Dental management of patients receiving antiresorptive therapy

Jon Suzuki, Eddie Scher, Cemal Ucer, and Cameron Lee present the updated ADI guidance on bisphosphonates in full.

Introduction
Bisphosphonates belong to a class of drugs referred to as antiresorptive 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 antiresorptive therapy has been implicated in the pathoetiology 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 2012, in view of continuous new scientific clinical research findings, he and Professor Cameron YS Lee were invited to update that information.

This was presented in their new paper, the ADI White Paper on Antiresorptive Therapy and Osteonecrosis of the Jaws (ARONJ) for the Dental Practitioner, from which the ADI Review Group produced two short guideline documents: Dental Management of Patients Receiving Antiresorptive Treatment and The Diagnosis and Management of Patients with ARONJ.

While it is highly recommended that clinicians read the full text of the white paper to gain a complete understanding of the disease, the summaries that follow aim to help the decision-making process when managing dental patients on antiresorptive therapies. These guidelines replace the previous ADI guidance published in 2009.

Cemal Ucer
ADI President

PART ONE: Dental management of patients on antiresorptive therapy

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.

Aims and objectives
The aim of this article is to present the most up to date guidance for treating patients receiving antiresorptive therapies.

Readers will:
• Learn the process of bone turnover in the healthy and compromised human jaw
• See how the effect of antiresorptive therapies on this process can hinder dental implant treatment
• Understand the different risk between oral and intravenous administration of these therapies

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Patients on orally-administered antiresorptive medication

No deviation in dental treatment is necessary for patients who are on oral antiresorptive agents prescribed by a medical practitioner.

The dental clinician should always discuss the recommended treatment plan with the patient, and all other alternatives that may decrease the patient’s level of risk of developing ARONJ.

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 (eg, 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. Discontinuing antiresorptive therapy prior to initiating surgical procedures that involves the jawbones – referred to as a ‘drug holiday’ – is not recommended. 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 recommended if there are any issues about discontinuing antiresorptive 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 ONJ.

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

7. All patients should take systemic
antiresorptive agents. Patients prescribed orally-administered routine restorative dental procedures in There are no contraindications to performing procedures Restorative and prosthetic dental antiresorptive medication of patients on orally-administered Specific dental treatment of patients on orally-administered antiresorptive medication

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 antibiotics (see White Paper) prior to any dental procedure that may involve trauma to the soft and hard tissues, such as extractions, implant placement, bone grafting and deep periodontal debridement or surgery.

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

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.

The 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 antiresorptive treatment when compared with the normal patient population. Bone graft augmentation is not a contraindication for the patient prescribed antiresorptive medications.

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 patient diagnosed with a malignancy that is scheduled to receive the intravenous form of

### TABLE 1: PARENTAL ANTIRESORPTIVE AGENTS

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name</th>
<th>Dosage</th>
<th>Indications</th>
</tr>
</thead>
<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 IV</td>
<td>Ibandronate sodium</td>
<td>3 mg/3mL single dose</td>
<td>Treat osteoporosis in postmenopausal women</td>
</tr>
<tr>
<td>Prolia</td>
<td>Denosumab</td>
<td>60mg SQ injection every six 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>5 mg/100mL infusion 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 three months</td>
<td>Hypercalcemia of malignancy; complications of MM and bone metastases</td>
</tr>
</tbody>
</table>

### TABLE 2: ORAL ANTIRESORPTIVE AGENTS

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name</th>
<th>Dosage</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actonel</td>
<td>Risedronate sodium</td>
<td>5mg/day; or 35mg per week</td>
<td>Prevent and manage osteoporosis in postmenopausal women, and men with osteoporosis; Paget disease of bone</td>
</tr>
<tr>
<td>Atelvia</td>
<td>Risedronate sodium</td>
<td>35mg tablet once weekly.</td>
<td>Treatment of osteoporosis in post-menopausal women.</td>
</tr>
<tr>
<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 osteolyisis from malignancy; reduce bone metastasis in primary breast cancer</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Didronel</td>
<td>Etidronate disodium</td>
<td>400mg tablet</td>
<td>Paget disease of bone; hypercalcemia of malignancy; heterotopic ossification</td>
</tr>
<tr>
<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/ cholecalciferol</td>
<td>70mg tablet; 70mg oral solution</td>
<td>Treat osteoporosis in post-menopausal women; increase BMD in men with osteoporosis</td>
</tr>
<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>
</tr>
<tr>
<td>Skelid</td>
<td>Tiludronate disodium</td>
<td>240mg tablets</td>
<td>Paget disease of bone</td>
</tr>
</tbody>
</table>

SRE: Skeletal related events  BMD: Bone mineral density  MM: Multiple myeloma  SQ: Subcutaneous
A 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 four to six 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.

**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 includes the following: extraction of teeth, dental implant surgery, bone graft surgery, sinus elevation procedures, periapical surgery and periodontal surgery.

**Patients on intravenously-administered antiresorptive medication**

Extreme caution is required when managing dental patients on the intravenous (IV) formulary of antiresorptive 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). The incidence of ARONJ appears to be time- and dose-dependent.

No definitive standard of care, nor any definitive consensus guidelines have been established for ARONJ (Marx et al, 2007; Ruggiero et al, 2009; Hellstein et al, 2011).

Patients on IV antiresorptive 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, when necessary, a microbiologist who is experienced in the management of ARONJ.
PART TWO: Management strategies for patients diagnosed with antiresorptive 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. The use of antimicrobial agents alone without surgical intervention appear not to be effective in the majority of ARONJ cases.

Conservative surgical and non-surgical intervention

The management of ARONJ remains controversial as the exact pathophysiology remains unknown. In absence of specific prospective studies, there is no consensus on how best to manage ARONJ and when non-surgical or surgical management may be indicated (Marx et al, 2007, Bedogni et al, 2007, Magopoulous et al, 2007, Ruggiero et al, 2009, Hellstein et al, 2011).

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 & Obied, 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 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.

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 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. Early specific dental radiological signs may include:
• Sclerosis of the lamina dura around the roots of the teeth
• Widening of the periodontal ligament space.

In advanced cases of ARONJ, osteolysis, sequestration of bone, and pathologic fracture have all been observed.

Diagnosis

The diagnosis of ARONJ is based on the following characteristics:
a) A history of antiresorptive therapy;
b) Exposed jaw bone for eight weeks or greater;
c) No history of radiation therapy where the jaw bones were in the field of radiation.

Management

Conservative non-surgical management

Treatment of ARONJ is difficult, and strategies for its management depend on its staging.

Conservative non-surgical management, using antimicrobial therapy, oral antimicrobial rinses, and analgesics to control pain is usually advised as an initial line of treatment. In some instances, minor localised surgical debridement of sinus tracts and devitalised bone and soft tissues is 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 (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).

It has been demonstrated that conservative management in many advanced cases (Stage 2 and 3) results in only a 50% resolution and surgical intervention may result in a more definitive treatment and resolution of ARONJ.

Surgical management

In cases of advanced ONJ or cases that have proven to be refractory to conservative treatment, a more surgically aggressive approach is indicated, which includes surgical resection of all infected and necrotic bone to permit wound healing in the form of primary closure of soft tissues (Abu-Id et al, 2008; Pauluk et al, 2009; Carlson & Basile, 2009; Stockmann et al, 2010; Curi et al, 2011; Wilde et al, 2011).

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 maxillolfacial region or area of exposed bone. It must be emphasised that high levels of plaque control are essential in preventing and controlling the progression of ARONJ.

Surgical intervention should be considered early in the course of management of the ARONJ.

Delaying surgical intervention may result in increased bone and soft tissue complications, progressive spread of osteonecrosis, infection and pathologic fractures. 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.
Treatment objectives
A successful treatment outcome is considered when there are no longer any clinical signs and symptoms of exposed bone, infection, and purulent discharge; minimal to no pain; and when imaging studies such as plain radiography or CT scans demonstrate healing of osseous tissues.

Antibiotic therapy
There are no controlled trials evaluating the choice or duration of antibiotic therapy (Schuster 1987; Brooks et al 2001; Naik and Russo 2009).


The ‘standard’ recommendation is for two to six weeks of high-dose daily intravenous antibiotic therapy followed by oral therapy for three to 12 months depending on the size and response of jaw osteonecrosis (Brooks et al, 2001; Naik & Russo, 2009).

There is a strong 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).

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, etkenella, and moraxella, are sensitive to the penicillin class of antibiotics.

Penicillin VK 500mg four times per day is the recommended regimen. For the patient that is allergic to penicillin, zithromycin (Zithromax) 250mg per 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 per 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) 500mg 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 500mg (Unasyn 1.5 GM, Pfizer, New York) every six hours.

When actinomyces organisms have been identified in the soft or hard tissue biopsy specimen, low dose and long-term oral antibiotic therapy is recommended (Lee & Suzuki, 2012).

Finally, routine biopsy should also be considered in every suspected case of ARONJ to rule out occult malignancy. IDT