Doi: 10.32481/djph.2023.04.009

Update on Medication Related Osteonecrosis of the Jaws

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Introduction

Osteonecrosis of the jaws (ONJ) has emerged as a clinical condition with case reports appearing at least 20 years ago. Early cases were discovered in patients receiving treatment for primary and metastatic bone neoplasia as well as in those being treated for non-neoplastic conditions including osteoporosis and metabolic bone disease processes. Many of the reported cases involved patients treated with bisphosphonates and the term Bisphosphonate Related Osteonecrosis of the Jaws (BRONJ). Other terms later evolved including Antiresorptive agent Related Osteonecrosis of the Jaws (ARONJ) and more recently Medication Related Osteonecrosis of the Jaws (MRONJ). Patients in need of these medications receive much needed, highly effective treatment of primary and metastatic bone malignancies and osteoporosis, including improvement in survival as well as immeasurable improvements in quality of life. However rare, osteonecrosis—depending upon the severity—may have negative impacts upon quality of life for some.

Clinical Features and Stages

Osteonecrosis of the jaws was first documented in case reports in the scientific literature dating back to 2003 and 2004. Since then the clinical entity has been studied extensively, but there remains much to be learned about the pathophysiology, and evidence-based treatment is still to be determined. At best, the etiology of the process is thought to be multifactorial. There are several hypotheses regarding the etiology of MRONJ, including bone remodeling inhibition, inflammation and infection, angiogenesis inhibition and soft tissue toxicity.[1] Although much study has been devoted to role of antiresorptive agents in development of MRONJ, steroids, chemotherapy agents and compromises of the immune system are also associated with the process.[2,3]

The American Association of Oral and Maxillofacial Surgeons has convened panels of experts in the specialty that developed a position paper in 2007, with revisions in 2009, 2014 and most recently in 2020. The definition of MRONJ has remained constant since the first position paper and requires the following three criteria based on history and clinical examination:

1. Current or past treatment with antiresorptive therapy alone or in combination with immune modulators or antiangiogenic medications;
2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than eight weeks; and
3. No history of radiation therapy to the jaws or metastatic disease of the jaws.

To aid diagnosis and prioritization of treatment, the AAOMS panelists developed a staging system (1 through 3) described in the 2009 position paper. In the 2014 position paper, a stage 0 was added (analogous to stage 0 of femoral head avascular necrosis described in the orthopedic surgery literature). The stage 0 classification includes several non-specific symptoms without

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clinically evident bone exposure. Stages 1 through 3 remain unchanged in the most recent position paper.[2]

Stage 0 (Non-exposed bone)

- Odontalgia in absence of pulpal pathology
- Dull bone pain
- Sinus pain with possible antral mucosal or bone changes
- Trigeminal neurosensory alterations
- Intraoral or extraoral swelling
- Loosening of teeth in absence of periodontal pathology
- Alveolar bone resorption in absence of chronic periodontal disease
- Sclerotic trabecular changes or lack of new bone in extraction sites
- Osteosclerosis of alveolar bone and/or basilar bone
- Thickened lamina dura, sclerosis, obscuring of periodontal ligament space

Stage 1

Exposed necrotic bone or fistula that probes in asymptomatic patient with no evidence of inflammation or infection. May also have alveolar resorption, sclerotic trabecular patterns paucity of new bone in extraction sites and periodontal ligament space reductions

Stage 2

Exposed, necrotic bone or fistula that probes to bone with inflammation and or infection with symptoms. May also have radiographic signs described above.

Stage 3

Exposed, necrotic bone or fistula that probes to the bone with one or more of the following:

- Exposed, necrotic bone extending beyond alveolus to inferior border of mandible, antrum and zygoma (maxilla);
- Pathologic fracture;
- Extraoral fistulae;
- Oral antral/oral nasal communication; and/or
- Osteolysis to inferior border of mandible or maxillary sinus floor.

The bisphosphonates include orally administered alendronate risedronate and parenteral agents zoledronic acid and ibandronate. These agents directly inhibit osteoclast activity through several different mechanisms. They remain within bone for many years and have half-lives approaching ten years. The Receptor activator of nuclear factor Kappa-B ligand (RANK-L) denosumab is an antibody against RANK ligand which inhibits bone resorption through osteoclast inhibition.[1] In contrast to the bisphosphonates, RANK-L inhibitors do not bind to bone and inhibition of bone remodeling declines significantly after six months of withdrawal of therapy.[2,3]

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Prevention

A multidisciplinary approach to prevention of ONJ is recommended by the AAOMS panel, including dental providers and medical providers who direct therapy with any of the associated agents. Optimization of overall health with special emphasis on dental health optimization is critical. Patient education must take place at all levels of care, including education on the risks of medication therapy and risks imposed by compromised oral health. Management of active periapical and periodontal inflammation prior to initiation of therapy with antiresorptive agents is preferred to minimize the need for extractions or other bone trauma after initiation of therapy.[2]

For patients requiring dentoalveolar surgery after initiation of antiresorptive therapy, several strategies have been employed including minimal access surgery, perioperative antibiotics, antimicrobial rinses and primary closure of extraction sites. The level of evidence to support the drug holiday concept is low and as such the panel has not been able to reach a consensus. The use of bone turnover markers to determine optimal timing of dentoalveolar surgery for patients on antiresorptive agents has not been validated.[2] Patients receiving antiresorptive agents for non-malignant conditions may proceed with dentoalveolar surgery with consideration of preventive strategies. Patients receiving antiresorptive agent for malignant conditions should avoid dentoalveolar surgery if at all possible. Consideration for root retention strategies should receive priority given the greater risks of MRONJ in this population.

Treatment

Treatment of MRONJ is based on clinical history, exam, stage of disease, and on overall patient health and risks imposed by the signs symptoms, as well as the risks and morbidity of the treatment. The most recent AAOMS Position Paper provides algorithms to guide decision making in care of the MRONJ patient. The guidelines emphasize shared decision making between providers, patients, and patient families to guide selection from non-operative versus operative management for stages 1 through 3. Non-operative approaches have merit in stable or resolving disease at all stages. For stages 2 and 3, risk/benefit analysis with consideration of patient co-morbidity and surgical risk, as well as quality of life considerations must be weighed. Conversely, operative management at all stages has been recognized as a viable option to reduce progression of MRONJ and enhance patient benefit.

Current and Future Research

The use of adjunctive agents in the management of MRONJ is the subject of current studies including the use of vitamin E and pentoxifylline. Teriparatide, recombinant parathyroid hormone has been evaluated in small randomized controlled studies of ONJ patients with clinical improvement seen in enrolled subjects reaching clinical significance.[2,4] The use of dose reducing schedules, drug holidays and biomarkers in preventive strategies warrant future research efforts.

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