



Treatment Strategies and Outcomes of Medication Related Osteonecrosis of the Jaw (MRONJ)

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Abstract

Medication Related Osteonecrosis of The Jaws (MRONJ); Caused by maxillofacial surgical procedures performed during or after antiresorptive, antiangiogenic and bisphosphonate treatments; It is a newly defined disease and its etiopathogenesis is still not fully understood. Studies on the definition, staging and treatment approaches of the disease are evaluated by the commission formed by the American Association of Maxillofacial Surgeons, and guidelines expressing opinions on these issues are published; Discussions still continue on the treatment approaches of the disease. Conservative, surgical, alternative and their combinations methods are used in the treatment of the disease, depending on the level of bone and soft tissues affected.

Keywords: Bisphosphonates, MRONJ, Outcomes, Management

Introduction

Bisphosphonates (BPs) represent a group of drugs used in various disciplines such as endocrinology, oncology, and orthopedics.^{1,2} They are often used for the treatment of bone diseases such as osteoporosis, Paget's disease, malignant hypercalcemia, osteolytic bone metastases and osteolytic lesions of multiple myeloma.^{1,3,4} They reduce the need for radiotherapy and surgery by providing a statistically significant reduction in skeletal complications, including pathological fractures, spinal cord compression, and malignant disease hypercalcemia.⁵

BPs are synthetic analogs of the natural pyrophosphate molecule. They can be classified according to whether or not they contain nitrogen, and it is known that nitrogen-containing BPs have higher potential than those without nitrogen content.⁶

The first lesion in the jaws after long-term BP use was described by Marx in 2003.⁷ Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is considered the main side effect of BP treatment.^{8,9}

Recently, osteonecrosis of the jaw was encountered with oncological doses of other antiangiogenic (sunitib) or antiresorptive

(denosumap) agents without use of BPs.¹⁰⁻¹² This condition caused the name and definition of the disease to change, and a new definition was made by AAOMS (American Association of Oral and Maxillofacial Surgeons) in 2014. This definition is formulated as follows: "Without application of radiotherapy to the jaw and bone metastasis in the jaws; open necrotic bone or bone necrosis with intra-oral or extra-oral fistula for 8 weeks or longer despite being treated by a clinician in the maxillofacial region, with the previous or current use of antiresorptive and antiangiogenic agents."¹³

The true incidence of MRONJ is not known exactly. Reported rates range from 0.028% to 18.6%, depending on the indication of treatment, study population and sample size.^{14,15}

MRONJ: Diagnosis and Staging

Patient history and clinical examination remain the most sensitive diagnostic tools for MRONJ. Despite the treatments performed, the presence of exposed bone in the oral area for 8 weeks or longer is the most consistent diagnostic criteria for MRONJ.¹⁶ Differential diagnosis of BRONJ should be made from previously defined and known clinical pathologies such as alveolar osteitis, sinusitis, gingi-

Quick Response Code:



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Received: 31 May, 2021

Published: 06 July, 2021

Citation: Gol EB. Treatment Strategies and Outcomes of Medication Related Osteonecrosis of the Jaw (MRONJ). *Mod Res Plast Recon Sur.* 2021;1(2):1-4. DOI: [10.53902/MRPRS.2021.01.000510](https://doi.org/10.53902/MRPRS.2021.01.000510)

vititis / periodontitis, periapical pathologies and some sequestering forms of cemento-osseous dysplasia.¹⁶

Open and necrotic areas of bone may remain asymptomatic for weeks, months or even years.¹⁷ These lesions often become symptomatic following infection of the surrounding tissues. Clinically, signs and symptoms including pain, mobility of teeth, mucosal swelling, erythema, ulceration, paresthesia, even anesthesia of the relevant trigeminal nerve branch may precede the development of osteonecrosis.^{18,19} In some patients, impaired sensory perception may occur in the relevant region due to the compression of the resulting infection on the neurovascular bundle.^{20,21} These symptoms

may occur spontaneously or mostly occur after dentoalveolar surgery.²²⁻²⁷

In many MRONJ patients, the radiological findings are within normal limits or are similar to those seen in osteoradionecrosis or osteomyelitis.

The first classification of MRONJ was made by Marx in 2009 based on the clinical appearance of the disease.²⁸ This classification was formalized in a report published by AAOMS in the same year.²⁹ Five separate stagings have been made in this classification (Table 1).

Table 1: Staging and Treatment Strategies of BRONJ (Ruggiero 2014).

| BRONJ Stage | Clinical Appearance | Treatment Strategies |
|-------------|---|--|
| At Risk | No apparent necrotic bone in patients who have been treated with oral or intravenous bisphosphonates | -No treatment indicated -Patient education |
| Stage 0 | No clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms | -Systemic management, including use of pain medication and antibiotics |
| Stage 1 | Exposed and necrotic bone or fistulas 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 fistulas that probes to bone associated with infection as evidenced by pain and erythema in the region of 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 \$1 of the following: exposed and necrotic bone extending beyond the region of alveolar bone (ie, inferior border and ramus in mandible, maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to inferior border of the mandible or sinus floor | -Antibacterial mouth rinse -Antibiotic therapy and pain control -Surgical debridement or resection for longer-term palliation of infection and pain |

Pathophysiology and Treatment Methods of MRONJ

Many hypotheses have been put forward that lead to development of empirically based treatment methods for MRONJ. However, it is not possible to explain the pathophysiology of MRONJ with a single hypothesis and to use the same type of treatment for all patients.³⁰ Although the pathophysiology of MRONJ cannot be fully explained, five different hypotheses have been suggested.

Bisphosphonates are known to reduce bone resorption by impairing osteoclast function and inducing apoptosis of osteoclasts. With these effects, they affect bone healing negatively by disrupting the bone turnover and causes osteonecrosis, especially in the jaw bones.

In addition to the use of bisphosphonates, MRONJ has developed in animal models with dental pathology. This result shows that infection and / or inflammation have an effect on the etiology of MRONJ.³⁰

It is known that nitrogen-containing bisphosphonates (especially Zoledronate) reduce microvascular density in vivo. Impaired

vascularization is known to be effective in the formation of osteonecrosis, but post-mortem histological studies showed areas of osteonecrosis with normal vascularization. Therefore, it is thought that inhibition of angiogenesis is not an etiological factor per se.

Soft tissue toxicity was the first pathophysiological hypothesis proposed for BRONJ. The demonstration of the affinity of nitrogen-containing BPs for epithelial cells is equivalent to that of bone cells in some in vitro studies has reinforced this hypothesis. However, this hypothesis has largely lost its validity as no such effect was observed in patients using denosumab.³⁰

Finally, It has been demonstrated that infusion of mesenchymal stem cells or T-regulator cells prevents and attenuates BRONJ-like lesions in studies performed in animals where immune deficiency is effective and impaired immunity promotes the development of MRONJ.³⁰

Treatment of MRONJ

There is no universally accepted treatment protocol for MRONJ. The methods used for treatment are varied, controversial and em-

pirical. Three broad categories of intervention have been defined. Classical "wound healing" conservative treatment, various surgical techniques and different "supportive" treatments. These 3 approaches are often used simultaneously or in successive combinations (Table 2).^{29,31}

Conservative treatment includes providing optimal oral hygiene, elimination of active dental and periodontal diseases, use of topical antibiotics and, if necessary, systemic antibiotics. Although conservative treatment is not sufficient for complete recovery, it forms the basis of MRONJ therapy, as it provides long-term disappearance of symptoms and reduction of patient complaints.^{26,32}

The basic principle in surgical treatment is to stop the progression of the disease with conservative treatment as much as possible without starting surgical treatment. However, many studies have reported successful results with surgery.³³⁻³⁵

With surgery, a full thickness flap should be elevated, the exposed bone should be determined to the limits where there is no osteonecrosis and normal blood supply and it should be removed by resection. The sharp edges and corners should be rounded, and the surgical area should be closed primarily with a tension-free absorbable suture one week later.^{16,36} Some researchers have reported better results with surgical treatment compared to debridement and conservative treatment.³⁷⁻³⁹

Table 2: Treatment methods for BRONJ management BRONJ (Ruggiero 2009).

| |
|---|
| Conservative treatment: |
| - Disinfectant mouth rinses (saline, chlorhexidine, chlorine, peroxide) |
| - Antibiotic therapy (local, systemic or both) |
| - Antifungal therapy |
| Surgical techniques: |
| - Surgical debridement, sequestrum removal, surgical sinus drainage procedures (antrostomy) |
| - Extraction of teeth within osteonecrotic bone, management of implants |
| - Bone resection |
| - Surgical wound closure, reconstructive surgery, grafts |
| - Laser-assisted surgery |
| - Fluorescence-assisted surgery |
| Adjuvant non-surgical treatment strategies: |
| - Hyperbaric oxygen therapy |
| - Pentoxifylline and tocopherol (vitamin E) |
| - Ozone therapy |
| - Low Level Laser Therapy (LLLT) for biostimulation and pain relief |
| - Er:YAG, Nd:YAG, Nd:YAP laser treatment for anti-inflammatory treatment |
| - Platelet-rich plasma |
| - Parathyroid hormone and teriparatide |
| - Bone Morphogenetic protein (BMP) |

Alternative treatment methods include growth and differentiation factors that increase wound healing, autologous bone marrow stem cell transplantation into the lesion, and the use of agents such as pentoxifylline and α -tocopherol in addition to antimicrobial therapy. In addition, autofluorescence-guided surgery and low-energy laser therapy are among the alternative therapies that have been studied recently.⁴⁰

Conclusion

It is known that MRONJ is a progressive disease. There is no generally accepted treatment method for MRONJ. The clinical treatment of MRONJ is arranged according to clinical signs and symptoms. Traditional treatments still maintain their place in MRONJ treatment. However, it has been observed that the success rates of supportive treatments are higher.

Acknowledgments

None.

Funding

None.

Conflicts of Interest

Author declares that there is no conflict of interest.

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