

Therapeutic Approach in the Treatment of Medication-Related Osteonecrosis of the Jaw: Case Series of 3 Patients and State of the Art on Surgical Strategies

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ABSTRACT

Background: Bisphosphonates and receptor activator of nuclear factor kappa-B ligand inhibitors are currently the most widely used antiresorptive therapies in bone metabolism diseases treatment. Unfortunately they can evoke medication-related osteonecrosis of the jaws. The present case series study proposes to evaluate clinical features, evolution and the surgical therapeutic approaches in three patients affected by medication-related osteonecrosis of the jaw and to review the state of art regarding the management of this complication in light of the most recent literature.

Methods: Three cases of medication-related osteonecrosis of the jaws are discussed, two related to bisphosphonates therapy (ibandronic acid) and one due to denosumab.

Results: All three patients were aged female and had probably a dental trigger agent. The lesions located in posterior mandible were treated in one case with the surgical approach alone and, in the other case, with surgical approach associated with Er:YAG laser. The lesion related to denosumab was treated with surgical approach and platelet rich fibrin application. A complete healing was always achieved.

Conclusions: Dentists should be aware of the potential risk of developing medication-related osteonecrosis of the jaws for patients who take or had taken antiresorptive drugs. The side effects of denosumab and bisphosphonates are partly overlapping and currently there is still no consensus about the therapeutic surgical options. Prevention and early detection of the lesions should be the primary strategy.

Keywords: antiresorptive drugs; laser therapy; oral surgery; osteonecrosis; platelet-rich fibrin.

Accepted for publication: 8 May 2021

To cite this article:

Vettori E, Pipinato G, Bussani R, Costantinides F, Nicolin V, Bevilacqua L, Maglione M.

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J Oral Maxillofac Res 2021;12(2):e6

URL: <http://www.ejomr.org/JOMR/archives/2021/2/e6/v12n2e6.pdf>

doi: [10.5037/jomr.2021.12206](https://doi.org/10.5037/jomr.2021.12206)

INTRODUCTION

Osteonecrosis of the jaws (ONJ) is a severe bone disease related to various medicaments: antiresorptive drugs (including bisphosphonates and receptor activator of nuclear factor kappa-B ligand [RANKL] inhibitors) and antiangiogenic drugs [1].

Osteoclasts activity is depressed by antiresorptive agents, therefore, bone resorption is inhibited. Among these agents bisphosphonates, denosumab and selective estrogen modulators are the most used, rather than hormone replacement therapy and calcitonin which are mostly abandoned [2]. Typical and frequent indications for the use of these drugs are postmenopausal osteoporosis, bone malignant lesions secondary to breast or prostate cancer, and multiple myeloma [3].

Bisphosphonates, classified as being non-nitrogenous (etidronate, tiludronate and clodronate) or nitrogen-containing (pamidronate, alendronate, risendronate, zolendronate, ibandronate and neridronate) [1,4], are currently the most widely used antiresorptive therapies for malignant and nonmalignant diseases characterized by various kinds of bone loss [3,5]. Oral administration of bisphosphonates is generally used to treat osteometabolic disease such as osteoporosis, osteopenia or more rare syndromes such as Paget's disease and osteogenesis imperfecta. Intravenous administrations is used for cancer-related conditions such as breast, prostate or lung cancer metastases and for the management of multiple myeloma [1].

Since 2003, Marx [6] report of bone necrosis induced by bisphosphonate-related osteonecrosis of the jaw (BRONJ) has generated great concern regarding the side effects of these drugs. Nitrogen-containing bisphosphonates are the only kind of bisphosphonates associated with osteonecrosis [1]. BRONJ is characterized by exposed necrotic bone in the maxillofacial region for more than 8 weeks in bisphosphonate users with no history of head and neck radiotherapy [4]. In the early stages of BRONJ there are often no symptoms and radiographic features may not be present, advanced stages, instead, are characterized by pain, paraesthesia, mucosal ulceration and exposed necrotic bone.

In 2006, a classification based on the clinical presentation of the disease has been proposed by American Association of Oral and Maxillofacial Surgeons (AAOMS) [7]. This classification defines three stages of BRONJ:

- Stage I, asymptomatic necrotic bone exposure;
- Stage II, bone necrosis with exposure, pain and infection;

- Stage III, bone necrosis with exposure, pain, infection and pathological fractures, or cutaneous fistulas.

The site of major prevalence of BRONJ has been reported to be the mandible although the maxilla can also be involved and both maxillary bones can be affected [4,8].

Because of the side effects related to the use of bisphosphonates, other therapeutic strategies for osteoporosis and bone metastasis or particular bone pathologies (such as Paget's disease) have been developed. The discovery of RANKL, that induces osteoclast differentiation, have led to the development of denosumab, a fully human monoclonal antibody that can bind and inhibit RANKL [5,9]. Like bisphosphonates, denosumab has been associated with ONJ [10]. In spite of bisphosphonates, whose side effects persist for years depending on the cumulative dose, the effects of RANK ligand inhibitors diminish rapidly after the end of administration [1].

Although ONJ related to non-antiresorptive anticancer agents is rare, its incidence is increasing (from 0.8% to 12%) [7]. Antiangiogenic agents do not block tumour cell growth, but interfere with new blood vessels formation.

In substance there are two types of drug related to ONJ: one that inhibits the angiogenetic growth factor or its receptor (bevacizumab, a monoclonal antibody), and the other one is a molecule which binds the tyrosine kinase receptor (sunitinib and sorafenib) [1].

ONJ related to non-antiresorptive agents has a better prognosis in terms of percentage of healing and healing time compared to antiresorptive drugs, even though histology, radiology and management is similar [11].

Medication-related osteonecrosis of the jaw (MRONJ) has been defined as exposed necrotic bone in the oral cavity that does not heal within 8 weeks in patients who had taken antiresorptive (e.g. bisphosphonates and denosumab) or antiangiogenetic (bevacizumab) drugs [12].

For the treatment of MRONJ different conservative therapeutic approaches have been established, reserving surgery to cases of necessity in light of a risk-benefit ratio. In 2014 the AAOMS [13] published an update on the position paper regarding the staging and relative treatment of MRONJ (Table 1). Treatment approaches for MRONJ are still controversial; the lack of consensus has led to the development of new therapeutic strategies such as the use of platelet-rich fibrin (PRF) and laser therapy [12].

This study proposes to evaluate clinical features, evolution and surgical therapeutic approaches in three cases of medication-related osteonecrosis of

Table 1. American Association of Oral and Maxillofacial Surgeons MRONJ position paper 2014 update [13]

	MRONJ staging	Treatment Strategies
At risk category	No apparent necrotic bone in patients who have been treated with either oral or intravenous (IV) bisphosphonates.	- No treatment indicated. - Patient education.
Stage 0	No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms.	Systemic management, including the use of pain medication and antibiotics.
Stage 1	Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection.	- Antibacterial mouth rinse. - Clinical follow-up on a quarterly basis. - Patient education and review of indications for continued bisphosphonate therapy.
Stage 2	Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage.	- Symptomatic treatment with oral antibiotics. - Oral antibacterial mouth rinse. - Pain control. - Debridement to relieve soft tissue irritation and infection control.
Stage 3	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone, (i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor.	- Antibacterial mouth rinse. - Antibiotic therapy and pain control. - Surgical debridement/resection for longer term palliation of infection and pain.

MRONJ = medication-related osteonecrosis of the jaw.

the jaw and to review the state of art regarding the management of medication-related osteonecrosis of the jaw in light of the most recent literature.

CASE DESCRIPTION AND RESULTS

Three different cases of MRONJ were diagnosed and treated at the Maxillofacial and Dental Surgical Unit (Department of Medical, Surgical and Health Sciences, University of Trieste) between June 2014 and December 2016.

An informed written consent was obtained from each patient to use data for the research that was conducted in agreement with the guidelines of the Helsinki Declaration as revised in 1975 and amended in October 2003.

For each case pain assessment has been made with Numeric Rating Scale (NRS) which is an unidimensional measure of pain intensity whereby the patients rates the pain from 0 (no pain) to 10 (worst possible pain) [14].

Case 1

A 77-years old woman was admitted at the Dental Emergency Unit because of an unresolved perimplantitis in the site of left mandibular second premolar, with local pain (reported as 6 in NRS), gingiva swelling, dysesthesia of the left side of the lower lip and purulent discharge. The infection signs persisted despite of a long antibiotic therapy (about one month) and the dental implant removal done one

month before.

The medical history showed hypertension, gastritis, hypercholesterolemia and osteoporosis.

The patient had taken alendronate - Fosamax® (Merck Sharp & Dohme B.V.; Haarlem, The Netherlands) from 2010 until 2015 following by a therapy with ibandronic acid - Bonviva® (F. Hoffmann-La Roche Ltd.; Basel, Switzerland).

An orthopantomography (OPG) and a computed tomography (CT) were executed and revealed an osteolytic lesion with a bone sequestrum around the left mandibular second premolar site.

Clinical and radiographic features are shown in Figure 1.

Antibiotic therapy with amoxicillin and clavulanic acid 875 mg/125 mg - Neoduplamox® (GlaxoSmithKline; London, United Kingdom) *Ter In Die (TID)* and chlorhexidine mouthwashes (Curasept S.p.A.; Varese, Italy) were prescribed. Surgical intervention was performed under local anaesthesia (mepivacaine chlorohydrate with epinephrine 1 : 100000 - Molteni Dental S.r.l.; Firenze, Italy), the left mandibular first premolar and the implant in the site of left mandibular first molar were extracted. Sequestrectomy and debridement of the necrotic tissue were executed until a bleeding bone was observed. Interrupted sutures with silk were applied.

The biopsy of the necrotic bone was performed. Histologic examination revealed the presence oral mucosa with massive reactivated chronic phlogosis and micro-abscessual areas (Figure 2). Diagnosis of MRONJ at Stage 2 was made. Antibiotic therapy was continued for one week after surgery.

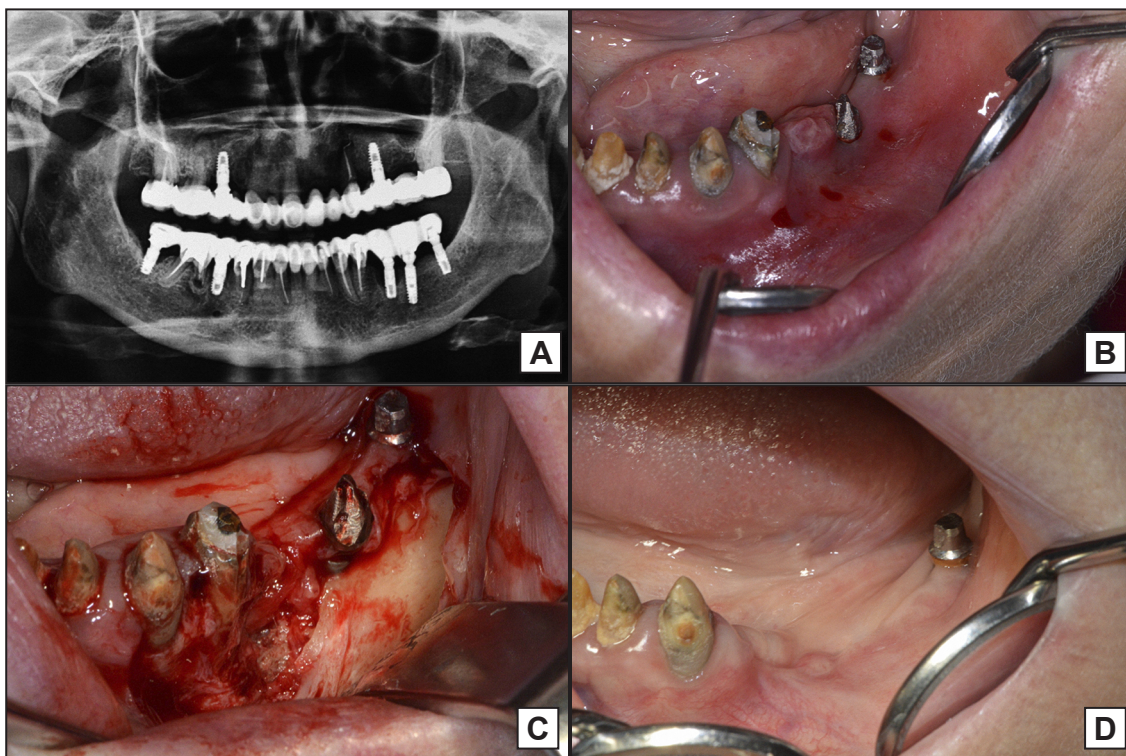


Figure 1. Case 1. A = orthopantomography before surgery; B = preoperative clinical features; C = surgical debridement; D = 8-months follow-up.

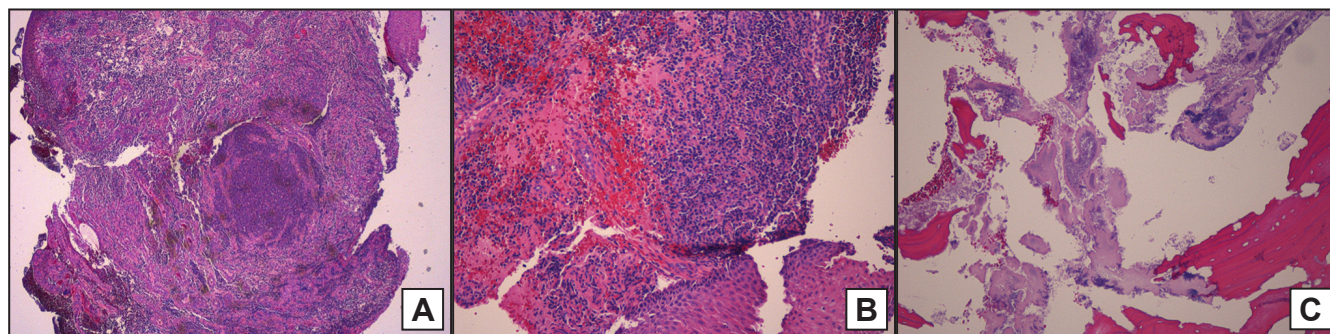


Figure 2. Case 1. Oral mucosa with massive reactivated chronic phlogosis and micro-abscessual areas. Hematoxylin and eosin stain: A = original magnification x2.5; B = original magnification x10; C = original magnification x10.

All along follow-up's span, presence of paraesthesia was evaluated asking the patient about sensibility of tongue, lip and chin; tests like 2-point discrimination, light touch and pinprick have been performed [15].

After three weeks, the debrided region was covered by normal mucosa. Dysesthesia of the left side of the lower lip improved.

After 8 months, a new CT was performed revealing a radiolucent area with well-defined borders and without surrounding periosteal reaction. There were no infections signs. Paraesthesia at the lower lip was the same as the one before the surgical debridement, but pain has regressed.

Case 2

A 66-years old woman was admitted at the Emergency

Unit of the Dental School because of pain, bad breath and exposed necrotic bone in the anterior lower jaw (Figure 3). Three months before the woman underwent inferior tooth extraction, she had eight teeth extracted in the inferior incisal and right molar region by her dentist.

The review of the patient's medical history revealed that for 21 months she had received monoclonal antibody therapy with denosumab - Xgeva® (Amgen; Singapore) because of bone metastases from breast cancer diagnosed two years before.

The OPG showed a wide osteolytic area without defined borders in the anterior lower jaw (Figure 3). CT was requested to plan the surgery.

Antibiotic therapy with amoxicillin and clavulanic acid 875 mg/125 mg - Neoduplamox® TID and chlorhexidine mouthwashes were prescribed.

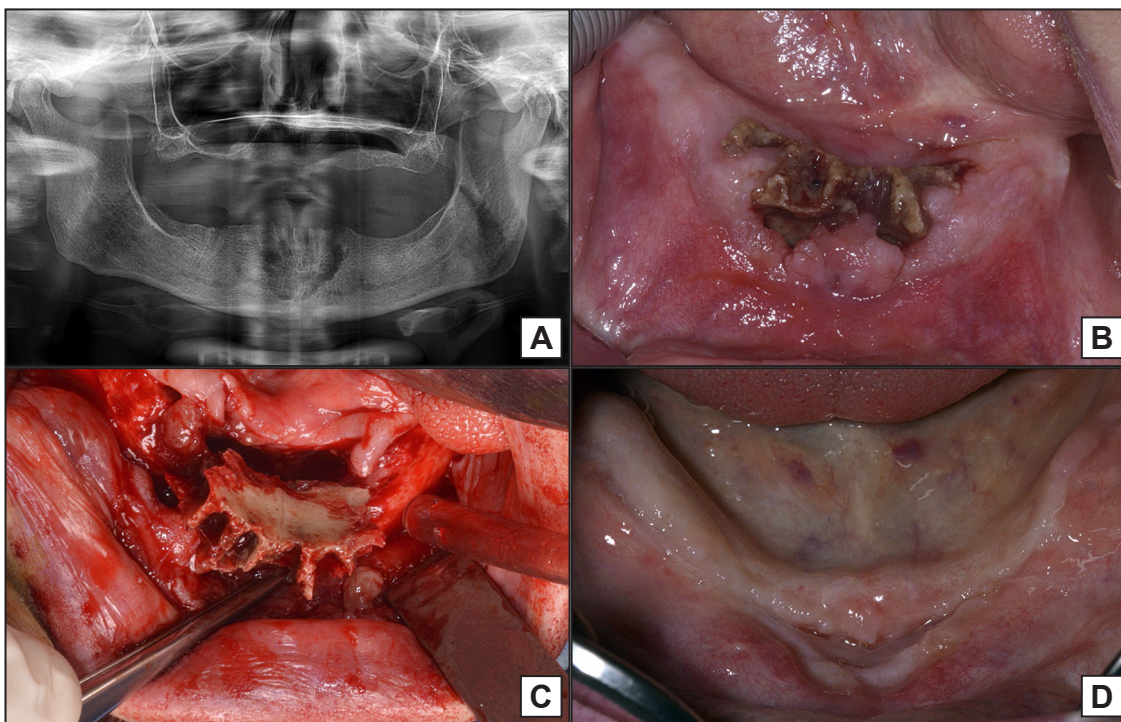


Figure 3. Case 2. A = Orthopantomography before surgery; B = preoperative clinical features; C = surgical debridement; D = 12-months follow-up.

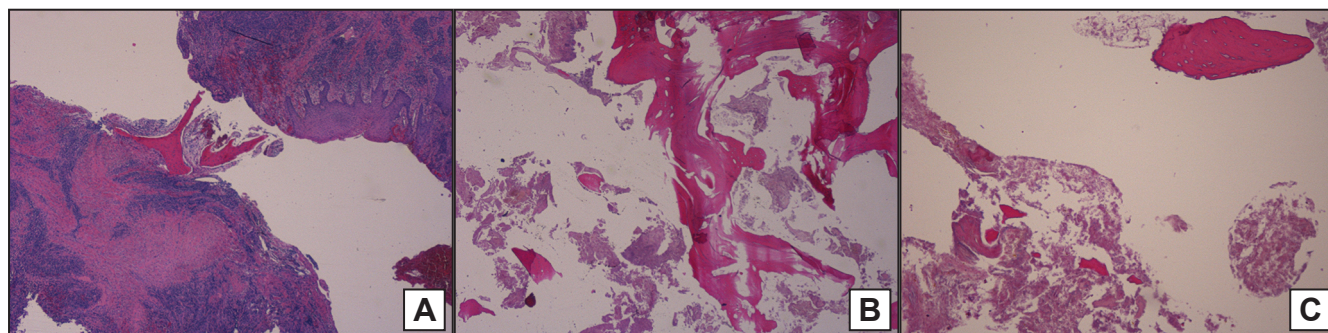


Figure 4. Case 2. Necrotized and regressed bone tissue with intense reactivated chronic phlogosis Hematoxylin and eosin stain: A = original magnification x2.5; B = original magnification x2.5; C = original magnification x10.

Surgical resection of bone necrosis was performed in operating room under local anaesthesia (mepivacaine chlorohydrate - Molteni Dental S.r.l.). Patient underwent bone surgical toilette and debridement until a bleeding bone was observed. The biopsy of necrotic bone were performed. Two swabs of macroscopically health bone were executed. PRF was used on the remaining bone in order to provide growth factors and improve wound healing and bone regeneration. Absorbable interrupted sutures with Vicryl® (Henry Schein Inc.; Melville, New York, USA) were placed. Antibiotic therapy was continued for 1 week after surgery.

Histologic examination revealed the presence of necrotic bone with chronic inflammatory cell infiltrate and muscle-connective tissue with stromal lymphoplasmacellular infiltrates and hemorrhagic imbibition (Figure 4). Stage 2 MRONJ diagnosis was

made.

After 2 weeks a wound dehiscence was observed and a new CT (performed after 5 weeks from the first one) revealed a well-defined area of surgical resection with clear areas where bone bleeding was obtained.

After 7 weeks the debrided region was covered by normal mucosa.

OPG performed after about one year from the surgery revealed a good bone healing. The surgical wound was definitively healed, even if the patient has always reported discomfort with NRS = 3 in the operated area.

Case 3

A 80-years old woman was admitted at the Dental Emergency Unit because of a paraesthesia of the left lower lip and pain reported as 5 in NRS scale. In her medical history it was reported she was suffering

by hypertension, hypothyroidism, diabetes type II and osteoporosis.

Symptoms appeared after dental extractions approximately 3 years before.

An accurate review of her medical history was performed and it was emerged that she had started a therapy with Bonviva® - ibandronic acid 150 mg once per month, 8 years before.

Clinical examination revealed abnormal posture of the left lower lip associated with low thermic and pain sensitivity. Mandibular profile was altered because of the presence of a non-mobile hard swelling without defined borders. Intraoral examination revealed the presence of a dental implant in 3.6 site with clinical evidence of purulent discharge and the presence of a vestibular soft mucosal swelling (Figure 5).

The OPG showed a large osteolytic lesion without defined borders; the bone inside this area had a cotton wool appearance (Figure 5).

Antibiotic therapy with amoxicillin and clavulanic acid 875 mg/125 mg - Neoduplamox® TID was prescribed and a biopsy of the sick bone was performed. A head and neck CT was requested to plan the surgery.

Patient underwent bone surgical toilette under general and local anaesthesia (mepivacaine chlorohydrate - Molteni Dental S.r.l.) and contextual removal of the implant with sequestrectomy and debridement until a bleeding bone was observed; the residual cavity was also treated with Er:YAG laser device (2940 nm, LightWalker AT - Fotona; Ljubljana, Slovenia).

Antibiotic therapy was continued for one week after surgery.

Histologic examination revealed the presence of necrotic bone with chronic inflammatory cell infiltrate, hyperplasia and parakeratosis of stratified squamous epithelium with underlying hyperplastic granulation tissue (Figure 6). Diagnosis of Stage 2 MRONJ was performed.

After three weeks the debrided region was covered by normal mucosa and a new CT (performed after 16 weeks from the first one) showed a radiolucent area with well-defined borders and without surrounding periosteal reaction. Hypoesthesia disappeared after surgery.

At one year follow-up no signs of relapse or recurrence appeared.

DISCUSSION

Thanks to their antiresorptive properties, bisphosphonates reduce morbidity and mortality in malignant and non-malignant bone diseases.

These drugs have an effect on increasing apoptosis and osteoclastic inhibition by binding the mineral component of bone: this action is well known even though their mechanism is not yet fully understood.

The way bisphosphonates work is that they disrupt the osteoblast-osteoclast interaction so they interfere with the mechanism of bone remodelling [4,6,16].

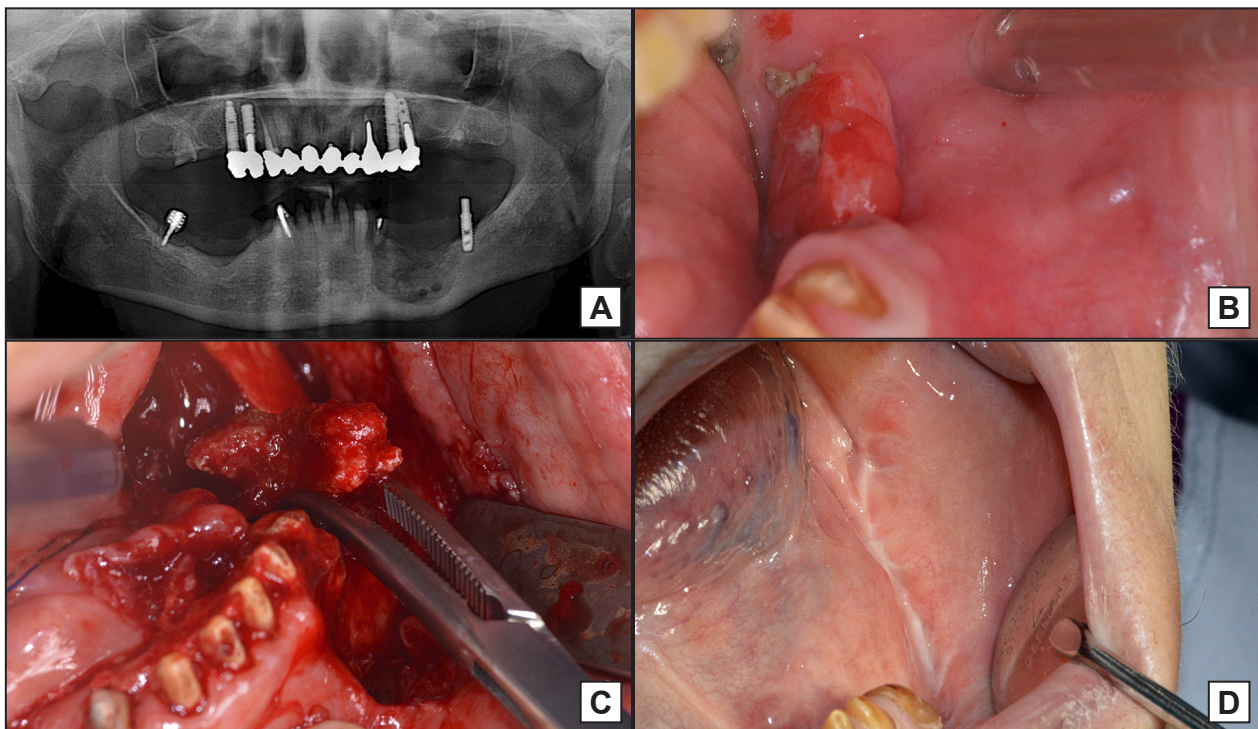


Figure 5. Case 3. A = Orthopantomography before surgery; B = preoperative clinical features; C = surgical debridement; D = 18-months follow-up.

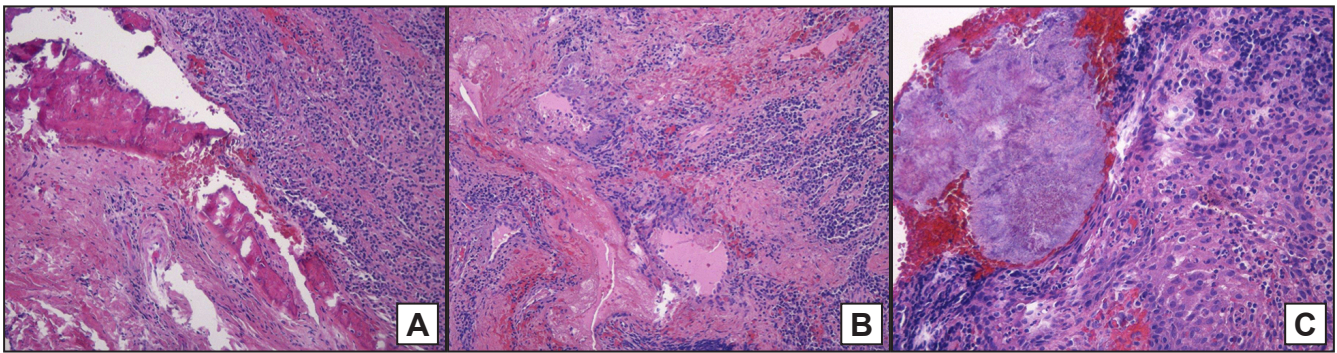


Figure 6. Case 3. Oral mucosa with intense phlogosis and aggregates of bacterial flora. Hematoxylin and eosin stain: A = original magnification x1; B = original magnification x10; C = original magnification x20.

Bisphosphonates can be administered orally, usually for the treatment of osteoporosis, or intravenously because of the higher power, generally in cases of bone metastases [4,7,17]. Like the bisphosphonates, denosumab has been associated with ONJ. Denosumab's pharmacodynamics and pharmacokinetics differ from that of bisphosphonates, for this reason, denosumab-related-ONJ may resolve more rapidly.

Denosumab is injected subcutaneously; the dosing ranges from 60 mg every 6 months in postmenopausal women to 120 mg every 4 weeks in the setting of malignant diseases. Instead of bisphosphonates, denosumab circulatory half-life is about 26 days, in fact its effect is reversible because it does not accumulate in the bone [3,4,18]. Denosumab prevents the interaction of RANKL (a cytokine secreted by bone marrow stromal cells, osteoblasts and T cells, essential to induce osteoclast differentiation) with RANK (receptors present on osteoclasts and their precursor cells), blocking the formation, functional ability and survival of osteoclastic cells. The indications of denosumab are principally similar to bisphosphonates, that bind to the calcium hydroxyapatite present in bone and reduce bone resorption by affecting the function and survival of osteoclasts. However they do not affect the formation of osteoclasts [9,19,20].

The side effect profile of denosumab and bisphosphonates is partly overlapping: ONJ occur with similar frequency under treatment with denosumab and zoledronic acid, the most potent among bisphosphonates [3,21,22]. The greater prevalence of osteonecrosis in the maxillary bones can be explained by the major concentration of antiresorptive drugs in these structures, because of the continuous bone remodelling resulting from the constant functional trauma [4,23]. The site of the greater prevalence of ONJ has been reported to be the mandible; maybe, the antiangiogenic properties of bisphosphonates has a relevant effect in mandible

because of its physiologic characteristic of elevate blood supply and high turnover [4,23].

Several risk factors can be related to the onset of the disease, including the nature of the drugs, its potency and absorption rate, local and systemic factors and the duration of administration. Osteonecrosis can develop spontaneously; however, dental surgery is considered to be the main triggering factor, followed by prosthetic trauma, periodontal disease, and dental implant placement [4,24]. Regarding the treatment of ONJ, reported therapeutic options include the use of antiseptic agents as 0.12% chlorhexidine, systemic antibiotics, and surgical debridement, either alone or combined with biological modulators such as platelet-rich plasma, an high autologous platelet concentrated that provides a source of growth factors improving wound healing and bone regeneration [4].

Also PRF has proved to be useful after surgery, in fact PRF releases growth factors such as platelet-derived growth factors, insulin-like growth factor and vascular endothelial growth factor which are important healing promoters [25].

Fernando de Almeida Barros Mourão et al. [26] in their study presented a series of patients treated with PRF applied after necrotic bone removal and showed a positive effect on promoting soft tissue healing and reducing post-operative pain.

Also Giudice et al. [27] in their paper found that the use of PRF to cover bone surface after surgical debridement of necrotic area brought to better short-term results in terms of mucosal healing and quality of life. Although long-term evaluation showed no statistical differences between using or not PRF after surgery, with the cited study they demonstrated a significant improvement in short-term quality of life and a reduction of necessity of re-intervention.

Several studies [28-31] have described MRONJ surgical treatment performed with Er:YAG laser. Vescovi et al. [28] affirmed that a surgical approach performed with Er:YAG laser was associated with significantly better results when compared with traditional surgical treatment.

Table 2. Personal and clinical characteristics of patients with MRONJ and treatment received (n = 3)

Case	Sex	Age	Antiresorptive agent	Indication for treatment	Treatment duration (years)	Lesion site	Stage AAOM	Triggering factor	Treatment for MRONJ	Follow-up outcome
1	F	77	Ibandronic acid (alendronate)	Osteoporosis	(5) +1	Mandible	2	Implant removal due to perimplantitis	Surgical debridement	Good wound healing, paraesthesia remained
2	F	66	Denosumab	Bone metastases (breast cancer)	1	Mandible	2	Dental extraction	Surgical debridement + PRF	Good wound healing, remained discomfort (NRS = 3)
3	F	80	Ibandronic acid	Osteoporosis	8	Mandible	2	Dental extraction	Surgical debridement + Er:YAG laser	Good wound healing, no more paraesthesia

AAOM = American Association of Oral and Maxillofacial Surgeons; MRONJ = medication-related osteonecrosis of the jaw; F = female; PRF = platelet-rich fibrin; NRS = numeric rating scale.

Er:YAG laser emits a wavelength of 2940 nm which is highly affine to water and hydroxyapatite; laser technology allows an efficient ablation of hard tissues without producing important thermal increasing which could determine necrotizing effects on tissues [29-31].

Laser works producing water vapour that expands increasing pressure until micro-explosions develop. The result is tissue removal and this process is called thermally-induced mechanical ablation [32].

The cold ablation produced by Er:YAG laser has been demonstrated to be effective and safe in removal of granulation tissue and root surface debridement. Furthermore it also promotes new bone formation in periodontal surgery also because of the lower increase of the temperature compared with rotary tools [30,31,33].

Discontinuing the drug after ONJ diagnosis is controversial: denosumab’s related ONJ, due to its different mechanism of pathogenesis, may resolve more rapidly after a drug holiday compared to BRONJ [10]. Usually, when a drug use causes a serious side effect, the drug is interrupted but, as these medications are also used to inhibit bone metastases growing, benefits of their continuation is almost always overweigh their risks.

There is still no consensus about the treatment of the ONJ because the pathological mechanism of disease is not fully understood, but there is agreement on the importance of prevention for bisphosphonate users. In the present study, all the analysed cases have been diagnosed after symptoms developing; this is according to literature’s findings that ONJ diagnosis is not easy during asymptomatic, reinforcing the importance of an accurate medical history and of prevention [34,35]. Clinical and radiographic evaluation of patient’s dental status is required before starting therapy with antiresorptive drugs, in order

to identify and remove possible sites of infections, such as teeth with periodontal disease, residual roots, chronic infections. At risk patients must have acceptable oral health when antiresorptive therapy begins, for the purpose of avoid the necessity of tooth extractions during (and after) the antiresorptive therapy [36].

In our experience all the three surgical options used gave us good results; all patients were Stage 2 MRONJ and have been treated with surgery associated with antibiotic therapy and antimicrobial rinses as indicated by the AAOMS position paper [13]. Moreover, in one case Er:YAG laser was also used and in another one PRF was applied. Due to our results all the three strategies have been revealed to be effective in MRONJ treatment. The three cases presented in this paper are summarized in Table 2.

CONCLUSIONS

Medication-related osteonecrosis of the jaw is a complication that can cause oncologic treatment interruptions and can deteriorate quality of life. It is necessary and very important for dentists to be aware of the potential risk of developing medication-related osteonecrosis of the jaw in patients who take or had taken in the past antiresorptive drugs. Prevention and a particular care toward these patients with periodic checks should be the primary strategies for antiresorptive drugs users. The use of platelet-rich fibrin and Erb:YAG laser seems promoting therapeutic options in the treatment of medication-related osteonecrosis of the jaw but more studies should be developed to establish a precise way to assess the medication-related osteonecrosis of the jaw risk and to define the more effective treatment strategies in light of a benefit-risk ratio.

ACKNOWLEDGMENT AND DISCLOSURE STATEMENTS

The authors report no conflicts of interest related to this study. No external funding to declare.

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To cite this article:

Vettori E, Pipinato G, Bussani R, Costantinides F, Nicolin V, Bevilacqua L, Maglione M.

Therapeutic Approach in the Treatment of Medication-Related Osteonecrosis of the Jaw: Case Series of 3 Patients and State of the Art on Surgical Strategies

J Oral Maxillofac Res 2021;12(2):e6

URL: <http://www.ejomr.org/JOMR/archives/2021/2/e6/v12n2e6.pdf>

doi: [10.5037/jomr.2021.12206](https://doi.org/10.5037/jomr.2021.12206)

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