The relationship between osteonecrosis of the jaw and bisphosphonate therapy was initially established more than 10 years ago. Since that time, our understanding of this disease process has evolved as the direct result of clinical, basic science, and animal research initiatives. Medication-related osteonecrosis of the jaw (MRONJ) is a well-known entity now known to be associated with various antiresorptive therapies and recently with antiangiogenic medications. This article reviews the recently modified diagnostic criteria for MRONJ with a focus on the clinical, histopathologic, and imaging characteristics of this disease process.

Osteonecrosis of the jaw (ONJ) is a multifactorial disease in patients with primary or metastatic bone malignancy or osteoporosis undergoing systemic antiresorptive therapy, where pathophysiology has not yet been fully determined. The staging of ONJ is based on severity of symptoms and extent of clinical and radiographic findings. Treatment strategies range from conservative local wound care to aggressive resective surgery of all necrotic bone. The first ONJ cases were reported in 2003 and 2004, and although significant progress has been made in our understanding of the disease, much more work needs to be done to completely explain its pathophysiology.

In the late 1990s and the early 2000s, bisphosphonates had become the clinical pillar of excellence for treating metabolic bone disease, and thus their connection with osteonecrosis of the jaw (ONJ) caused significant concern. Over the past decade, progress has been made in understanding what is now referred to as medication-related ONJ (MRONJ), because of its connections to agents other than bisphosphonates, although in many respects the progress has been slow. This review highlights the key basic science and translational (animal) studies in the area of MRONJ and suggests areas of focus as the field moves into the next decade.

This article provides the best current frequency estimate of medication-related osteonecrosis of the jaws (MRONJ) and identifies factors associated with the risk of developing osteonecrosis of the jaw (ONJ) among patients exposed to relevant...
medications (ie, antiresorptive or antiangiogenic agents). MRONJ is a rare but serious complication of cancer treatment or osteoporosis management. This review confirms that antiresorptive medications such as oral or intravenous bisphosphonates and denosumab are the most common risk factors for developing ONJ. The risk of MRONJ is greater in patients with cancer than in those receiving antiresorptive treatments for osteoporosis by a factor of 10.

Management of Medication-Related Osteonecrosis of the Jaw 517
William Bradford Williams and Felice O’Ryan

Medication-related osteonecrosis of the jaw (MRONJ) primarily involves patients receiving intravenous bisphosphonates for treatment of skeletal-related malignancies, oral bisphosphonates, and denosumab. There is no consensus regarding the clinical management of MRONJ. Successful treatment may be that which results in a cure, with complete mucosal coverage and elimination of disease, or that which improves the quality of life without a cure (palliation). Helping patients to understand the chronicity and potential progression of the disease is essential to a satisfactory outcome. This review aims to share our treatment approach to patients with MRONJ. Treatment can be divided into medical and surgical therapies.

Preventive Strategies for Patients at Risk of Medication-related Osteonecrosis of the Jaw 527
Reginald H. Goodday

For patients at risk of osteonecrosis of the jaw (ONJ), information can be provided by the pharmaceutical manufacturer, pharmacist, prescribing physician, dentist, and oral and maxillofacial surgeon. Prevention strategies to reduce the incidence of osteonecrosis should be applied as soon as it is determined that a patient will be placed on antiresorptive medication. Proper screening involves a comprehensive oral examination with radiographs followed by oral hygiene instruction and necessary dental treatment; surgical techniques and adjunctive therapies that favor optimum healing of bone and soft tissue decrease the risk of ONJ. No dental procedures are absolutely contraindicated.

Pharmacogenetics of Bisphosphonate-associated Osteonecrosis of the Jaw 537
P.L. Fung, P. Nicoletti, Y. Shen, S. Porter, and S. Fedele

Osteonecrosis of the jaws (ONJ) is a potentially severe disorder that develops in a subgroup of individuals who have used bisphosphonate (BP) medications. Several clinical risk factors have been associated with the risk of ONJ development, but evidence is limited and in most instances ONJ remains an unpredictable adverse drug reaction. Interindividual genetic variability can contribute to explaining ONJ development in a subset of BP users, and the discovery of relevant associated gene variants could lead to the identification of individuals at higher risk. No genetic variant has been found to be robustly associated with susceptibility to ONJ.

The Role of Antiangiogenic Therapy in the Development of Osteonecrosis of the Jaw 547
John E. Fantasia

There is an increasing use of established and newer medications that have antiangiogenic properties. Inhibition of angiogenesis likely has either a primary or secondary role in the development of osteonecrosis of the jaw (ONJ). These medications are
being used in the treatment of various cancers and in the treatment of several non-oncologic conditions. Antiangiogenic medications, when used in combination with antiresorptive medications such as nitrogen-containing bisphosphonates or denosumab, seem to increase the likelihood of osteonecrosis of the jaw. This review highlights the role of inhibitors of angiogenesis and their role in the development of osteonecrosis of the jaws.

**Antiresorptive Therapies for Osteoporosis** 555

Stuart Weinerman and Gianina L. Usera

Osteoporosis is a disease of low bone density, translating to increased fragility and risk for fracture. It is a significant public health problem that is widely undertreated, despite the many options of treatment available. Among these, the most effective are the antiresorptive medications, such as bisphosphonates. There is an abundance of evidence about the efficacy and safety profile of these medications. However, there is mounting evidence that, after 10 years on treatment with a bisphosphonate, patients are at a higher risk of developing some of the serious side effects of atypical femur fractures and osteonecrosis of the jaw.

**Antiresorptive Therapies for the Treatment of Malignant Osteolytic Bone Disease** 561

Bhoomi Mehrotra

Osteolytic bone disease contributes to morbidity and mortality. Antiresorptive therapies reduce the morbidity of metastatic bone disease and alter the natural progression of malignant bone pathophysiology. Several trials showed improvement in quality of life, delay of skeletal-related events, and improvement in bone pain with these agents. Evolving data suggest a role of improvement in morbidity related to other cancer therapies that have potential side effects. Early indication shows they may alter survival in a subset of patients. This article reviews data confirming the efficacy of antiresorptive agents and discusses preliminary data on preventative therapy.

**Indications and Outcomes of Osteoporosis and Bone Modulation Therapies** 567

Stuart Weinerman and Gianina L. Usera

Osteoporosis is a disorder of bone strength that leads to an increased risk of fractures. It is most commonly seen in patients aged 50 or older, although it can sometimes occur at a younger age if there are other comorbidities present. The most common cause of osteoporosis by far is menopause, although it also occurs in men, usually with higher morbidity rates than those seen in women. There are many treatment options available, such as anabolics and antiresorptives, with many more currently being developed. However, osteoporosis remains grossly unrecognized and untreated, resulting in a significant strain on the American economy.

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