ADI GUIDANCE PAPER ON DENTAL MANAGEMENT OF PATIENTS RECEIVING ANTI-RESORPTIVE BONE THERAPY

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:
Rob Dyas David Offord Cemal Ucer Eddie Scher Tim Collard

ADI © 2012

Association of Dental Implantology UK

ADI GUIDELINES

DENTAL MANAGEMENT OF PATIENTS ON ANTI-RESORPTIVE THERAPY:

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 anti-resorptive 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).

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 incidence of ARONJ appears to be time and dose dependent and may be affected by patient specific co-morbidities.

Terminology: The osteonecrosis of the jaw associated with bisphosphanate use was previously referred to as osteonecrosis of the jaw (ONJ), bisphosphonate-related osteonecrosis of the jaw (BRONJ) and bisphosphonate–induced osteonecrosis of the jaw (BIONJ, Nase & Suzuki, 2006, “bisphosphonate-associated osteonecrosis”(BON) (Table 5: Am Dent Assoc., 2008; Migliorati et al., 2005). Recently the term “Anti-resorptive therapy induced osteonecrosis of the jaw” (ARONJ) was proposed but this terminology has not yet become universally established.

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 (Table 1) are used in the treatment of various malignant and benign metabolic conditions, 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) 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).

ADI © 2012

Antiresorptive agents decrease bone resorption and skeletal fracture by chemically binding to calcium hydroxyapatite in the mineral phase of bone remodeling, 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).

A regimen consisting of a once a year intravenous infusion of Zoledronic acid (Zometa, Novartis Pharmaceuticals) has been introduced as an alternative to the use of weekly oral anti-resorptive therapy (Black et al, 2007). 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). Use of annual infusion of bisphosphonate medication must however, be carefully questioned as some patients may not associate this as part of their drug history.

Pathogenesis of Anti-resorptive Agent-Induced Osteonecrosis of the Jaw (ARONJ)
ARONJ appears to be multifactorial, as several hypotheses have been presented in the literature to explain its pathogenesis. 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 el 2011).

Moreover, there is emerging evidence that ARONJ could be, at least, in part due to infections arising from bacteria from intraoral plaque and the biofilm.

The most common entry site of the bacteria to the jaw bones is the alveolus during extraction of teeth (Marx et al, 2005; Marx et al, 2007).

MANAGEMENT OF THE DENTAL PATIENT:

The following recommendations have been condensed from 2012 ADI White paper by Professors Suzuki and Lee to assist the clinician in their professional judgment in managing dental patients on anti-resorptive therapy. The information and advice contained in this guide is based on peer-reviewed case reports and expert opinion, as strong prospective clinical data to guide decision making is currently scarce. Clinicians are strongly advised to keep up to date on the subject by periodically appraising the emerging new evidence.

A) Patients On Orally Administered Anti-Resorptive Medication:

- For patients who are on oral antiresorptive agents prescribed by a medical practitioner, no deviation in dental treatment is necessary.
- The dental clinician should always discuss with the patient the recommended treatment plan and all other alternatives that may decrease the patient's level of risk of developing ARONJ.

ADI © 2012

- In addition, a complete disclosure of the benefits versus risks of the proposed dental treatment is recommended if any oral surgical procedure is planned. This should be completely documented in the patient's records which the patient should acknowledge in writing.

- Written informed consent with full disclosure of potential risks must be obtained from each patient before initiating treatment. The following information should be presented to each patient (preferably in writing) during the consultation and examination visit.

1. There is a low risk (approximately 0.1%) of developing ONJ when taking orally administered antiresorptive agents (Hellstein et al, 2011).

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

3. It is not recommended to discontinue anti-resorptive therapy prior to initiating surgical procedures that involves the jawbones, referred to as a "drug holiday". The benefits of antiresorptive therapy outweigh the risk of developing ARONJ for the patient taking oral antiresorptive agents. Consultation with the patient's medical practitioner is essential if there are any issues about discontinuing anti-resorptive therapy.

4. Patients with oral pathology, such as dental caries, periodontal disease, endodontic lesions and osseous pathology are not a contraindication to treatment.

5. Oral pathology that extends beyond the dentist's level of management and experience should be referred to an appropriate specialist. Examples include periapical pathology, odontogenic infections, and advanced periodontal disease that involves the cortical and medullary bone that could initiate ARONJ.

6. All patients should rinse for one minute using a 0.2% chlorohexidine aqueous oral solution prior to dental treatment and to continue rinsing twice daily for seven days after treatment.

7. All patients should take systemic antibiotics (see White Paper) prior to any dental procedure which may involve trauma to the soft and hard tissues, e.g. extractions, implant placement, bone grafting and deep periodontal debridement or surgery.

8. Patients on anti-resorptive therapy should be encouraged to continue dental assessment and periodontal maintenance. The importance of ensuring a high standard of oral hygiene should be emphasized to reduce the need for possible future dental surgical intervention. Patients who smoke should also be encouraged to discontinue this social habit.

ADI © 2012

Association of Dental Implantology UK

SPECIFIC DENTAL TREATMENT OF PATIENTS RECEIVING ANTI-RESORPTIVE MEDICATION:

(based on American Dental Association Council on Scientific Affairs (Hellstein et al, 2011))

Restorative and Prosthetic Dental Procedures. There are no contraindications to performing routine restorative dental procedures in patients prescribed orally administered antiresorptive agents. It is advised that the patient avoid using any prostheses that increase the risk of developing ulcerations of the gingiva or mucosa that could lead to exposed bone.

Endodontic Procedures. Routine endodontic therapy is not a contraindication for the patient on orally administered antiresorptive agents. The clinician must be careful not to instrument beyond the apex of the tooth and out into the bone. There are no contraindications for surgical endodontic procedures. Primary soft tissue wound closure is recommended, if possible. Use of prophylactic antibiotics and 0.2% chlorhexidine oral rinses twice per day is recommended for a period of seven days after the procedure.

Periodontal Disease. Active periodontal disease should be treatment planned and managed appropriately. Patients on orally administered antiresorptive agents are not a contraindication to non-surgical and surgical periodontal procedures.

Implant Treatment. The risk of developing ARONJ in the dental implant patient is low. No differences in the implant failure rate have been demonstrated for patients on anti-resorptive treatment when compared with the normal patient population. Bone grafting/ augmentation procedures are not contraindicated in patients prescribed antiresorptive medications. However, dental patients may be at increased risk for ARONJ when “extensive implant placement or guided bone regeneration is necessary to augment deficient alveolar ridges prior to implant placement” (ADA Council on Scientific Affairs, 2008). In this context, presence of co-morbidities that may have a further impact on the risk of ARONJ must be carefully assessed and considered as part of the decision making process.

Oral and Maxillofacial Surgery. In addition to discussing the treatment plan, alternative options of treatment must be presented to the patient. It is recommended that extraction of teeth be performed prior to initiation of antiresorptive therapy, especially for the patient diagnosed with a malignancy that is scheduled to receive the intravenous form of antiresorptive agents. Conservative, atraumatic surgical technique is mandatory. Primary soft tissue wound closure should always be attempted, but is not absolute. Prophylactic use of antibiotic coverage for seven days after surgery is highly recommended. In addition, use of 0.2 % chlorhexidine oral rinses twice daily is also recommended for a period of 4-6 weeks (Lodi et al, 2010).

Orthodontic Procedures. Orthodontic treatment is not a contraindication for the patient on antiresorptive therapy. 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. Therefore, during the consultation procedure the issue of inhibited tooth movement that could prolong treatment time should be discussed.

ADI © 2012

Medical Co-morbidities

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 Co-morbidities

Dental conditions (Ruggiero et al 2004; Marx et al, 2005; Marx et al 2007) that increase the risk of developing ARONJ include the following: periodontal disease, dental decay, intraosseous infections of the jaw, failed endodontic treatment, tooth extractions, tori removal and pressure necrosis from removable partial dentures. Dentoalveolar surgery increases the risk of developing ARONJ, and include the following: extraction of teeth, dental implant surgery, bone graft surgery, sinus elevation procedures, periapical surgery and periodontal surgery.

B) Patients on Intravenously Administered Anti-Resorptive Medication:

- Extreme caution is required when managing dental patients on the intravenous (IV) formulary of anti-resorptive therapy. The incidence of ARONJ for patients taking the IV form is estimated at 2% to 18 % (Bamias et al, 2005; Wang et al, 2007). It should also be noted that the incidence of ARONJ appears to be time and dose dependent.
- No definitive standard of care, as well as no definitive consensus guidelines have been established for ARONJ (Marx et al, 2007; Ruggiero et al, 2009; Hellstein et al, 2011).
- Patients on IV anti-resorptive therapy pose the highest risk of developing ARONJ. Therefore, all elective oral surgical treatment should be deferred. If treatment is highly indicated, this should be undertaken in conjunction with a multidisciplinary team that may consist of an oral and maxillofacial surgeon; a periodontist; a prosthodontist and a microbiologist, when necessary, who are experienced in management of ARONJ.
- Currently there is lack of data on the risk of ARONJ associated with annual infusion of bisphosphonates.

ADI © 2012

Table 1. Parental Antiresorptive Agents

Brand Name	Generic Name	Dosage	Indications
Bonefos	Clodronate disodium	60 mg/mL; 1,500 mg single dose	Paget disease of bone; hypercalcemia of malignancy; multiple myeloma; parathyroid carcinoma
Boniva	Ibandronate sodium	3 mg/3 mL single dose	Treat osteoporosis in postmenopausal women
Prolia	Denosumab	60 mg SQ injection every 6 months	Treat postmenopausal women at high risk for SRE
Reclast (USA); Aclasta (Europe)	Zoledronic acid	5mg/100 mL infuse solution	Treat and prevent osteoporosis in postmenopausal women; increase BMD in men with osteoporosis; Paget disease of bone; treat and prevent glucocorticoid-induced osteoporosis
Zometa	Zoledronic acid	5mg/5mL every months	Hypercalcemia of malignancy; complications of MM and bone metastases.

SRE: Skeletal related events; BMD: Bone mineral density; MM: Multiple myeloma; SQ: Subcutaneous

ADI © 2012

Table 2. Oral Antiresorptive Agents

Brand Name	Generic Name	Dosage	Indications
Actonel	Risedronate sodium	5 mg/day; or 35 mg per week	Prevent and manage osteoporosis in postmenopausal women, and men with osteoporosis; Paget disease of bone
Atelvia	Risedronate sodium	35mg tablet once weekly	Treatment of osteoporosis in post-menopausal women.
Bonefos	Clodronate disodium	400mg capsules (Canada); 800mg capsules (Europe)	Prevent and manage osteoporosis in postmenopausal women; hypercalcemia and osteolysis from malignancy; reduce bone metastasis in primary breast cancer
Boniva	Ibandronate sodium	2.5mg/day, or 150mg per month	Prevent and treat osteoporosis in postmenopausal women
Didronel	Etidronate disodium	400mg tablet	Paget disease of bone; hypercalcemia of malignancy; heterotopic ossification
Fosamax	Alendronate sodium	10mg/day, or 70mg per week	Prevent and treat osteoporosis in postmenopausal women; increase BMD in men with osteoporosis; Paget disease of bone
Fosamax Plus D	Alendronate sodium	70mg tablet; 70mg oral solution	Treat osteoporosis in post-menopausal women; increase BMD in men with osteoporosis.
Alendronate	Alendronate sodium	10mg/day, or 70mg per week	Prevent and treat osteoporosis in postmenopausal women; increase BMD in men with osteoporosis; Paget disease of bone.
Skelid	Tiludronate disodium	240 mg tablets	Paget disease of bone.

ADI © 2012