Management of Medication-Related Osteonecrosis of the Jaw

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KEYWORDS

• MRONJ • Bisphosphonate • Denosumab • Oral surgery • Maxillofacial surgery • BRONJ

KEY POINTS

- Treatment of medication-related osteonecrosis of the jaw (MRONJ) should be based on the patient's symptoms, comorbidities, and goals.
- Collaboration with members of the patient's dental and medical team is encouraged.
- Effective medical management of MRONJ includes topical and oral antimicrobials, pentoxifylline, and vitamin E.
- Plain films are inadequate for surgical planning.
- Successful surgery is predicated on primary wound closure and complete excision of necrotic bone.

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) was first reported in 2003 and primarily involved patients receiving intravenous bisphosphonates for treatment of skeletal-related malignancies.[1] Soon thereafter, similar cases involving oral bisphosphonates and denosumab began appearing. Although the mechanism of action of these drugs may differ, both involve osteoclast inhibition and disruption of normal bone turnover and healing.[2]

There is no consensus regarding the clinical management of patients with MRONJ. Among the reasons for this are an incomplete understanding of the etiopathogenesis of the disease and the difficulty in defining successful treatment. 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). The American Association of Oral and Maxillofacial Surgery 2014 *Position Paper on Medication-Related Osteonecrosis of the Jaws* states that the "Treatment objectives for patients with an established diagnosis of MRONJ are to eliminate pain, control infection of the soft and hard tissue, and minimize the progression or occurrence of bone necrosis."[3] Additionally, we feel that helping patients to understand the chronicity and potential progression of the disease is essential to a satisfactory outcome.

The aim of this review is to share our treatment approach to patients with MRONJ once the diagnosis has been made. Fundamentally, treatment can be divided into medical and surgical therapies, although a combination is often used. For purposes of clarity, when referring to disease stage in this review we employ the staging system as described in the 2014 American Association of Oral and Maxillofacial Surgery position paper.[3]

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MEDICAL MANAGEMENT

In our practice, treatment of MRONJ with medical therapy alone is most commonly employed for patients with less severe disease, those who decline surgery, or those whose comorbidities preclude them from surgery. Medical therapies currently in use include topical, oral and intravenous antimicrobials, other medications and hyperbaric oxygen (HBO).

Antimicrobials

Topical antimicrobials

Chlorhexidine gluconate 0.12% is a topical bactericidal and bacteriostatic agent[4–6] that has been shown to be effective in treatment of patients with MRONJ.[3,7] Although the pathogenesis of MRONJ remains unclear, there is evidence that the oral flora, and more specifically biofilms, contribute to the disease process.[8] The use of chlorhexidine is thus rationalized by its ability to decrease total bacterial counts, including potentially pathologic organisms. Advantages of chlorhexidine include low cost, ease of use, availability, patient acceptance, and efficacy. Disadvantages include patient intolerance, lack of compliance associated with long-term use, dental staining, and opportunistic infection, as well as alterations in taste. In our practice, we commonly recommend chlorhexidine for management of stage 1 disease as a singular therapy (**Fig. 1**). For more advanced stages, we routinely recommend chlorhexidine in addition to other medical and surgical therapies.

Fig. 1. Stage 1 medication-related osteonecrosis of the jaw of the right alveolar ridge, which was asymptomatic but noted on routine dental examination after dental extractions. There was no exposed bone in the extraction sites. The patient had a 12-year history of oral bisphosphonate exposure for treatment of osteoporosis and no other comorbidities. Treatment included chlorhexidine oral rinses and routine oral hygiene practices. Resolution of the lesion was seen at 3 months.

Oral antimicrobials

Antimicrobials are a mainstay in the management of MRONJ.[3,7,9,10] Antimicrobial therapy is based on clinical observation and scientific literature suggesting that pathogenic bacteria may contribute to MRONJ. The precise organism(s) responsible remain to be identified but it seems that most infections are polymicrobial.[3,11,12] Systemic antibiotics may decrease bacterial counts in the oral cavity, including pathogenic organisms. Selection of specific antibiotics should be based on patient tolerance, compliance, and prior antibiotic exposure. One should also consider therapies targeted against common colonizers of MRONJ lesions, including Actinobacteria, Firmicutes, Fusobacteria, and Bacteroidetes.[13–15] Members of these phyla include aerobic and anaerobic organisms commonly susceptible to penicillin; therefore, penicillin remains our first antibiotic choice. Our most common penicillin alternates are clindamycin, fluoroquinolones, and/or metronidazole (**Fig. 2**). Although there are no data to clarify the most appropriate duration of antibiotic therapy for MRONJ, we generally prescribe a 2-week course for patients with persistent stage 1 disease and up to a 4- to 6-week course for more severe cases.

Intravenous antimicrobials

Intravenous antimicrobials may be of benefit in patients with pathogenic organisms resistant to oral agents and may provide greater tissue penetration in certain cases. However, there have been no satisfactory trials demonstrating greater efficacy of intravenous agents compared with oral medications in management of MRONJ.[16,17] When all available oral agents have been exhausted and no less invasive option exists, it is our practice to employ long-term (6 weeks) intravenous antimicrobials. In the future, it is conceivable that antimicrobial therapy may be more effective in MRONJ treatment when combined with developing delivery mechanisms most capable of penetrating biofilms.

Other Medications

Pentoxifylline and vitamin E

The combination of pentoxifylline and vitamin E has been used successfully in the treatment of jaw osteoradionecrosis and MRONJ; however, the specific mechanism of action in MRONJ remains unclear.[18–22] Pentoxifylline (Trental), a xanthine derivative with an excellent safety profile, is used primarily for the treatment of intermittent