bone. Clinical signs of infection, such as pain, extraoral fistula formation, oroantral/oral nasal communication, pathologic jaw fracture, osteolysis of jaw.</td>
<td>All of the above treatment, plus more aggressive surgical intervention, such as resection of jaw.</td>
</tr>
</tbody>
</table>

Staging and treatment strategy of ARONJ according to the position paper of the 2009 American Association of Oral and Maxillofacial Surgeons (AAOMS)

**Figure 1. Illustration of the Basic Multicellular Unit and Bone Remodeling**

Bone is remodeled by the actions of the bone resorbing osteoclasts and bone forming osteoblasts in basic multicellular units. Bone remodeling is essential for repair of bone microdamage and calcium homeostasis.
Figure 2. Illustration of Osteoclast Function

The multinucleated osteoclast attaches to the bone mineral matrix and secretes hydrogen ions that result in the dissolution of calcium ions from the bone surface. This results in the formation of resorption pits (Howship’s Lacuna). Further proteolysis occurs due to the actions of acidic enzymes produced from lysosomes and cathepsin K.

Figure 3. Illustration of the RANKL/RANK Signaling Pathway

RANKL is directly involved in osteoclast differentiation and action. Osteoprotegerin produced by osteoblasts acts as a natural decoy receptor for RANKL and inhibits its actions.
Antiresorptive therapy after several months results in osteoclasts apoptosis as well as a decrease in osteoclastogenesis. The result is a decrease in bone resorption. However, osteoblastogenesis and bone formation is also decreased due to the pharmacologic actions of antiresorptive medications.

Figure 5. Exposed osteonecrotic bone due to long-term antiresorptive therapy.

Figure 6. Pathologic fracture of left body of mandible represents Stage III of antiresorptive-associated osteonecrosis.
Figure 7. Widening of periodontal ligament space and osteosclerosis are radiographic signs of antiresorptive alveolar bone toxicity.

Figure 8. Colonies of bacterial pathogens identified as Actinomyces are established deep in the bone that could represent biofilms. Note the empty lacunae of osteonecrotic bone from antiresorptive therapy.
Figure 9. Stage III antiresorptive-associated osteonecrosis. Orocutaneous fistula with exposed bone and weeping purulent discharge on right cheek of patient from intravenous Zometa therapy to treat multiple myeloma.

Figure 10. Cone beam CT scan demonstrates exposed bone of pathologic fracture of right body of mandible that represents Stage III of antiresorptive-associated osteonecrosis.
Figure 11 A and B.

A. Photo on left demonstrates extensive debridement and localized resection of osteoncrotic bone of bilateral anterior mandible that resulted in large osseous defects.

B. Photo on right demonstrates post-operative result 6-weeks after extensive debridement and resection procedure with use of Platelet Rich Plasma (PRP) to enhance soft and hard tissue wound healing. Note the mature gingival and mucosa tissues that is bright pink in color consistent with wound healing observed with PRP therapy.

Figure 12. Intraoral photograph of soft tissue lesion in right mandible presumed to be due to long-term antiresorptive therapy in 90-year old Asian female without a significant medical history.
Figure 13 A and B.
Histopathology of patient in Figure 12 diagnosed as lymphoma.

A. Photo on left demonstrates infiltrate of atypical large lymphocytes consistent with lymphoma. Note mitotic figures present throughout microscopic specimen. Magnification 100x.

B. Photo on right demonstrates tumor cells that are immunopositive for B-cell marker CD20. Magnification 100x.