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Published

2018

Journal Title

Journal of Evidence Based Dental Practice

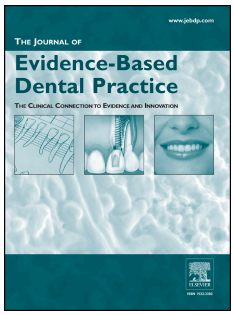
Version

Accepted Manuscript (AM)

DOI

10.1016/j.jebdp.2017.12.001

Accepted Manuscript



Insufficient Evidence to Compare the Efficacy of Treatments for Medication-related Osteonecrosis of the Jaws

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PII: S1532-3382(17)30370-6

DOI: 10.1016/j.jebdp.2017.12.001

Reference: YMED 1248

To appear in: *The Journal of Evidence-Based Dental Practice*

Please cite this article as: McGowan K, Insufficient Evidence to Compare the Efficacy of Treatments for Medication-related Osteonecrosis of the Jaws, *The Journal of Evidence-Based Dental Practice* (2018), doi: 10.1016/j.jebdp.2017.12.001.

Review Analysis and Evaluation

DECLARATIVE TITLE: Insufficient evidence to compare the efficacy of treatments for medication-related osteonecrosis of the jaws.

REVIEWER: Kelly McGowan

PURPOSE/QUESTION: The authors conducted a systematic review and meta-analysis of prospective cohort studies, non-randomized trials, and randomized controlled trials to compare the effectiveness of different therapies used to treat patients with medication-related osteonecrosis of the jaws (MRONJ).

ARTICLE TITLE AND BIBLIOGRAPHIC INFORMATION: Effectiveness of treatments for medication-related osteonecrosis of the jaw: A systematic review and meta-analysis. El-Rabbany M, Sgro A, Lam DK, Shah Ps, Azarpazhooh A. J Am Dent Assoc 2017;148(8):584-94

Strength of Recommendation Taxonomy (SORT) Grading

STRENGTH OF RECOMMENDATION GRADE:

Grade B	Inconsistent or limited-quality patient-oriented evidence

LEVEL OF EVIDENCE:

Level 2	Limited-quality, patient-oriented evidence

SOURCE OF FUNDING: Non-profit: Canadian Association of Oral & Maxillofacial Surgeons and the Alpha Omega Foundation of Canada

TYPE OF STUDY/DESIGN: Systematic review with meta-analysis of data

KEY WORDS: Jaw diseases, Osteonecrosis, Bisphosphonate-associated osteonecrosis of the jaw, Bone, Bone density conservation agents, Angiogenesis inhibitors

Summary

Selection Criteria: Three electronic databases (MEDLINE, Embase, and the Cochrane Library) plus Scopus and Google Scholar were searched for prospective cohort studies, non-randomized trials, and randomized controlled trials that evaluated the effectiveness of therapies used to manage MRONJ, as defined by the American Association of Oral and Maxillofacial Surgeon's 2014 diagnostic criteria.

Key Study Factor: This review did not set any limitations on the type of intervention used to manage MRONJ and instead used the type of study as the key inclusion factor. All prospective cohort studies, non-randomized trials, and randomized controlled trials whose participants were receiving any type of treatment for their diagnosed MRONJ were eligible for inclusion.

Main Outcome Measure: The primary outcome was a measurable improvement in clinical signs and symptoms of MRONJ, which included complete resolution of the lesion, changes in bony exposure and/or mucosal coverage, changes in radiographic lesion size, quality of life, and the presence of pain and/or neurosensory changes.

Main Results: Of the 3226 records identified in the search, 51 full-text articles were assessed for eligibility and 13 met the specified inclusion criteria. Thirty-eight articles were excluded due to ineligible study designs. Two studies were included in the meta-analysis, which compared odds ratios for the complete resolution of MRONJ in patients who received surgical and non-surgical treatment.

The 13 included studies reported on 9 different interventions: conservative surgical therapy, aggressive surgical therapy, nonsurgical therapy, supplemental hyperbaric oxygen therapy, antibiotic therapy, flap repair, discontinuation of antiresorptive medications, teriparatide therapy, and plasma rich in growth factors. The review found that surgical therapy may result in higher rates of MRONJ resolution than non-surgical (medical) therapy. Insufficient data were available to draw conclusions on the other treatment modalities identified in the review.

Conclusions: Limited data suggest surgical treatment for MRONJ may result in a higher rate of complete resolution than medical therapy. Further well-designed research is required to confidently recommend a particular mode of therapy for this disease.

Commentary and Analysis

This systematic review assessed the efficacy of different treatment modalities for MRONJ using prospective studies. The review was generally well-conducted and attempted to answer an important clinical question; however, it was not able to draw any firm conclusions due to the paucity of high-quality data available. This is a common issue in research investigating MRONJ, as the unclear pathogenesis and low incidence of disease make it difficult to design and conduct well-controlled and adequately powered studies. The considerable number of management options for MRONJ reported in the literature also makes it difficult to conduct a systematic review and meta-analysis with conclusive findings. Fliefel and colleagues published a similar systematic review of MRONJ treatment strategies in 2015 that included both retrospective and prospective studies, and even with a larger data set (97 studies, n = 4481), it was not possible to determine which course of care was most effective [1]

There were limitations to the quantitative analysis that must be considered when interpreting the results of this review. As the study set no inclusion criteria for the type of intervention, the 13 included studies investigated 9 different treatment modalities, with multiple data sets only available for non-surgical vs surgical treatment (4 studies, n = 223) and bisphosphonate drug holidays (3 studies, n = 113). Meta-analysis was only performed on 2 of the 4 studies reporting non-surgical vs surgical data (n = 76), and neither of the included studies reported data on the stage of MRONJ. Directly comparing surgical vs non-surgical treatment outcomes without grouping patients by their disease stage may be an oversimplification of a complex clinical decision, and the findings of the review should be cautiously interpreted in this context.

Treatment recommendations for MRONJ are stage-specific, with conservative therapy recommended for Stage 1 lesions and surgical management recommended for Stage 3 lesions, while both are considered for Stage 2 lesions depending on other patient factors [2-4]. The comprehensive systematic review of MRONJ diagnosis and management conducted by the International Task Force on Osteonecrosis of the Jaws (ITFONJ) in

2015 recommends an individualized treatment approach with careful consideration of the stage of MRONJ and lesion size, the patient's prognosis and life expectancy, the effect of the MRONJ lesion on the patient's quality of life, and any medical and pharmacological co-morbidities [3]. Given the recommendations for the treatment of Stage 1 and Stage 3 lesions are generally well-defined [4], a targeted review of the effectiveness of surgical vs non-surgical management for Stage 2 lesions would be highly relevant.

While conclusive data to support treatment decisions is still lacking, there is a growing body of evidence to suggest that the occurrence of MRONJ can be significantly reduced with preventative dental care and regular follow-up [5-9]. Considering the complexity of MRONJ management once it develops, identifying at-risk patients and stabilizing and maintaining their oral health to prevent the occurrence of MRONJ should be a priority for all clinicians.

Despite sustained research efforts since MRONJ was first reported in 2003 [10], it remains a difficult and unpredictable disease to treat. While multiple management strategies have been reported in the literature, their application remains primarily opinion-based rather than evidence-based [2, 3, 11].

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REFERENCES:

1. Fliefel, R., et al., *Treatment strategies and outcomes of bisphosphonate-related osteonecrosis of the jaw (BRONJ) with characterization of patients: a systematic review.* International journal of oral and maxillofacial surgery, 2015. **44**(5): p. 568-585.
2. Ruggiero, S.L., et al., *American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update.* Journal of Oral and Maxillofacial Surgery, 2014. **72**(10): p. 1938-1956.
3. Khan, A.A., et al., *Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus.* Journal of Bone and Mineral Research, 2015. **30**(1): p. 3-23.
4. Khan, A.A., et al., *Case-Based Review of Osteonecrosis of the Jaw (ONJ) and Application of the International Recommendations for Management From the International Task Force on ONJ.* Journal of Clinical Densitometry, 2016. **20**(1): p. 8-24.
5. Bonacina, R., et al., *Preventive strategies and clinical implications for bisphosphonate-related osteonecrosis of the jaw: a review of 282 patients.* J Can Dent Assoc, 2011. **77**(5): p. b147.
6. Dimopoulos, M., et al., *Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid.* Annals of Oncology, 2008. **20**(1): p. 117-120
7. Ripamonti, C., et al., *Decreased occurrence of osteonecrosis of the jaw after implementation of dental preventive measures in solid tumour patients with bone metastases treated with bisphosphonates. The experience of the National Cancer Institute of Milan.* Annals of Oncology, 2008. **20**(1): p. 137-145

8. Vandone, A., et al., *Impact of dental care in the prevention of bisphosphonate-associated osteonecrosis of the jaw: a single-center clinical experience.* Annals of oncology, 2012. **23**(1): p. 193-200.
9. Mücke, T., et al., *Prevention of bisphosphonate-related osteonecrosis of the jaws in patients with prostate cancer treated with zoledronic acid–A prospective study over 6 years.* Journal of Cranio-Maxillofacial Surgery, 2016. **44**(10): p. 1689-1693
10. Marx, R.E., *Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic.* Journal of Oral and Maxillofacial Surgery, 2003. **61**(9): p. 1115-1117.
11. Beth-Tasdogan, N.H., et al., *Interventions for managing medication-related osteonecrosis of the jaw (MRONJ).* The Cochrane Library, 2016.