



Mel Mupparapu

Medication-related osteonecrosis of the jaw (MRONJ): Bisphosphonates, antiresorptives, and antiangiogenic agents. What next?

From a recent recommendation of the special committee on medication-related osteonecrosis of the jaws of the American Association of Oral and Maxillofacial Surgeons (AAOMS)¹ came the name change: bisphosphonate-related osteonecrosis of the jaw (BRONJ) or anti-resorptive agent-related osteonecrosis of the jaw (ARONJ) to medication-related osteonecrosis of the jaw (MRONJ). Various drug groups that promote the osteonecrosis of the jaw include intravenous bisphosphonates, oral bisphosphonates, RANK ligand inhibitors, and angiogenesis inhibitors. There is a variety of local factors that influence the effect of these medications; often for the worse. These factors include dentoalveolar surgery, anatomical factors, and concomitant oral disease, as well as less confirmed risk factors such as sex, age, steroid therapy, smoking, and anemia in cancer patients.²

It has been noted that the prevalence of MRONJ is more in cancer patients receiving antiresorptive therapies compared to those receiving treatment for osteoporosis alone. The common oral bisphosphonates used¹ are alendronate sodium, risedronate sodium, and ibandronate sodium. The common intravenous bisphosphonates used are ibandronate, pamidronate disodium, and zoledronate. Denosumab (Xgeva[®] and Prolia[®]) is a new group of medication that is essentially a humanized monoclonal antibody administered subcutaneously. Other antiangiogenic agents include sunitinib and sorafenib (tyrosine kinase inhibitors); bevacizumab, another humanized monoclonal antibody; and last but not the least, sirolimus, a mammalian target of rapamycin pathway that is given to patients who are at risk of developing organ rejection secondary to renal transplant.¹

Currently, there are four distinct clinical stages of MRONJ. Stage 0 was added in the 2009 AAOMS guidelines³ as a new entity where there are distinct radiographic signs suggestive of ONJ but no other clinical signs confirm the presence of MRONJ. When someone is treated with bisphosphonates or other antiresorptive medications but shows no clinical or radiographic signs of ONJ, they are considered to be in an “at risk” category. In stage 1, there is evidence of exposed bone with possible sinuses that probe to bone. The patient does not exhibit any sign of infection in stage 1. In stages 2 and 3, there is definitive presence of either sinuses or fistulae and, in addition, formation of sequestrum that might necessitate surgical intervention.

The complexity of diagnosis and treatment has multiplied with the increase in the types of medication that affect the normal bone metabolism. Bisphosphonates, antiresorptive agents, and antiangiogenesis agents are essential in order to reduce the incidence of vertebral and non-vertebral fractures, and to prevent the skeletal complications associated with malignancy such as bone pain, pathologic fracture, spinal cord compression, hypercalcemia, and the need for radiation therapy.⁴ The benefits of using these agents clearly outweigh the risks based on what we know so far. The incidence of MRONJ is negligible in patients receiving treatment for osteoporosis (1 in 10,000),⁴ hence dentists should consider these patients no different than others who never took the antiresorptive medication and routine dental care should be offered. Patients at slightly increased risk of MRONJ, for instance cancer patients who were on either bisphosphonates or denosumab (the annual risk being 1 in 1,004), should be



closely monitored and receive dental check-ups with increased frequency. All other patients who receive high doses of antiresorptive medication, for instance patients with multiple myeloma, should be assessed medically before any dental treatment. These recommendations⁴ are supported by the British Association of Oral Surgeons and the Faculty of Dental Surgery of the Royal College of Surgeons of England, London.

For the general dentist, the strategies are quite simple for the prevention of MRONJ: identify, observe or intervene, and follow-up. The key is the identification of the patients in stage 0. Dental treatment in this group needs special attention as the chances of transformation to stage 1 or higher is more based on the risk factors for these patients. Routine dental care can still be given. If the patients are already progressed to stages 1 or beyond, then halting the infection is the main goal followed by removal of the necrotic bone as atraumatically as possible. The dental treatment can be provided with utmost care.

Recent research has suggested an increase in the duration of drug holiday for better prognosis after sur-

gical debridement in stages 1 to 3.⁵ We are beginning to understand the pathophysiology of the complex bone remodeling processes in patients with osteoporosis or metastatic malignancies. We may have just seen the tip of the iceberg. A more important question, then, would be “What next?”

Mel Mupparapu
Scientific Associate Editor

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