Alessandria, sabato 5 maggio 2018

TRATTAMENTO NON CHIRURGICO DI MR-ONJ

Antonia Marciano', DDS

ONJ UPDATE 2018

OSTEONECROSI DELLE OSSA MASCELLARI (ONJ) DA BIFOSFONATI E ALTRI FARMACI: PREVENZIONE, DIAGNOSI, FARMACOVIGILANZA, TRATTAMENTO

ULTIMO UPDATE 2014

Position Paper

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American Association of Oral and Maxillofacial Surgeons

Medication-Related Osteonecrosis of the Jaw—2014 Update

Special Committee on Medication-Related Osteonecrosis of the Jaws:

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Introduction

The Special Committee recommends changing the nomenclature of bisphosphonate-related osteonecrosis of the jaw (BRONJ). The Special Committee favors the term **medication-related osteonecrosis of the jaw (MRONJ)**. The change is justified to accommodate the growing number of osteonecrosis cases involving the maxilla and mandible associated with other antiresorptive (denosumab) and antiangiogenic therapies.

MRONJ adversely affects the quality of life, producing significant morbidity. Strategies for management of patients with, or at risk for, MRONJ were set forth in the American Association of Oral and Maxillofacial Surgeons (AAOMS) updated *Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws* and approved by the Board of Trustees in 2009.[1] The *Position Paper* was developed by a Special Committee appointed by the Board and composed of clinicians with extensive experience in caring for these patients and basic science researchers. The knowledge base and experience in addressing MRONJ has expanded, necessitating modifications and refinements to the previous *Position Paper*. This Special Committee met in September 2013 to appraise the current literature and revise the guidelines as indicated to reflect current knowledge in this field. This update contains revisions to diagnosis, staging, and management strategies, and highlights current research status. AAOMS considers it vitally important that this information be disseminated to other relevant health care professionals and organizations.

Purpose

The purpose of this updated position paper is to provide:

1. Risk estimates of developing MRONJ
2. Comparisons of the risks and benefits of medications related to osteonecrosis of the jaw (ONJ) in order to facilitate medical decision-making for the treating physician, dentist, dental specialist, and patients
3. Guidance to clinicians regarding:

QUALITA' DELLA VITA

EORTC

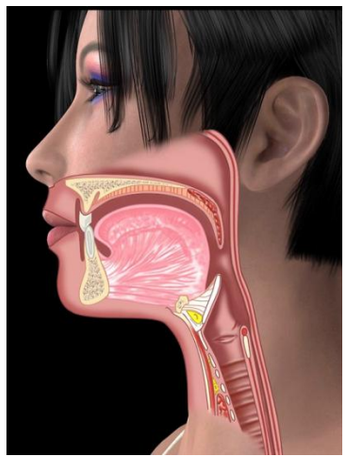
The future of cancer therapy

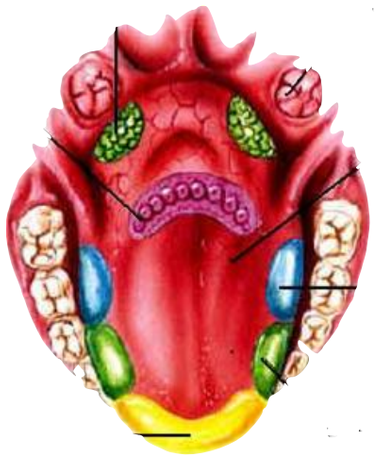
Gentile paziente, la consapevolezza dell'impatto del dolore orale/dentale sulla qualità della vita rappresenta un elemento importante nelle decisioni terapeutiche.

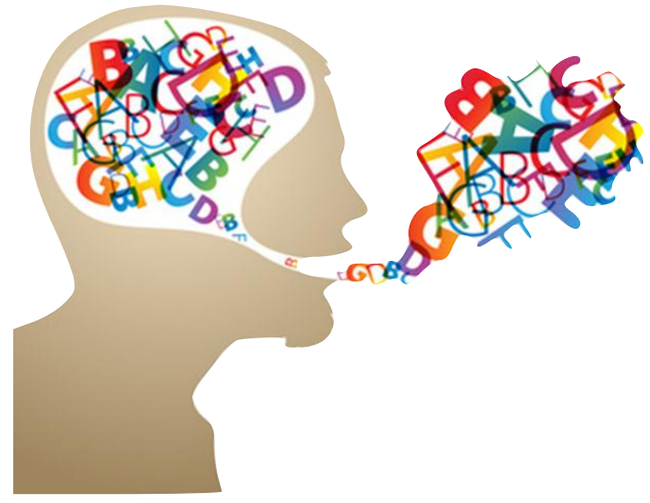
Questi questionari le sono somministrati allo scopo di valutare fino a che punto la condizione danneggia i diversi aspetti del benessere complessivo analizzeremo non soltanto il dolore ma anche alcuni elementi psicosociali e le attività della vita quotidiana.

QUALITA’ DELLA VITA CORRELATA ALLA SALUTE ORALE

Dolore **Problemi Sociali** **Problemi Dentali** **Sfera sessuale**

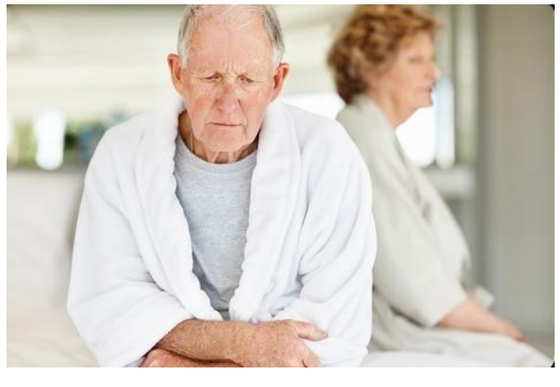






Alterazioni sensoriali

Difficoltà nel parlare in pubblico

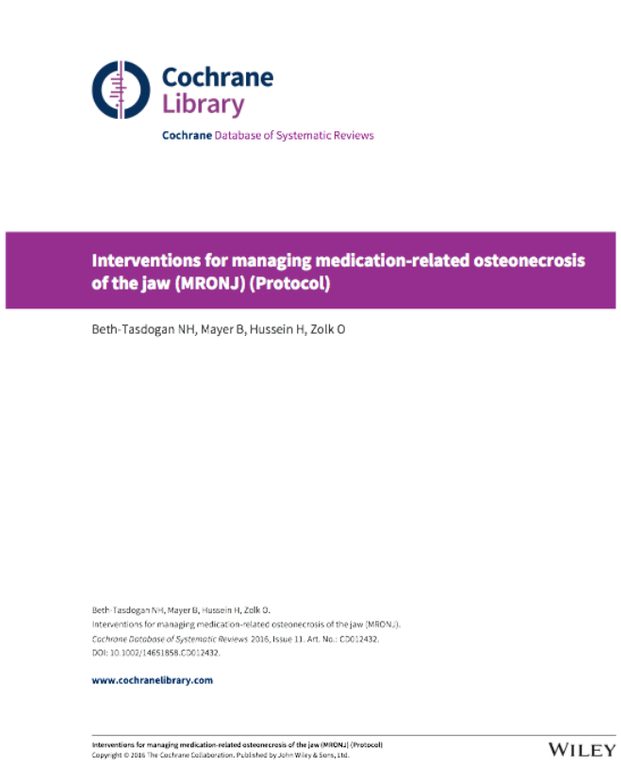


Difficoltà nel mangiare in pubblico

TRATTAMENTO NON CHIRURGICO DI MR-ONJ

Definitions

• By non-surgical management, we mean use of topical or systemic interventions.



Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for managing medication-related osteonecrosis of the jaw (MRONJ) (Protocol)

Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O

Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O.
Interventions for managing medication-related osteonecrosis of the jaw (MRONJ).
Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD012432.
DOI: 10.1002/14651858.CD012432.

www.cochranelibrary.com

Interventions for managing medication-related osteonecrosis of the jaw (MRONJ) (Protocol)
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[Intervention Protocol]

Interventions for managing medication-related osteonecrosis of the jaw (MRONJ)

Natalie H Beth-Tasdogan[1], Benjamin Mayer[2], Heba Hussein[3], Oliver Zolk[1]

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Contact address: Oliver Zolk, Institute of Pharmacology of Natural Products & Clinical Pharmacology, Ulm University, Helmholtzstr. 20, Ulm, 89081, Germany. oliver.zolk@uni-ulm.de.

Editorial group: Cochrane Oral Health Group.
Publication status and date: New, published in Issue 11, 2016.

Citation: Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O. Interventions for managing medication-related osteonecrosis of the jaw (MRONJ). *Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No.: CD012432. DOI: 10.1002/14651858.CD012432.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

(A) To assess the effects of interventions versus no treatment, placebo or an active control for prophylaxis of MRONJ in patients exposed to antiresorptive or antiangiogenic drugs.

(B) To assess the effects of nonsurgical or surgical interventions (either single or in combination) versus no treatment, placebo or an active control for treatment of patients with manifest MRONJ.

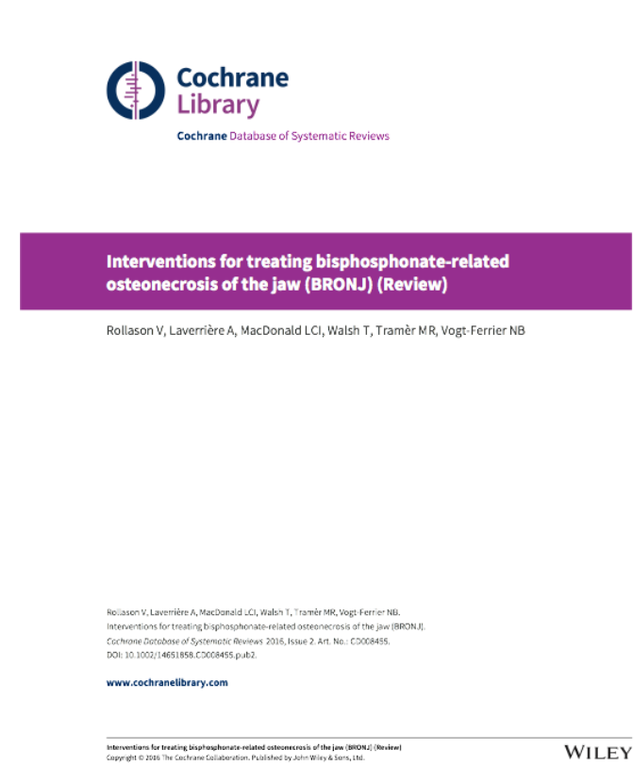
BACKGROUND

Description of the condition

Osteonecrosis of the jaw (ONJ) was first reported in 2003 by Marx in association with bisphosphonate (BP) treatment (Marx 2003; Ruggiero 2007; Sigua-Rodriguez 2014). Subsequently, ONJ was observed in individuals who took denosumab, an antiresorptive medication unrelated to the bisphosphonate class. Currently, a growing number of case reports suggest that ONJ is also associated with antiangiogenic agents such as bevacizumab, aflibercept, sunitinib, temsirolimus or everolimus. The condition formerly referred to as 'bisphosphonate-related ONJ' has been renamed 'medication-related ONJ' (MRONJ) due to the growing number of ONJ cases associated with non-bisphosphonate treatments (Ruggiero 2014).

The exact mechanisms underlying MRONJ are still unknown. Interestingly, MRONJ is mainly limited to the maxillofacial region. In contrast to other skeletal bones, jaw bones (alveolar process and periodontium) have relatively high vascularity, bone turnover and remodelling because of continuous mechanical stress, which possibly makes them vulnerable to the adverse effects of drugs. Proposed hypotheses that attempt to explain the localisation of MRONJ exclusively to the jaws include altered bone remodelling, angiogenesis inhibition, constant microtrauma, suppression of innate or acquired immunity, and possible effects of inflammation or infection (Ruggiero 2014).

According to the case definition provided by the American Society for Bone and Mineral Research and the American Association of



Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ) (Review)

Rollason V, Laverrière A, MacDonald LCI, Walsh T, Tramèr MR, Vogt-Ferrier NB

Rollason V, Laverrière A, MacDonald LCI, Walsh T, Tramèr MR, Vogt-Ferrier NB.
Interventions for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ).
Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD008455.
DOI: 10.1002/14651858.CD008455.pub2.

www.cochranelibrary.com

Interventions for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ) (Review)
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WILEY

[Intervention Review]

Interventions for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ)

Victoria Rollason[1], Alexandra Laverrière[1], Laura CI MacDonald[2], Tanya Walsh[3], Martin R Tramèr[4], Nicole B Vogt-Ferrier[1]

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Contact address: Nicole B Vogt-Ferrier, Division of Clinical Pharmacology and Toxicology, Department APSI, Geneva University Hospitals, Hopital Cantonal de Geneve, Geneva, 1211, Switzerland. Nicole.B.Vogt-Ferrier@hcuge.ch.

Editorial group: Cochrane Oral Health Group.
Publication status and date: Edited (no change to conclusions), published in Issue 2, 2016.
Review content assessed as up-to-date: 15 December 2015.

Citation: Rollason V, Laverrière A, MacDonald LCI, Walsh T, Tramèr MR, Vogt-Ferrier NB. Interventions for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ). *Cochrane Database of Systematic Reviews* 2016, Issue 2. Art. No.: CD008455. DOI: 10.1002/14651858.CD008455.pub2.

ABSTRACT

Background

Bisphosphonate drugs can be used to prevent and treat osteoporosis and to reduce symptoms and complications of metastatic bone disease; however, they are associated with a rare but serious adverse event: osteonecrosis of the maxillary and mandibular bones. This condition is called bisphosphonate-related osteonecrosis of the jaw or BRONJ. BRONJ is diagnosed when people who are taking, or have previously taken, bisphosphonates have exposed bone in the jaw area for more than eight weeks in the absence of radiation treatment. There is currently no "gold standard" of treatment for BRONJ. The three broad categories of intervention are conservative approaches (e.g. mouth rinse, antibiotics), surgical interventions and adjuvant non-surgical strategies (e.g. hyperbaric oxygen therapy, platelet-rich plasma), which can be used in combination.

Objectives

To determine the efficacy and safety of any intervention aimed at treating BRONJ.

Search methods

We searched the following databases to 15 December 2015: the Cochrane Oral Health Group Trials Register, the Cochrane Breast Cancer Group Trials Register (28 September 2011), the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via Ovid, EMBASE via Ovid, CancerLit via PubMed, CINAHL via EBSCO and AMED via Ovid. We scanned the references cited in retrieved articles and contacted experts in the field, the first authors of included papers, study sponsors, other bisphosphonates investigators and pharmaceutical companies. We searched for ongoing trials through contact with trialists and by searching the US National Institutes of Health Trials Register (clinicaltrials.gov) and the World Health Organization Clinical Trials Registry Platform. We also conducted a grey literature search to September 2015.

Selection criteria

Randomised controlled trials (RCTs) comparing the effects of any treatment for BRONJ with another treatment or placebo.

TRATTAMENTO NON CHIRURGICO DI MR-ONJ

Management of Medication-Related Osteonecrosis of the Jaw

William Bradford Williams, DMD, MD, Felice O'Ryan, DDS*

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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Oral Maxillofacial Surg Clin N Am 27 (2015) 517–525
http://dx.doi.org/10.1016/j.coms.2015.06.007

oralmaxsurgery.theclinics.com

- **Antisettici**
- **Antibiotici and antifungini**
- **Teriparatide**
- **Pentossifillina e tocoferolo**
- **Ozono terapia (OT)**
- **Terapia iperbarica (HBO)**
- **Laser terapia (LLLT)**
- **Plasma ricco in piastrine (PRP)**
- **Proteine morfo-genetiche dell'osso**

TERAPIA ANTISETTICA ORALE

ARTICLE IN PRESS

Journal of Cranio-Maxillo-Facial Surgery xxx (2015) 1–5

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Value of nonsurgical therapeutic management of stage I bisphosphonate-related osteonecrosis of the jaw

Jens Philipp Bodem, Steffen Kargus, Michael Engel, Jürgen Hoffmann, Christian Freudlsperger*

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ARTICLE INFO

Article history:
Paper received 30 January 2015
Accepted 26 May 2015
Available online xxx

Keywords:
Bisphosphonate
Bisphosphonate-related osteonecrosis of the jaw
BRONJ
MRONJ
Nonsurgical
Therapy

ABSTRACT

There is still controversy about the best treatment strategy for patients with bisphosphonate-related osteonecrosis of the jaw (BRONJ) stage I. Therefore, the aim of the present study was to analyse the effect of a nonsurgical treatment protocol in patients with BRONJ stage I.

During the study period we included 17 patients (11 male; 6 female) who presented with a total of 24 separate areas of BRONJ, stage I. All patients were exclusively treated with a monthly intravenous regime of zoledronic acid due to an underlying malignant disease. All patients were treated using a standardized nonsurgical protocol consisting of antimicrobial mouth rinsing with chlorhexidine (CHX) (0.12%) three times a day, and daily CHX gel application.

In 11 patients (45.8%) the surface area of the exposed jawbone was completely healed by nonsurgical treatment. In seven patients (29.2%), nonsurgical treatment reduced the size of the exposed bone area by a mean of 64.7% (range 20.0–96.8%). None of the patients showed an increase in size of the area of exposed jawbone, or a worsening of the BRONJ from stage I to stages II or III. However, the duration of nonsurgical treatment or the duration of intravenous bisphosphonate therapy did not significantly influence the treatment outcome ($p = 0.6628$, $p = 0.6077$, respectively).

The results of the present study support the beneficial role of nonsurgical treatment in patients presenting with BRONJ stage I. Surgical therapy of BRONJ should be restricted to patients with advanced stages with clinical symptoms and local signs of infection.

1. Introduction

For nearly four decades bisphosphonates (BPs) have been widely used as potent inhibitors of bone resorption in various diseases (Rogers et al., 1997). In multiple myeloma, BPs reduce metastasis-dependent hypercalcemia (Berenson, 1997), and their use was increased in other bone metastatic diseases including breast and prostatic cancer to avoid skeletal-related complications (Lipton, 1997; McKeage et al., 2008; Saad and Hotte, 2010). But their application is not limited to the oncologic field, as BPs are used prophylactically in the management of osteoporosis or metabolic diseases such as osteogenesis imperfecta (Delmas, 2005; McClung, 2003).

On the molecular level, BPs negatively influence bone remodelling by inhibition of the osteoclasts' function and additionally by reducing the number of osteoclasts (Russell et al., 2007). Furthermore, there is evidence, that BP therapy has a direct influence not only on the bone cells but also on the soft tissue of the mucosa, by inhibiting the growth of epithelial cells, which leads to an attenuated healing capacity of the mucosa (Cornish et al., 2011). Finally, intravenous BP therapy, especially with zoledronic acid might reduce the level of vascular endothelial growth factor leading to anti-angiogenic and antineoplastic effects (Santini et al., 2003).

Bisphosphonate-related osteonecrosis of the jaws (BRONJ) was first described by Marx in 2003 who suggested a relationship between the development of avascular necrosis of the jaw and therapy with intravenous BPs in 36 patients (Marx, 2003).

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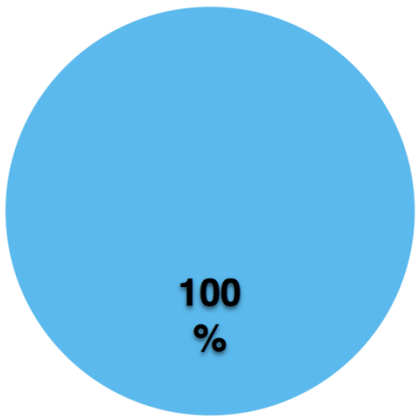
http://dx.doi.org/10.1016/j.jcms.2015.05.019
1010-5182/

Please cite this article in press as: Bodem JP, et al., Value of nonsurgical therapeutic management of stage I bisphosphonate-related osteonecrosis of the jaw, Journal of Cranio-Maxillo-Facial Surgery (2015), http://dx.doi.org/10.1016/j.jcms.2015.05.019

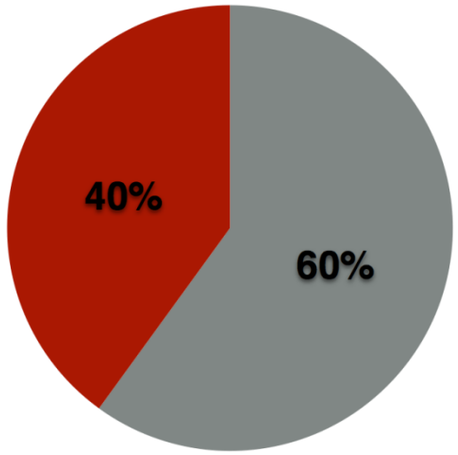


Studio di coorte monocentrico

MRONJ stage I

TERAPIA ANTIBIOTICA

Presenza/assenza di segni clinici di infezione



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American Association of Oral and Maxillofacial Surgeons
Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw—2009 Update
Approved by the Board of Trustees January 2009

TERAPIA ANTIBIOTICA

Journal section: Medically compromised patients in Dentistry
Publication Types: Review

doi:10.4317/medoral.20980
http://dx.doi.org/doi:10.4317/medoral.20980

Treatment of osteonecrosis of the jaw related to bisphosphonates and other antiresorptive agents

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Rodríguez-Lozano FJ, Oñate-Sánchez RE. Treatment of osteonecrosis of the jaw related to bisphosphonates and other antiresorptive agents. Med Oral Patol Oral Cir Bucal. 2016 Sep 1;21 (5):e595-600.
http://www.medicinaoral.com/medoralfree01/v21i5/medoralv21i5p595.pdf

Article Number: 20980 http://www.medicinaoral.com/
© Medicina Oral S. L. C.I.F. B 96689336 - pISSN 1698-4447 - eISSN: 1698-6946
eMail: medicina@medicinaoral.com
Indexed in:
Science Citation Index Expanded
Journal Citation Reports
Index Medicus, MEDLINE, PubMed
Scopus, Embase and Emcare
Indice Médico Español

Received: 31/07/2015
Accepted: 25/04/2016

Abstract

Background: The clinical management of medication-related osteonecrosis of the jaw (MRONJ) in patients treated with bisphosphonates and other antiresorptive agents is subject to controversy. The American Association of Oral and Maxillofacial Surgeons (AAOMS) has developed guidelines for the correct management of the disorder which are revised and updated by a panel of experts.

Material and Methods: The present systematic review analyzes the different treatments currently used to treat this clinical condition, based on the PRISMA® (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement published in 2009. An electronic Medline search was made of the PubMed database, covering the period 2006-2014. The last search date was 31 December 2014.

Results: A total of 29 articles were selected from the initial search according to the different drugs implicated in the appearance of osteonecrosis; the treatment modality used according to the stage of the disease; and the recorded success rate.

Conclusions: It is currently still recommended that the management of MRONJ should be decided according to the stage of the disease – conservative treatment being preferred in early stages without symptoms, while surgical management is preferred in the case of bone exposure with symptoms.

Key words: *Osteonecrosis, medication, bisphosphonates, treatments, review.*

The last search date was 31 December 2014.

TYPE OF TREATMENT	AUTHOR / YEAR	No. PATIENTS HEALED / No. PATIENTS TREATED (%)
Antibiotic treatment	Melea *et al.* (2014) (15) Van den Wyngaert *et al*. (2009) (21) Scoletta *et al.* (2010) (22) Nicolatou-Galitis *et al.* (2011) (23)	23/38 (60%) 16/33 (53%) 18/30 (62%) 7/47 (14.9%)

TERAPIA ANTIBIOTICA

Studio Retrospettivo

Accepted Manuscript

The impact of surgical intervention and antibiotics on MRONJ stage II and III – retrospective study

Matthias Zirk, MD, DMD, Matthias Kreppel, MD, DMD, PhD, Johannes Buller, MD, DMD, Julij Pristup, DMD, Franziska Peters, MD, Timo Dreiseidler, MD, DMD, PhD, Max Zinser, MD, DMD, PhD, Joachim E. Zöller, MD, DMD, PhD

PII: S1010-5182(17)30193-2

DOI: 10.1016/j.jcms.2017.05.027

Reference: YJCMS 2690

To appear in: *Journal of Cranio-Maxillo-Facial Surgery*

Received Date: 19 January 2017

Revised Date: 22 May 2017

Accepted Date: 29 May 2017

Please cite this article as: Zirk M, Kreppel M, Buller J, Pristup J, Peters F, Dreiseidler T, Zinser M, Zöller JE, The impact of surgical intervention and antibiotics on MRONJ stage II and III – retrospective study, *Journal of Cranio-Maxillofacial Surgery* (2017), doi: 10.1016/j.jcms.2017.05.027.

Batteri isolati prevalentemente Gram-negativi facoltativi anaerobi (39.1%)

Maggiormente suscettibili a ampicillina/sulbactam (79.1%)

TERAPIA ANTIBIOTICA

Accepted Manuscript

Bacterial diversity in medication-related osteonecrosis of the jaws

Fredrik Hallmer, Tore Bjørnland, Gunilla Andersson, Jonas P. Becktor, Anne K. Kristoffersen, Morten Enersen

PII: S2212-4403(16)30705-2

DOI: 10.1016/j.oooo.2016.11.011

Reference: OOOO 1659

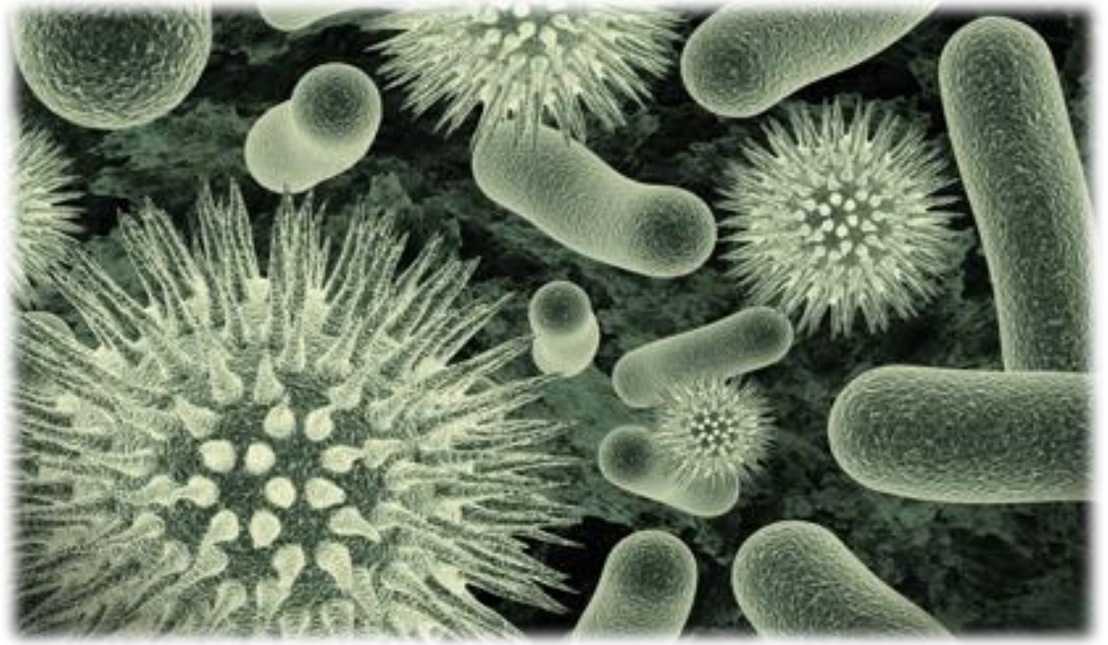
To appear in: *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*

Received Date: 20 June 2016

Revised Date: 17 October 2016

Accepted Date: 25 November 2016

Please cite this article as: Hallmer F, Bjørnland T, Andersson G, Becktor JP, Kristoffersen AK, Enersen M, Bacterial diversity in medication-related osteonecrosis of the jaws, *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* (2017), doi: 10.1016/j.oooo.2016.11.011.



MICROFLORA PARODONTALE

PORPHYROMONAS, LACTOBACILLUS, PREVOTELLA, ACTINOMYCES, TREPONEMA, STREPTOCOCCUS FUSOBACTERIUM.

TERAPIA ANTIBIOTICA TOPICA

Journal of
Oral Pathology & Medicine

doi: 10.1111/jop.12419

J Oral Pathol Med
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BRIEF REPORT

Modified protocol including topical minocycline in orabase to manage medication-related osteonecrosis of the jaw cases

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OBJECTIVE: Management of medication-related osteonecrosis of the jaw (MRONJ) with active infection can be a serious challenge for clinicians. Based on Association of Oral and Maxillofacial Surgeons (AAOMS) recommendations, we have tested a modified treatment protocol using topical minocycline.

STUDY DESIGN: Five patients diagnosed with stage II or III MRONJ lesions were willing to consent to our protocol. In addition to conventional treatment as suggested by the AAOMS, such as, surgical debridement, chlorhexidine irrigation, and systemic antibiotics, we applied 10% minocycline to the lesions once a week for sustained local antibiotic delivery.

RESULTS: All five patients reported pain relief after the first minocycline application. Complete healing occurred in three patients; case three healed completely after the third application, one case continues to improve toward resolution and one withdraws due to other non-relevant medical problem.

CONCLUSIONS: In this study, we are reporting favorable results using a modified protocol with topical minocycline to treat MRONJ lesions.

J Oral Pathol Med (2016)

Keywords: biofilm; bisphosphonate; minocycline; medication-related osteonecrosis of the jaw

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is defined by the American Association of Oral and Maxillofacial Surgeons (AAOMS) as 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 8 weeks in a patient with current or previous treatment with antiresorptive or anti-angiogenic agents and no history of radiation therapy to the jaws or obvious metastatic disease to the jaws (1). A protocol to manage MRONJ cases is supported by the AAOMS, which aims to control infection by systemic antibiotics during the acute phase, conservative initial debridement, control pain if present, and maintenance of a favorable environment in the mouth using antibacterial oral rinses (1).

Systemic antibiotics are commonly used for MRONJ treatment, but limitations include systemic toxicity and poor penetration into ischemic and necrotic bone tissue typical of MRONJ lesions (2, 3). Topical application of antibiotics addresses these disadvantages by maintaining a high local antibiotic concentration for an extended duration without systemic toxicity (4, 5).

Minocycline is a broad spectrum antibiotic, which has several biological actions beyond its antimicrobial activity, including inhibiting tissue collagenases and anti-inflammatory activities (6–8). Topical minocycline has the unique ability to bind bone and root surfaces and demonstrate slow release from these reservoirs (9), which makes it useful to sustain a therapeutic level in bony lesions. Furthermore, minocycline causes a significant stimulation of osteoblasts, which has the potential to increase bone matrix (10).

Therefore, the purpose of this study was to assess the effect of topical minocycline application in MRONJ lesions in a series of complicated cases and to evaluate the feasibility of including this procedure in an MRONJ treatment protocol.

Materials and methods

Five patients were willing to consent to our modified protocol for managing MRONJ lesions in accordance with the Declaration of Helsinki. These patients were being managed by us as part of an ongoing natural history study with appropriate approval by the institutional review board at University of Southern California

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Accepted for publication December 14, 2015

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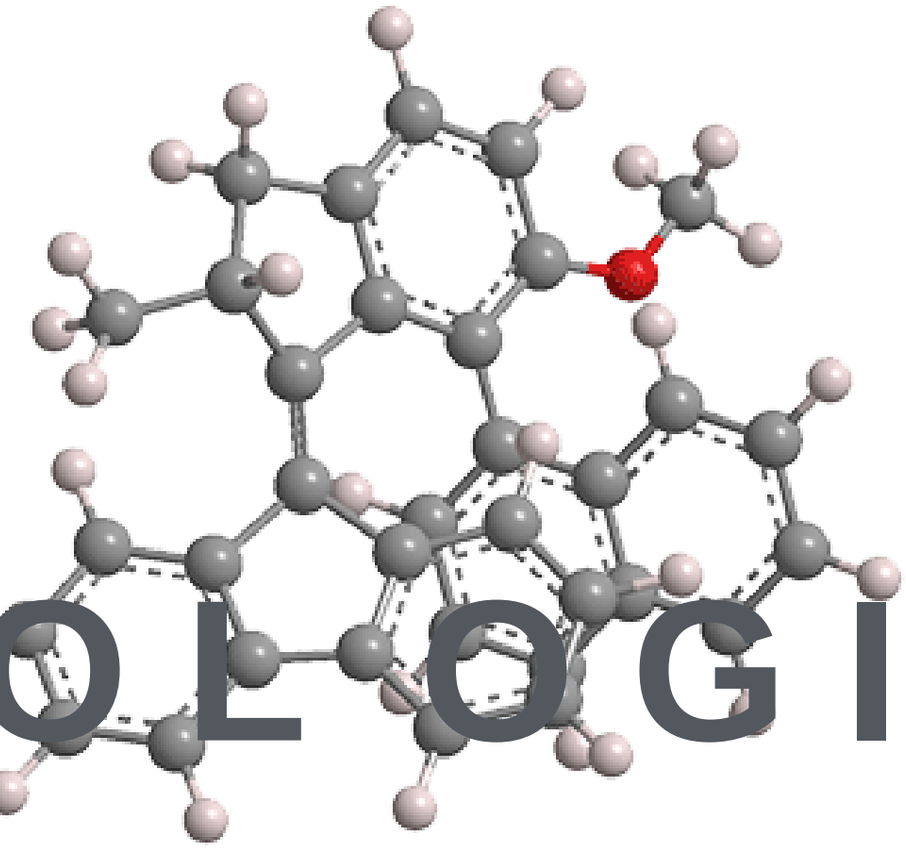
TRATTAMENTI NON CHIRURGICI INNOVATIVI



BIOTECNOLOGIE

NEL PAZIENTE CON OSTEOPOROSI: TERIPARATIDE

Studio preclinico

Accepted Manuscript

Effect of different doses and durations of teriparatide therapy on resolution of medication-related osteonecrosis of the jaw: A randomized, controlled preclinical study in rats

Mohammad Zandi, DDS, MSc., Arash Dehghan, M.D, MSc., Najmeh Zandipoor, D.D.S., Payam Amini, Shideh Doulati

PII: S1010-5182(17)30459-6

DOI: 10.1016/j.jcms.2017.12.027

Reference: YJCMS 2880

To appear in: *Journal of Cranio-Maxillo-Facial Surgery*

Received Date: 26 February 2017

Revised Date: 8 December 2017

Accepted Date: 21 December 2017

Please cite this article as: Zandi M, Dehghan A, Zandipoor N, Amini P, Doulati S, Effect of different doses and durations of teriparatide therapy on resolution of medication-related osteonecrosis of the jaw: A randomized, controlled preclinical study in rats, *Journal of Cranio-Maxillofacial Surgery* (2018), doi: 10.1016/j.jcms.2017.12.027.

NEL PAZIENTE ONCOLOGICO: PENTOSSIFILLINA + TOCOFEROLO

Studio di coorte retrospettivo

Accepted Manuscript

Pentoxifylline and Tocopherol in the Management of Cancer Patients with Medication-related Osteonecrosis of the Jaw: an observational retrospective study of initial case series

Adepitan A. Owosho, B.Ch.D, Cherry L. Estilo, DMD, Joseph M. Huryn, DDS, SaeHee K. Yom, DDS, MPH

PII: S2212-4403(16)30156-0

DOI: 10.1016/j.oooo.2016.06.019

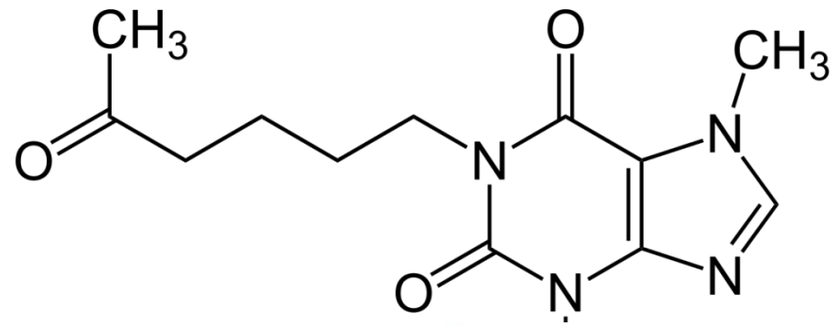
Reference: OOOO 1541

To appear in: *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*

Received Date: 16 April 2016

Revised Date: 8 June 2016

Accepted Date: 22 June 2016



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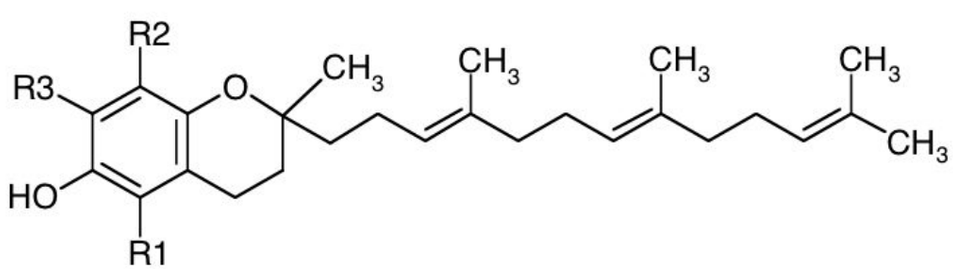

NEL PAZIENTE ONCOLOGICO: PENTOSSIFILLINA + TOCOFEROLO

ARTICLE IN PRESS

CASE REPORTS

Pentoxifylline and Tocopherol in the Treatment of Yearly Zoledronic Acid–Related Osteonecrosis of the Jaw in a Corticosteroid-Induced Osteoporosis

Michèle Magremanne, MD, DDS, and Hervé Reychler, MD, DMD†*

Osteonecrosis of the jaw (ONJ) is a well-known side effect of bisphosphonate (BP) therapy. ONJ is specifically related to the intravenous form of BPs and is usually seen in combination with other risk factors, such as dental surgery, concurrent corticosteroids, chemotherapy, and tobacco use. The risk of developing ONJ in patients treated with oral BPs for osteoporosis is lower than that in patients with cancer but is still significant. Zoledronic acid is a third-generation nitrogen-containing BP. It was first used in the treatment of malignancy as a monthly infusion and then approved for the treatment of osteoporosis as a yearly infusion

Pentoxifylline 400 mg a rilascio prolungato due volte al giorno

+

1000 UI di vitamina E una volta al giorno.

2004.* Since then, an increasing number of cases has been observed, particularly in patients with cancer. ONJ is related to the intravenous (IV) form of BPs and is usually seen in combination with other risk factors, such as dental surgery, concurrent corticosteroids, chemotherapy, or tobacco use.

Received from the Department of Oral and Maxillofacial Surgery, Cancer Center Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium.

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Received April 19 2013

Accepted June 3 2013

0278-2391/13/00793-3$36.00/0

http://dx.doi.org/10.1016/j.joms.2013.06.188

acid is a third-generation nitrogen-containing BP. It was first used in the treatment of malignancy as a monthly 4-mg IV infusion. It was approved in 2007 for the treatment of osteoporosis as a yearly 5-mg IV infusion and is an attractive option that is more reliable than the oral form. ONJ related to the use of yearly zoledronic acid is rarely reported in the literature and is most likely underestimated.

Pentoxifylline (PEN) and tocopherol (TO) have been used in the treatment of osteoradionecrosis for many years, with observed lesion improvement.

The authors present a case of ONJ development after 3 yearly zoledronic acid infusions for corticosteroid-induced osteoporosis. The patient was successfully managed using conservative treatment with PEN and TO.

Report of Case

A 58-year-old man was referred to the oral and maxillofacial department of the authors' clinic for recurrent infection, pain, and paresthesia or anesthesia of the left mandible.

Vol. 110 No. 5 November 2010

Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology

ORAL MEDICINE

Editor: Craig S. Miller

Management of bisphosphonate-associated osteonecrosis: pentoxifylline and tocopherol in addition to antimicrobial therapy. An initial case series

Matthew S. Epstein, BS,[a] Fredrick W. Wicknick, DMD,[b] Joel B. Epstein, DMD, MSD, FRCD(C), FDS RCS (Ed),[c] James R. Berenson, MD,[d] and Meir Gorsky, DMD,[e] Seattle and Bellingham, WA, Chicago, IL, W. Hollywood, CA, Tel Aviv, Israel

UNIVERSITY OF WASHINGTON, UNIVERSITY OF ILLINOIS, INSTITUTE FOR MYELOMA AND BONE CANCER RESEARCH, TEL AVIV UNIVERSITY

Background. Studies of the use of pentoxifylline and α-tocopherol in osteoradionecrosis of the jaw have suggested

nates (BP), including zoledronic acid, pamidronate, and others administered intravenously.[1,2] Among patients treated with oral BP for osteoporosis, BON is a rare potential complication.[3,4] A significant correlation has been reported between the administered dose and duration of BP and BON in cancer patients.[5] Comorbid risk factors identified include tobacco use, diabetes

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Received for publication Feb 4, 2010; returned for revision May 27, 2010; accepted for publication May 28, 2010.

1079-2104/$ - see front matter

doi:10.1016/j.tripleo.2010.05.067

prescribed BP, primarily based on expert opinion.[7-13] It is strongly recommended that all patients planned to receive BP treatment, and those already undergoing treatment, receive thorough dental assessments and appropriate preventive dental management before initiation of these drugs.[7]

Osteoradionecrosis (ORN) and other late radiation complications have been associated with radiation-induced fibrosis (RIF), which has led to studies that focus on a fibro-atrophic mechanism in the pathogenesis of ORN, rather than vascular insufficiency.[11] Combined pentoxifylline and α-tocopherol (PT) significantly reduce RIF[14] modulating fibroblast activity, perhaps because of their impact on cytokine production. A phase II clinical trial with PT induced a 66% regression of the RIF surface area after 12 months of treatment.[15] These results were confirmed in an experimental RIF model where a 70% regression of RIF volume was observed

GERANILGERANIOLO

Accepted Manuscript

In vivo effects of geranylgeraniol on the development of bisphosphonate-related osteonecrosis of the jaws

Filip Koneski, DMD, Danica Popovic-Monevska, PhD, Icko Gjorgoski, PhD, Jovanka Krajoska, B.S., Mirjana Popovska, PhD, Ilijana Muratovska, PhD, Boris Velickovski, PhD, Gordana Petrushevska, PhD, Vladimir Popovski, PhD

PII: S1010-5182(17)30381-5

DOI: 10.1016/j.jcms.2017.11.007

Reference: YJCMS 2832

To appear in: *Journal of Cranio-Maxillo-Facial Surgery*

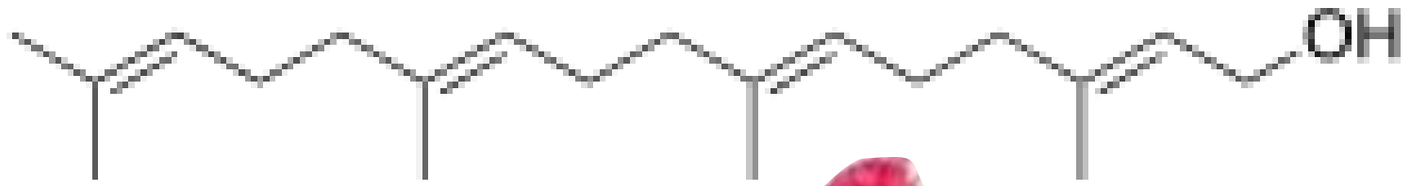
Received Date: 16 July 2017

Revised Date: 20 October 2017

Accepted Date: 13 November 2017

Please cite this article as: Koneski F, DMD Popovic-Monevska D, Gjorgoski I, Krajoska J, Popovska M, Muratovska I, Velickovski B, Petrushevska G, Popovski V, In vivo effects of geranylgeraniol on the development of bisphosphonate-related osteonecrosis of the jaws, *Journal of Cranio-Maxillofacial Surgery* (2017), doi: 10.1016/j.jcms.2017.11.007.

Studio preclinico



DURATA DEL TRATTAMENTO NON CHIRURGICO

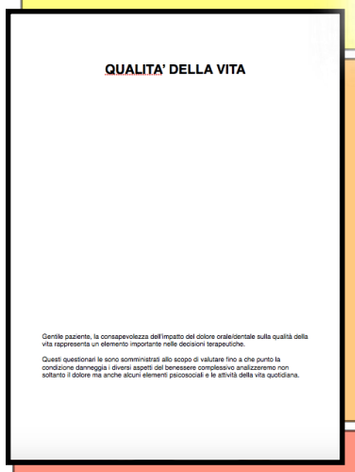
WORK-FLOW

- Clinical diagnosis
- Radiological diagnosis
- Staging ONJ lesions
- Quality of life assessment
- Conservative medical treatment
- Quality of life re-assessment
- Surgical treatment
- Follow-up

T 0

MR-ONJ diagnosis

medical treatment [a]



partial resolution,
and resolved.

progressive,
unchanged.

T 1

patients not eligible for surgery
diffuse osteosclerosis
extended surgery
limited life expectancy

surgical treatment [b]
patients eligible for surgery
areas of focal sclerosis

T 2

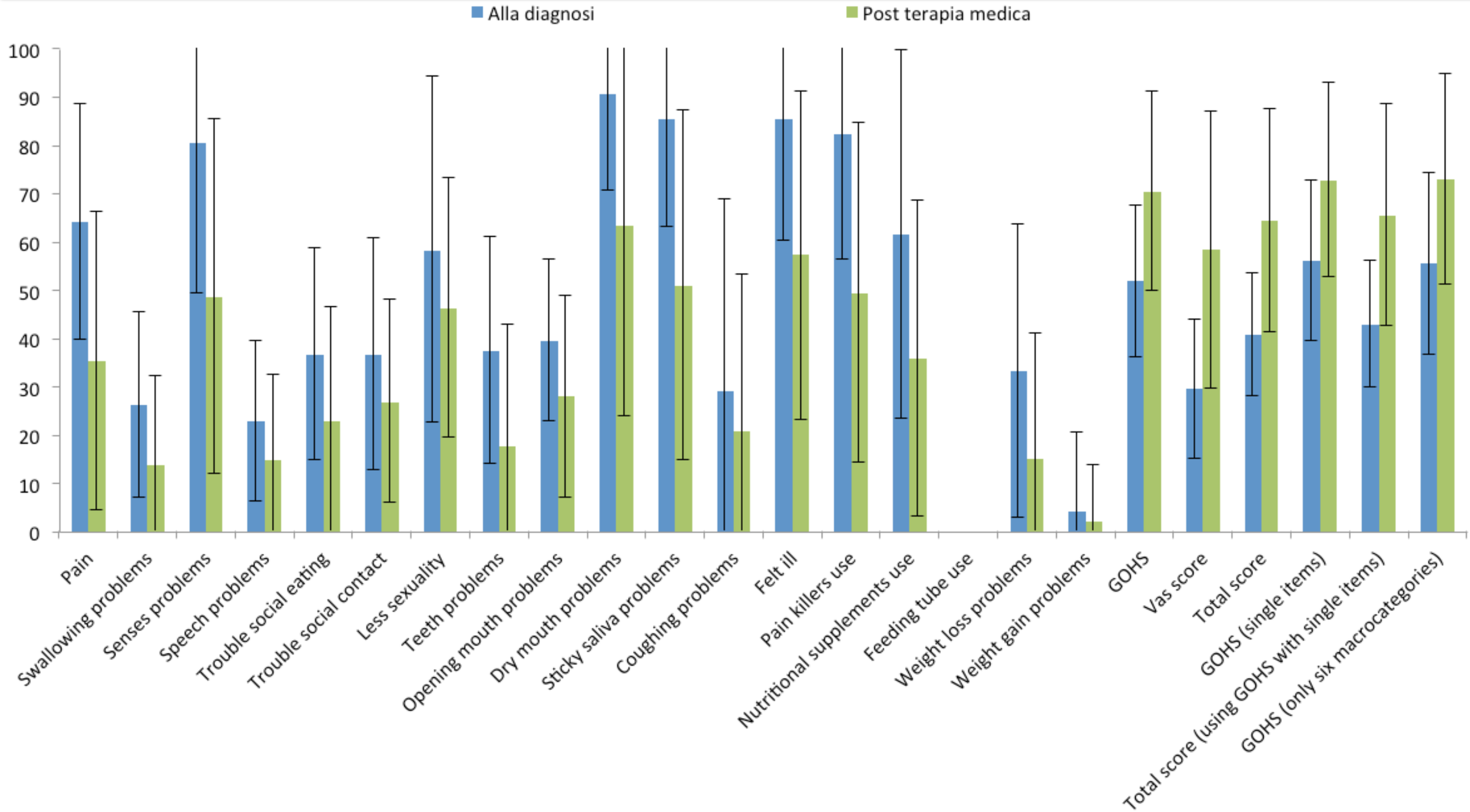
partial resolution,
and resolved.

progressive,
unchanged.

routine follow-up
as indicated in all adult patients

close and personalized
follow-up

OUTCOME DEL TRATTAMENTO NON CHIRURGICO



Oteri G, Trifirò G, Peditto M, Lo Presti L, Marcianò I, Giorgianni F, Sultana J, Marcianò A. Treatment of Medication-Related Osteonecrosis of the Jaw and its Impact on a Patient's Quality of Life: A Single-Center, 10-Year Experience from Southern Italy. Drug Saf. 2018 Jan;41(1):111-123.

OUTCOME DEL TRATTAMENTO NON CHIRURGICO

Review sistematica con meta-analisi

ORIGINAL CONTRIBUTIONS

ADA CE Program ARTICLE 3

Effectiveness of treatments for medication-related osteonecrosis of the jaw

A systematic review and meta-analysis

Mohamed El-Rabbany, DDS, MSc;
Adam Sgro; David K. Lam, MD, DDS, PhD;
Prakeshkumar S. Shah, MSc, MBBS, MD, DCH;
Amir Azarpazhooh, DDS, MSc, PhD

ABSTRACT

Background. The effectiveness of management strategies used for the treatment of medication-related osteonecrosis of the jaw (MRONJ) remains poorly understood. The authors evaluated systematically the effectiveness of the various treatment modalities used for MRONJ.

Types of Studies Reviewed. The authors conducted a comprehensive search of MEDLINE, Embase, the Cochrane Library, and Scopus to identify randomized controlled trials, nonrandomized controlled trials, and prospective cohort studies to evaluate comparatively the effectiveness of management strategies for the treatment of MRONJ. The authors conducted the identification of eligible studies in duplicate and synthesized the extracted data by means of a meta-analysis, when feasible.

Results. The authors found 13 studies with a medium-to-high risk of bias that met the inclusion criteria of this review. The authors found that, compared with medical treatment of local antimicrobials with or without systemic antimicrobials, the study investigators associated surgical treatment with higher odds of complete resolution of the condition (2 studies; 76 participants; unadjusted odds ratio, 3.55; 95% confidence interval, 1.12 to 11.19). The effectiveness of other therapies, such as bisphosphonate drug holidays, teriparatide, and hyperbaric oxygen, was uncertain.

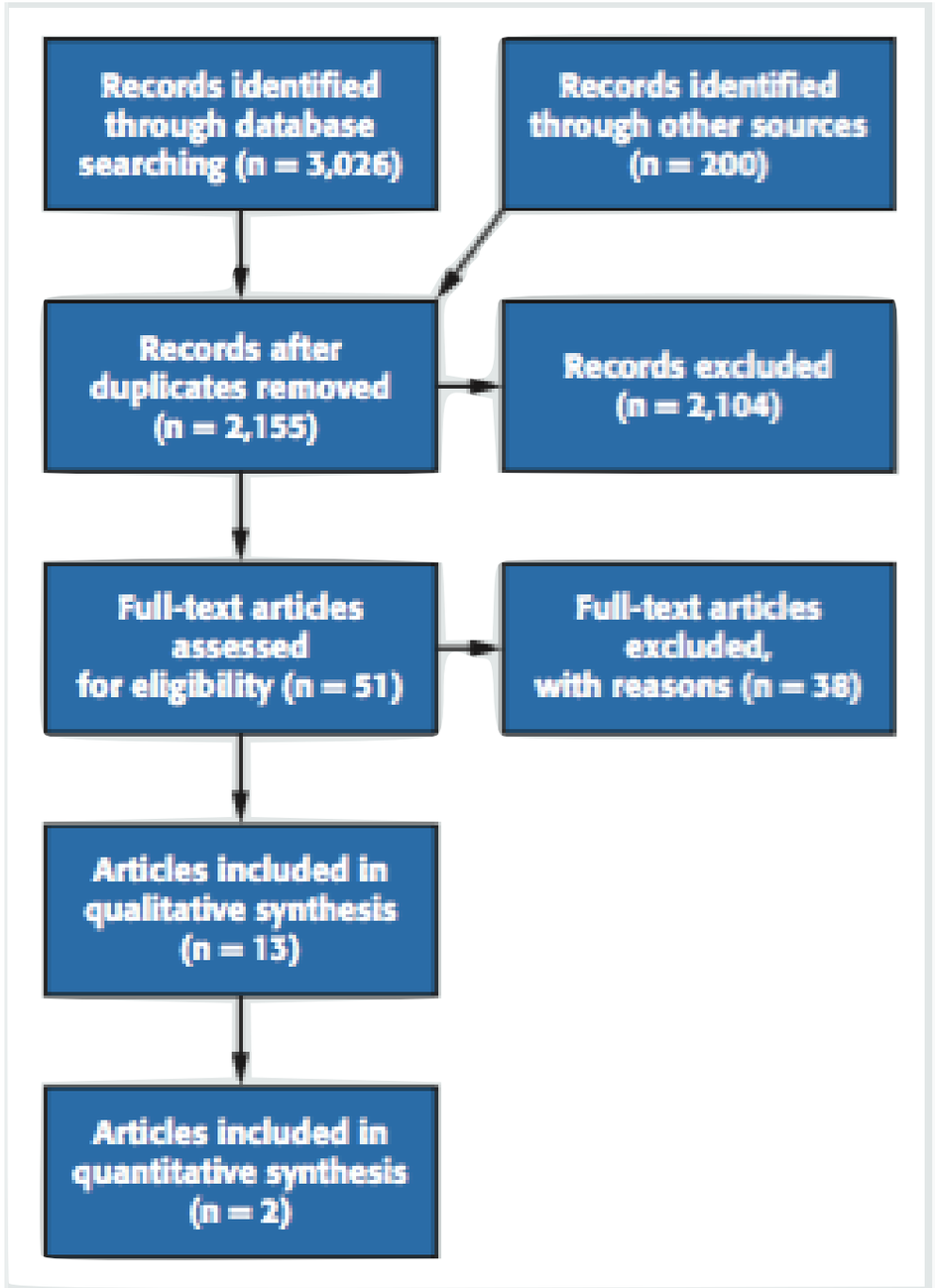
Conclusions and Practical Implications. On the basis of the results of an unadjusted analysis, the results of the studies that were deemed to be medium to low quality and to have medium-to-low statistical power suggested that there are higher odds of resolving MRONJ with surgical treatment compared with medical treatment. High-quality research is required for conclusive statements to be made regarding treatment strategies for management of MRONJ.

Key Words. Osteonecrosis; medication-related osteonecrosis of the jaw; bisphosphonate-associated osteonecrosis of the jaw; osteonecrosis of the jaw; oral and maxillofacial surgery; bone.
JADA 2017:148(8):584-594
http://dx.doi.org/10.1016/j.adaj.2017.04.002

Medication-related osteonecrosis of the jaw (MRONJ) is defined as exposed bone, in a susceptible patient who does not have a history of head and neck radiation, that fails to heal over a period of 8 weeks in the absence of any evidence of obvious metastatic disease.[1,2] Despite being relatively uncommon, with a prevalence of up to 0.01% in patients receiving oral bisphosphonates, 12% in patients receiving intravenous bisphosphonates, and 16% in patients receiving a combination of bisphosphonates and antiangiogenics, MRONJ presents major repercussions for both a patient's quality of life and health care resources.[1,3,4] Patients with MRONJ often have signs and symptoms that include pain, swelling, exposed bony sequestrum, fistulae, erythematous or ulcerated soft tissue, or pathologic fractures.[5] Because MRONJ occurs more commonly in the mandible

Supplemental material is available online.

This article has an accompanying online continuing education activity available at: http://jada.ada.org/ce/home.



OUTCOME DEL TRATTAMENTO NON CHIRURGICO

Med Oral Patol Oral Cir Bucal. 2017 Nov 1;22 (6):e788-95.

Journal section: Oral Surgery
Publication Types: Research

doi:10.4317/medoral.22013
http://dx.doi.org/doi:10.4317/medoral.22013

The assessment of surgical and non-surgical treatment of stage II medication-related osteonecrosis of the jaw

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Eguchi T, Kanai I, Basugi A, Miyata Y, Inoue M, Hamada Y. The assessment of surgical and non-surgical treatment of stage II medication-related osteonecrosis of the jaw. Med Oral Patol Oral Cir Bucal. 2017 Nov 1;22 (6):e788-95.
http://www.medicinaoral.com/medoralfree01/v22i6/medoralv22i6p788.pdf

Received: 22/05/2017
Accepted: 06/09/2017

Article Number: 22013 http://www.medicinaoral.com/
© Medicina Oral S. L. C.I.F. B 96689336 - pISSN 1698-4447 - eISSN: 1698-6946
eMail: medicina@medicinaoral.com
Indexed in:
Science Citation Index Expanded
Journal Citation Reports
Index Medicus, MEDLINE, PubMed
Scopus, Embase and Emcare
Indice Médico Español

Abstract

Background: Non-surgical treatment has generally been recommended for stage II medication-related osteonecrosis of the jaw (MRONJ) in preference to surgery. However, non-surgical treatment is not empirically effective. The aim of this study was to evaluate whether surgical or non-surgical treatment leads to better outcomes for stage II MRONJ.

Material and Methods: In this retrospective study, surgery was performed in a total of 28 patients while 24 patients underwent non-surgical treatment. The outcomes of both treatment approaches after 6 months were evaluated and statistically compared. In addition, risk factors for surgical and non-surgical treatments were assessed for each.

Results: Surgical treatment in 25 patients (89.3%) resulted in success, with failure in 3 patients (10.7%). Non-surgical treatment was successful for 8 patients (33.3%) and failed in 16 patients (66.7%). There was therefore a significant difference between surgical and non-surgical treatment outcomes (P<0.01). Regarding risk factors, in non-surgical treatment primary diseases, medications, and drug holiday had a significant effect on outcomes (P<0.01). Risk factors for surgical treatment could not be clarified.

Conclusions: Surgical treatment is more effective than non-surgical treatment for stage II MRONJ, and drug holiday, primary disease, and medication constitute risk factors in non-surgical treatment.

Key words: *Bisphosphonate, bisphosphonate-related osteonecrosis of the jaw, denosumab, management, medication-related osteonecrosis of the jaw.*

Introduction

Bisphosphonates (BPs) and denosumab are medications widely used to manage cancer-related conditions, including hypercalcemia; skeletal-related events associated with bone metastasis in the context of solid tumours such as breast, prostate, and lung cancer; lytic lesions in the setting of multiple myeloma; and osteoporosis, osteopenia, and Paget disease (1-7). However, these

Studio Retrospettivo

MRONJ stage II

SURGICAL N=28

Vs

NON SURGICAL N=24

89.3%

33.3%

CONCLUSIONI

Journal of International Society of Preventive & Community Dentistry

Wolters Kluwer -- Medknow Publications

Medication-related osteonecrosis of the jaw: Clinical and practical guidelines

Daniele Rosella, Piero Papi, [...], and Giorgio Pompa

Additional article information

Abstract

Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse drug

OUTCOME DEL TRATTAMENTO NON CHIRURGICO

Studio di coorte retrospettivo

MRONJ stage II

ELSEVIER

Available online at www.sciencedirect.com
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British Journal of Oral and Maxillofacial Surgery 55 (2017) 787–792

BRITISH Journal of Oral and Maxillofacial Surgery
www.bjoms.com

Medication-related osteonecrosis of the jaw in oncological patients with skeletal metastases: conservative treatment is effective up to stage 2

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Accepted 22 June 2017
Available online 29 July 2017

Abstract

There is currently no widespread strategy for treating medication-related osteonecrosis of the jaw (MRONJ), so our aim was to evaluate retrospectively the outcome of a minimally invasive treatment protocol for patients with both MRONJ and cancer. We designed a retrospective cohort study of patients with cancer who had been diagnosed with MRONJ after treatment with denosumab or bisphosphonates given intravenously. Primary outcome measures were improvement in the clinical stage of MRONJ and the time course to its resolution. Secondary outcome measures included the incidence of risk factors and patterns of treatment. Seventy-nine patients with 109 lesions were enrolled, and their characteristics, presentation of the lesions, complications, and relations to previous oral interventions were recorded. Treatment depended on the stage of disease, and included conservative medical, and minimally-invasive surgical, procedures. There was complete healing and resolution of disease in 38/57 stage 1 lesions, 30/47 stage 2 lesions, and 3/5 stage 3 lesions. The symptoms improved in 16/47 stage 2 lesions, and 2/5 stage 3 lesions. Fifteen of the stage 1 lesions, and one of the stage 2 lesions, failed to respond. Despite the possibility of an aggressive approach to the treatment of MRONJ, conservative treatment remains the first line of defence as regression is obvious, with evidence of no evolution to a higher stage. In our experience surgical intervention is recommended in persistent stage 3 MRONJ that has failed to respond to conservative treatment.

Keywords: MRONJ; osteonecrosis; risk factors; treatment; bisphosphonates; denosumab

Introduction

In 2003 Marx reported the first cases of what has become known as medication-related osteonecrosis of the jaw (MRONJ).[1] Initially, osteonecrosis was reported only after treatment with bisphosphonates and referred to as bisphosphonate-related osteonecrosis of the jaw (BRONJ). As other antiresorptive agents (for example, monoclonal antibodies such as denosumab) seemed to lead to the same outcome – it was soon referred to as antiresorptive-related osteonecrosis of the jaw (ARONJ).[2] Since 2014 the American Association of Oral and Maxillofacial Surgeons (AAOMS) has recommended the use of the term "medication-related osteonecrosis of the jaw" (MRONJ). The change is justified to accommodate the growing number of cases of osteonecrosis that are associated with other antiresorptive and antiangiogenic treatments in patients who have not used bisphosphonates previously.[3]

Current treatments of patients with skeletal metastases vary depending on the stage and severity of MRONJ, from conservative approaches (including long-term antibiotics,

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http://dx.doi.org/10.1016/j.bjoms.2017.06.014

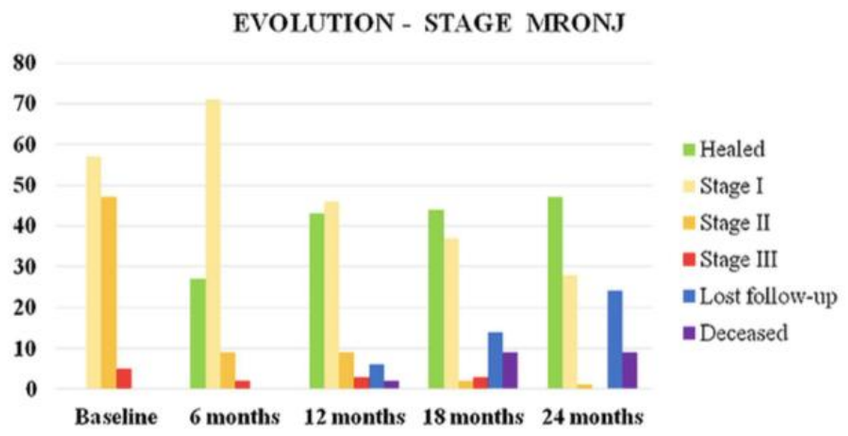

Fig. 1. Evolution of stages of disease during the 24 months' follow-up.

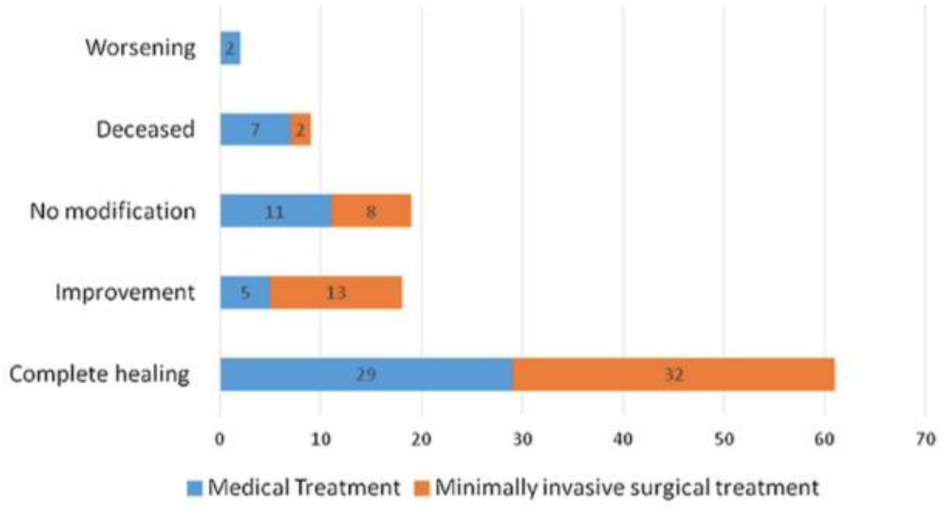

Fig. 2. Results of treatment during the 24 months' follow-up.


Painters of the Great Ming