An Update on Medication Related Osteonecrosis of the Jaw: 18 years of Experience

Vickas Agarwal, DDS MD
Parkland Memorial Hospital/UT Southwestern Medical Center, Dallas, TX

Thomas Schlieve, DDS MD
Parkland Memorial Hospital/UT Southwestern Medical Center, Dallas, TX

INTRODUCTION

Medication related osteonecrosis of the jaw (MRONJ) is a well-known phenomenon first described by Robert Marx (2003) and Salvatore Ruggiero (2004). Together, Marx and Ruggiero described a total 99 cases of presumed MRONJ associated with intravenous and oral bisphosphonates (Pamidronate, Zoledronate, Alendronate, Risedronate).\(^1\,^2\) Since the first descriptions of MRONJ, several case reports and series have been released documenting similar cases of osteonecrosis. The American Association of Oral and Maxillofacial Surgeons (AAOMS) has published numerous iterations of a position paper on MRONJ, with the most recent version published in 2014. The guideline paper uses the following criteria for diagnosis:

1. Current or previous treatment with antiresorptive or antiangiogenic agents.
2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region for more than eight weeks.
3. No history of radiation therapy to the jaws or obvious metastatic disease to the jaws.\(^3\)

Overall, the risk MRONJ associated with oral bisphosphonates or Denosumab when used for osteoporosis is less than 0.1%.\(^4\) There have been few updated epidemiologic studies on MRONJ, however, recent studies have shown that the incidence of MRONJ in patients with cancer on Denosumab is higher than the same with those on Zoledronate.\(^5\,^6\) Further, there also may be an increased incidence of MRONJ in patients switched from Zolendronate to Denosumab as compared to those solely on Zolendronate (5.4%).\(^7\)

This paper will provide an update on MRONJ including drugs with risk, pathogenesis of disease, and methods of treatment with an overview of the most recent literature. The clinician will gain a better understanding of the development of MRONJ and how to manage this disease with evidence for each treatment modality.

STAGES OF DISEASE

While there have been many proposed systems to stage this disease, this paper will use the AAOMS staging system to describe the degree of risk or disease present, as 1) it was the most commonly encountered classification system in these authors’ review of the literature, and 2) in these authors’ opinions the most useful in directing treatment and management strategies. AAOMS currently stages MRONJ into five categories \(^3\,^8\) to 18:
Patients at Risk. Absence of necrotic bone and symptoms

Stage 0. No clinical evidence of osteonecrosis, but with clinical or radiographic symptoms such as:

- Odontalgia of non-odontogenic origin
- Dull bone pain in body of mandible with possible radiation to temporomandibular joint
- Sinus pain with or without inflammation of maxillary sinus membrane
- Altered neurosensory function
- Mobility of teeth or loss of bone in absence of periodontal disease
- Periapical pathology in absence of dental caries
- Radiographic persistence of unremodeled bone in extraction socket
- Osteosclerosis of alveolar bone or surrounding basal bone
- Increased thickness of lamina dura and decreased thickness of periodontal ligament

Stage 1. Asymptomatic patients with necrotic bone or fistula(e) that sounds to bone without evidence of infection.

Stage 2. Symptomatic patients with necrotic bone or fistula(e) that sounds to bone with evidence of infection.

Stage 3. Patients with necrotic bone or fistula(e) that sounds to bone with evidence of infection and:

- Necrotic bone extending beyond alveolar bone
- Pathologic fracture
- Extraoral fistula
- Oroantral or oronasal communication
- Osteolytic process extending to inferior border of mandible or maxillary sinus floor

DRUGS WITH RISK

The following lists drugs with respective indications and mechanisms of action that are known to put patients at risk of developing osteonecrosis of the jaw.

Anti-resorptive Drugs – Bisphosphonates

Bisphosphonates (Alendronate, Etidronate, Clodronate, Ibandronate, Pamidronate, Risedronate, Tiludronate, Zoledronate) make up the drug class that is most well-known to put patients at risk of MRONJ, hence the previously used term ‘bisphosphonate-related osteonecrosis of the jaw (BRONJ)’.\textsuperscript{19-22} These medications are used for management and treatment of multiple skeletal disorders including osteoporosis, metastatic cancer (most commonly multiple myeloma or primary cancers of breast, prostate or lung), Paget’s disease, and genetic conditions (such as osteogenesis imperfecta) in the pediatric population.\textsuperscript{23-26} There has also been some lesser discussion in the literature regarding the use of bisphosphonates in other conditions such as Giant Cell lesions of the jaw, Giant cell tumors of bone, fibrous dysplasia, Gaucher’s disease, osteomyelitis, and in conjunction with orthopedic implants.\textsuperscript{27,28} A recent study by Greenberg and Lee described a novel method of adjuvant local treatment of Giant Cell tumors of bone with bisphosphonate loaded polymethylmethacrylate bone cement and reported a lower local recurrence rate with their technique as compared to conventional treatment.\textsuperscript{29} With the increasing indications of bisphosphonates for treatment of pediatric conditions such as osteogenesis imperfecta, questions have been raised regarding the risk for and
prevalence of MRONJ in this population. However, a recent systematic review by Duarte et al., found no reported cases or associations between the use of bisphosphonates and osteonecrosis of the jaw in the pediatric and young adult population (less than 24 years of age).30 Although current studies are limited, there have yet to be any documented cases of MRONJ reported in the pediatric population with diagnosed osteogenesis imperfecta on bisphosphonates.31

Physiologically, bisphosphonates are synthetic analogs of pyrophosphate, a naturally-occurring compound that has the capacity to bind hydroxyapatite and inhibit mineralization. Bisphosphonates have a high affinity for hydroxyapatite and inhibit its breakdown, thereby suppressing bone resorption. When osteoclasts resorb bone which has previously had bisphosphonates incorporated into it through the hydroxyapatite-binding mechanism, the bisphosphonates are released and prevent the formation of the ruffled border, thereby preventing the osteoclasts from reattaching to the bone surface and continuing the resorptive process. These drugs also downregulate the differentiation of cells into osteoclasts and induce osteoclast apoptosis, further slowing the rate of resorption.23,32

Chemically, bisphosphonates contain a central nonhydrolyzable carbon, while naturally-occurring pyrophosphate does not. Attached to a central carbon are multiple hydroxyl groups and flanking phosphate groups, which are responsible for bisphosphonates’ strong affinity for hydroxyapatite in bone. The hydroxyl groups (R1 position) increase this drug’s ability to bind calcium, and both the hydroxyl and phosphate groups create a tertiary interaction between bisphosphonates and the bone matrix (responsible for binding to bone and the specificity of this drug to bone). Bisphosphonates also limit osteoblast and osteocyte apoptosis, however the mechanism by which this occurs remains unclear to date. Potency is determined by the R2 position moiety (nitrogen or amino groups), which can increase antiresorptive potential exponentially as compared to first generation, non-nitrogen-containing bisphosphonates, such as Etidronate. (Other brand names for first generation bisphosphonates are Clodronate and Tiludronate). Second and third generation bisphosphonates with a nitrogen-containing R2 moiety are Alendronate, Risendronate, Ibandronate, Pamidronate, Zolendronate. Figure 1 illustrates the chemical structure of a bisphosphonate. Figure 2 illustrates the chemical structure of pyrophosphate.

Maximum suppression of bone resorption occurs within three months of starting oral therapy (dosing frequency ranges from daily, to weekly or monthly) and remains constant throughout treatment.23,33 The half-life of intravenous alendronate after a single dose is approximately 10-12 years.34,35

![Figure 1. Chemical structure of bisphosphonate.](image-url)
Anti-resorptive Drugs – Denosumab

The most common non-bisphosphonate, antiresorptive drug associated with MRONJ is Denosumab, which is a human monoclonal antibody (IgG2) that is specific for receptor activator of nuclear factor κβ ligand (RANKL). Denosumab binds at the osteoprotegrin binding site on RANKL, thereby mimicking osteoprotegrin itself. RANKL is essential for osteoclast differentiation and overall function. Denosumab acts extracellularly to prevent RANKL from binding to the RANK receptor, thereby inhibiting development and survival of osteoclasts. Since this drug works extracellularly, it does not permanently bind bone matrix, and residual effects of this drug are reported to be minimal four to six months after a single dose, and approximately 12-24 months after cessation of multiple doses. The half-life of Denosumab is approximately 25.4 days.

Anti-angiogenic Drugs

Anti-angiogenic drugs are used mostly to arrest tumor growth and work by inhibiting the formation of new blood vessels. These drugs are thought to decrease the ability of bone to regenerate, remodel, heal after an insult (such as a planned extraction or trauma), and recover from an infection. There are two primary types of anti-angiogenic drugs:

1. Anti-vascular endothelial growth factor (VEGF) (Bevacizumab, Aflibercept, Pazopanib, Cabozantinib, Lenvatinib)
2. Anti-tyrosine kinase inhibitors (TKI) (Sunitinib, Axitinib, Dasatinib, Imantinib, Erlotinib, Sorafenib)

Anti-VEGF drugs inhibit the ability of the body to form new vasculature and can inhibit chemotaxis of macrophages and differentiation of osteoblasts. Anti-TKI drugs inhibit differentiation of osteoclasts and monocytes thereby blunting a response to a bony insult. The incidence of MRONJ in patients on an anti-resorptive drug and either a VEGF inhibitor or TK inhibitor was estimated to be 11.1% in a recent study as compared to a control group incidence of 10.9% on anti-resorptive therapy only. A 2018 literature review found a total of 35 cases of MRONJ occurring in patients solely on anti-angiogenic therapy only without current or prior use of anti-resorptive drugs. The overall risk of MRONJ associated with these drugs alone is unknown, but there is evidence of an increased risk of MRONJ when an anti-angiogenic drug is used concomitantly with an antiresorptive.

Immunomodulators

Immunomodulators are drugs designed to target specific mediators of inflammation or immune response. They are commonly used in managing autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriasis, Crohn’s disease, ulcerative colitis, some cancerous processes etc. There have been few reported cases of MRONJ associated with drugs such as anti-tumor necrosis factor (TNF) alpha (Infliximab, Adalimumab), and anti-CD20

Figure 2. Chemical structure of pyrophosphate.
(Rituximab), however, at the present time there is not enough evidence in the literature to consider these drugs a significant risk. Methotrexate is a commonly prescribed drug used for numerous autoimmune diseases – its primary mechanism of action is to inhibit DNA synthesis by inhibiting dihydrofolate reductase (DHFR). At lower doses, it can inhibit both B and T lymphocyte functions and proliferations, and at higher doses it is cytotoxic. As with the other immunomodulators mentioned above, there are limited case reports of methotrexate-linked MRONJ. Methotrexate is a commonly prescribed drug used for numerous autoimmune diseases – its primary mechanism of action is to inhibit DNA synthesis by inhibiting dihydrofolate reductase (DHFR). At lower doses, it can inhibit both B and T lymphocyte functions and proliferations, and at higher doses it is cytotoxic. As with the other immunomodulators mentioned above, there are limited case reports of methotrexate-linked MRONJ.

Another category of immunomodulators that have limited linkage to MRONJ are mammalian target of rapamycin (mTOR) inhibitors that are primarily used in patients with a solid organ transplant to prevent rejection, or at higher doses to treat kidney or breast cancer. Again, there is limited evidence in the literature to confirm the link between mTOR inhibitors and MRONJ. Corticosteroids, which are prescribed for a multitude of different acute and chronic disorders, are another class of immunomodulators implicated in the development of MRONJ. As of yet, there is no evidence to state that corticosteroids alone can cause MRONJ, but rather that when taken concomitantly with bisphosphonates or Denosumab, a patient’s risk of developing MRONJ is greater than if taking either a bisphosphonate or Denosumab alone. Recent case reports in the literature have described the occurrence of MRONJ in patients taking either a bisphosphonate or Denosumab simultaneously with anti-neoplastic drugs such as Cyclophosphamide, Docetaxel, Lenalidomide, and Thalidomide.

**PATHOPHYSIOLOGY AND DISEASE PROCESS**

**Characteristics of the Jaws**

The pathophysiology of MRONJ is not entirely understood, however, there are several accepted theories. To understand the proposed pathogenesis of MRONJ, one must first consider the reasons why antiresorptive/antiangiogenic drugs selectively affect and cause osteonecrosis in the maxilla and mandible. Bisphosphonates and Denosumab are systemically administered drugs, but evidence in the literature has proven that these drugs preferentially concentrate in the jaws as compared to the appendicular and axial skeletons. Embryologically, the maxilla and mandible undergo intramembranous bone formation while long bones undergo endochondral ossification. Additionally, the mandible has been shown to contain higher concentrations of collagen as compared to long bones. Alveolar bone turnover also is significantly higher than that of other bones due the forces of mastication. These developmental and structural characteristics of the maxilla and mandible are possible reasons behind why bisphosphonates exhibit a preferentially higher uptake in the jaws versus other bones of the body.

**Influence of Medication**

There is a greater risk of developing MRONJ when a higher dose, more frequent intervals, and a parenteral dosing route of antiresorptive or antiangiogenic drugs is used. This method of dosing is generally utilized in patients suffering from metastatic cancer rather than those with osteoporosis. Antiresorptive drugs, both bisphosphonates and Denosumab, blunt the differentiation and proliferation of osteoclasts, thereby decreasing the ability of the maxilla and
mandible to undergo routine turnover and healing in the event of an insult, putting patients at risk for MRONJ.

Compared to bisphosphonates, Denosumab has shown a significant difference in time of onset from initial dose to development of MRONJ. Due to the extracellular activity of Denosumab, its effects on osteoclasts are more immediate as compared to that of bisphosphonates. A recent retrospective study conducted by Pautke et al. analyzed the time to onset in three different groups who had all been diagnosed with MRONJ: 1) patients on bisphosphonates only, 2) patients transitioned from bisphosphonates to Denosumab therapy, and 3) patients on Denosumab only. The median duration of antiresorptive therapy in the population studied was 6.6 years. The authors found a statistically significant difference among the three groups, with the shortest time to onset of MRONJ belonging to the Denosumab group with a median time of onset of 2.0 years, followed by the bisphosphate group with median time of 3.86 years, and finally the group that was transitioned from bisphosphonate to Denosumab, with a median time of 4.07 years. The results of this study suggest that patients on Denosumab may have a risk of earlier development of MRONJ as compared to those on bisphosphonates. Limones et al., conducted a systematic review and meta-analysis of six randomized controlled trials with a total of 13,857 patients and concluded that Denosumab is associated with significantly higher risk for MRONJ when compared to zolendronate, following one year and three years of exposure to the drugs, with no differences in prognosis.

Local Factors

There are several local risk factors for the development of MRONJ including poor bone healing following a trauma, procedure, or inflammatory event (i.e., tooth extraction), chronically ill-fitting denture, and odontogenic infections (e.g., periapical pathology, periodontal disease). Most commonly, the inciting event leading to development of MRONJ is the extraction of a tooth. Animal studies have shown that routine extraction of noninfected teeth in rats receiving bisphosphonates or Denosumab healed with woven bone fill in sockets and overlying mucosal coverage. This contrasts with extraction of teeth with periodontal disease or periapical pathology that exhibited delayed and/or incomplete mucosal healing, exposed bone, and areas of osteonecrosis. Hadaya et al., conducted an animal study with the hypothesis that extraction of teeth with periapical inflammation leads to MRONJ in rats treated with high dose bisphosphonates. The authors of this study gave eight-week-old rats an intraperitoneal dose of either endotoxin-free saline (control) or zoledronic acid twice weekly that was continued throughout the duration of the study. Following one week of treatment, rats underwent one of three procedures. The first group underwent a planned pulp exposure in mandibular molars with extraction of the teeth four weeks after the exposure. The second group underwent the pulp exposure, as well as injection of a pathogenic solution containing Porphyromonas gingivalis, Streptococcus gordonii, Aggregatibacter actinomycetemcomitans, and Fusobacterium nucleatum to create experimental periapical disease. The pulp exposure was covered with a temporary filling material and the animals were euthanized eight weeks after pulp exposure. The third group underwent pulp exposure, inoculation of pathogens, and tooth extractions at four weeks. The rats in groups with a planned pulp exposure alone and a planned pulp exposure with inoculation of pathogens did not show any soft tissue dehiscence or exposed bone. 62.5% of rats
in the third group treated with planned pulp exposure, inoculation of pathogens, and extraction at four weeks had mucosal defects with exposed bone. On radiographic assessment, 50% of rats in the third treatment group showed total absence of osseous healing and 20% showed only partial healing. On histologic analysis, rats in the third treatment group showed a higher incidence empty osteocyte lacunae and osteonecrosis, and a lower concentration of osteoclasts. Lastly, gram staining of the above subjects showed a significantly higher number of bacteria compared to all other treatment and control groups. The results of this study suggest that odontogenic infection combined with a tooth extraction in a subject on a nitrogen containing bisphosphonate has the highest risk of developing MRONJ. The presence of periodontal disease or periapical pathology increases the risk of developing MRONJ even in the absence of tooth extractions due to increased activity of osteoclasts in these clinical states. Antiresorptive medications can slow the progression of periodontal disease driven bone loss while still precipitating osteonecrosis. It has also been suggested by some studies that bisphosphonates and Denosumab can promote infection in the superficial bone surface secondary to their effects on the function of immune cells such as T cells, macrophages, neutrophils, dendritic cells, and monocytes. There has been some evidence to support that bone bound to bisphosphonates (i.e. hydroxyapatite) is more prone to infection by increased adhesion of biofilm and colonization of bacteria.

Accumulation of bisphosphonates in the periodontal ligament (PDL) may also contribute to the pathogenesis of MRONJ. A recent study by Taniguchi et. al. analyzed the effects of bisphosphonates on PDL fibroblasts versus human dermal fibroblasts. The authors determined that the addition of bisphosphonates created reactive oxygen species in the tissue, possibly contributing to the development of MRONJ. The authors further suggested that concomitant antioxidant treatment in patients on bisphosphonates could prevent the development of MRONJ. In a related study, Li et. al. analyzed the effects of bisphosphonates on human PDL in lesions sampled from patients with confirmed cases of MRONJ. Through histologic analysis, flow cytometry, micro-computed tomography scanning, cell assays, polymerase chain reaction, and immunofluorescence analysis, it was determined that PDL affected by MRONJ demonstrated decreased cell proliferation, adhesion, migration, and osteogenic differentiation as compared to the control PDL cells in the study. The authors concluded that the above could be evidence for the pathogenesis in MRONJ. On a related note, there have been reports of bisphosphonate related toxicity to gingival tissue and its contributory effect on MRONJ. Bisphosphonates can alter tissue expression of inflammatory mediators and collagen production, both of which play a crucial role in reaction to physical stress/trauma, and tissue healing. Several studies have analyzed the species of bacteria present in MRONJ lesions. Most often, Actinomyces species have been implicated as the predominant bacterium present in MRONJ lesions among other periodontal microflora including Streptococcus, Prophyromonas, Lactobacillus, Tannerella, Prevotella, Treponema, Fusobacterium, and Veillonella. Systemic Factors

Rheumatoid arthritis and diabetes mellitus have been linked to an increased risk of developing MRONJ in patients with the
Bisphosphonates are sometimes utilized in patients with rheumatoid arthritis to manage osteoporosis and decrease overall bone destruction. The exact link between systemic diseases and MRONJ has yet to be established, but one theory is that systemic disease has a negative effect on a patient’s immune system leading to an increasing susceptibility to infection. A recent retrospective study by Feng et al., aimed at identifying particular risk factors that correlated to more severe stages of MRONJ revealed that Stage 3 lesions were more likely when present in the maxilla, in posterior molar regions of either maxilla or mandible, and if the patient’s serum albumin level was <40 g/L. Other factors also listed as correlating with Stage 3 disease were patient age <= 65, concomitant use of chemotherapy, presence of MRONJ >= 12 months prior to intervention. While the results of this study are important, some of the aforementioned risk factors for Stage 3 disease are logical. In general, MRONJ lesions in the maxilla are more aggressive, and since the maxillary alveolus closely abuts the maxillary sinus, lesions may quickly progress into Stage 3 as compared to those in the mandible. Additionally, a vast majority of MRONJ lesions are located in the posterior regions of the maxilla and mandible, and therefore Stage 3 lesions are also more likely to be present in these locations. The two clinically relevant risk factors identified by this study are age <= 65 at time of diagnosis and albumin < 40 g/L.

**DRUG HOLIDAYS**

There have been some reports and recommendations for a drug holiday during which a patient halts antiresorptive therapy to undergo a tooth extraction or other oral surgical procedure. Current literature does not support the use of drug holidays in patients on bisphosphonates or Denosumab. A recent randomized clinical feasibility trial by Otteson et al., investigated whether a drug holiday (one month preoperatively and three months postoperatively of a high dose antiresorptive medication (Denosumab or intravenous bisphosphonate) related to a surgical tooth extraction (full thickness mucoperiosteal flap elevation, tooth extraction, minor bone removal, and closure with sutures) would have an impact on the development of MRONJ and patients’ self-reported state of health as compared to continuation of the medication. This study had 23 patients that met their inclusion and exclusion criteria and agreed to participate in the trial – 13 were assigned to the drug holiday group and 10 were assigned to the control, continuation group. At the three month follow up visit, all 10 patients in the continuation group and nine patients in the drug holiday group healed without complication. The remaining four patients, all of whom were in the drug holiday group and on antineoplastic drugs, developed MRONJ. Among these four patients, one suffered from a spontaneous hip fracture and another from a vertebral compression fracture. Additionally, three patients in the Denosumab drug holiday group developed progression of their primary cancer. The results of the study suggest that a drug holiday did not prevent MRONJ in patients on antiresorptive therapy undergoing a surgical tooth extraction and that holding an antiresorptive for a prolonged period of time could have devastating consequences. Although the number of patients analyzed in the study was low, the results align with the conclusions of other studies published in the literature.

**Treatment of Disease**

The following is a summary of treatment as recommended by AAOMS. For patients at
risk, no treatment is indicated. Patient education is key to prevent these patients from developing MRONJ. Dental clearance prior to the initiation of oral or IV bisphosphonates is often required. Generally, patients with Stage 1 or 2 disease can be treated with systemic and local antibiotics with pain medication as needed. All patients, regardless of stage, benefit from marginal alveolar debridement or removal of any necrotic or mobile bone to allow for soft and hard tissue healing. Patients with Stage 3 disease require surgical intervention in addition to medical therapy such as segmental osteotomy of the involved region, placement of a reconstruction plate, and immediate or delayed vascular or non-vascularized bone grafting.

Much debate exists today regarding the most effective method used to treat a patient affected by MRONJ, regardless of stage. There are several surgical and non-surgical methods proposed. Surgical methods of treatment include local sequestrectomy, marginal resection, and segmental resection of affected bone with or without non-vascularized/microvascular reconstruction, with or without extraction of adjacent teeth. Non-surgical methods include the use of local and systemic antimicrobial agents. Adjuncts to therapy described in recent literature include Teriparatide, Pentoxifylline and Tocopherol (vitamin E), and autologous platelet rich plasma (PRP).

The goal of treatment of MRONJ is to provide symptom relief and halt worsening of disease. This can be accomplished using different methods. Traditional surgical treatment involves definitive resection and removal of affected necrotic alveolar bone with primary soft tissue closure. Giudice et. al., conducted a prospective study with the purpose of evaluating success of surgical treatment of Stage 1 and 2 MRONJ lesions. In this study, success was determined based on time to mucosal integrity and downstaging of disease. The authors enrolled 129 patients with 133 MRONJ lesions in their study, of which 57 patients had Stage 1 disease and 72 had Stage 2. Each patient was treated with the same surgical protocol as follows: pre-operative antibiotics, antiseptic oral rinse, and dental hygiene prophylaxis, then sequestrectomy and debridement with piezoelectric instrumentation under local anesthesia until bleeding bone was encountered. Bone grafting or filers were not used, and surgical wounds were closed primarily with sutures under no tension. For Stage 1 lesions time to mucosal coverage was 56.4 +/- 54.5 days, and for Stage 2 time to mucosal coverage was 83.1 +/- 74.9 days. Downstaging of Stage 1 lesions occurred at 33.6 +/- 9.9 days post-operatively, and at 56.4 +/- 54.5 days for Stage 2 lesions. The differences between the two outcome variables for both stages were statistically significant. The results of this study suggest that surgical treatment of Stage 1 and 2 MRONJ lesions rapidly can cure patients of their disease with full mucosal healing and improve their quality of life. Further, the results beg the question if previously recommended non-surgical treatment is the most optimal treatment for Stage 1 and 2 lesions.

Palla et. al., recently published a study that measured outcomes of surgical treatment of MRONJ in patients on Denosumab. The authors concluded based on a literature review the success rate of surgical treatment for MRONJ secondary to Denosumab was 80%. Success was defined as mucosal closure after resection of necrotic bone. Similarly, a study by Pautke et. al., compared surgical treatment success in patients with MRONJ Stage 1 to 3 on either a bisphosphonate only, Denosumab only, or bisphosphonates then Denosumab after a switch in therapy. The same surgical protocol with fluorescence guided bone resection with
soft tissue closure and post-operative antibiotics was followed in all three drug groups regardless of disease stage. The overall treatment success was 89.1% with the highest success rate of 91.5% in the bisphosphonate then Denosumab group. Following this was the Denosumab only group at 90.3%, and the bisphosphonate only group at 84.7%. The success rate of cases taken for secondary surgical revision was 95.3% overall in this study.73 There have been few studies describing MRONJ in bone surrounding a dental implant. Nisi et. al., published a retrospective study analyzing 15 patient cases of peri-implant MRONJ. All patients listed in the study underwent conservative treatment with dental hygiene, use of Chlorhexidine mouth rinse, and systemic antibiotics, followed by surgical removal of dental implants in affected bone, sequestrectomy, bone debridement and curettage. Of note, histologic analysis of bone samples were conducted post operatively, which showed empty lacunae, Haversian systems, and Volkmann canals consistent with osteonecrosis. 86.7% of patients treated had a successful outcome from treatment with no necrotic bone, mucosal defects, fistulas, and symptoms at 12 months post treatment.74 These recent studies provide evidence that surgical treatment of early and late stage MRONJ lesions can provide predictable and high rates of success.

With respect to bone grafting, Marschall et. al., investigated factors that influence the survival of immediate non-vascularized bone grafting in patients who underwent mandibular segmental resections. Of the 47 patients studied, 22 were diagnosed with osteomyelitis or MRONJ pre-operatively, and the average size of resection for this group was 7.8 +/- 3.1 cm. The success rate in the osteomyelitis and MRONJ group was 86.3%. Overall, the length of successful grafts was 6.5 +/- 2.0 cm and of those that failed was 10.7 +/- 3.5 cm. The authors concluded that success of immediate non-vascularized bone grafting for segmental mandibular resections is influenced by the length of the graft.75

Soutome et. al., published a retrospective study on the effect of radiographically evident periosteal reaction (PR) on the success of surgical treatment (i.e., marginal or segmental resection) in patients with MRONJ of the mandible. Thirty-eight of the 181 patients analyzed in this study demonstrated PR on preoperative computed tomography. 55.3% of patients with PR underwent total healing of the wound on clinical exam, as compared to 73.4% of patients without PR who fully healed. One hundred percent of the patients with PR who had the area PR included in the resection margins healed fully. This contrasts with 41.4% of patients with PR who did not have the area of PR included in their surgical resection and subsequently did not completely heal. Although the sample size of this study was small, the results suggest that PR associated with MRONJ lesions may negatively impact the outcome of surgically treated MRONJ lesions if adequate resection margins are not obtained. However, if an acceptable margin inclusive of PR was achieved, there was 100% mucosal healing.76 This would lead to the conclusion that a larger resection margin is more likely to achieve cure than minimal to no margin surgery, such as that performed with debridement alone.

Non-surgical treatment of MRONJ has long been discussed as an alternative to definitive surgical resection. As described above, current AAOMS guidelines recommend non-surgical treatment for most Stage 1 and 2 lesions. Recently, there has been some evidence in favor of non-surgical treatment for those patients who may not be able to undergo surgery or elect to forgo surgery at the time of diagnosis. Hadaya et. al.,
implemented a retrospective cohort study of 106 patients with 117 MRONJ lesions. Primary outcome variables were resolution of disease and time to disease resolution (further defined as disease progression, improvement, or resolution). These patients were treated with local wound care (debridement with topical Chlorhexidine 0.12% with a toothbrush or cotton swab with detailed instructions), systemic antibiotics (three weeks of amoxicillin 500mg TID or doxycycline 100mg BID), and removal of a detached mobile sequestrum, if applicable. Patients with Stage 1 disease received Chlorhexidine only, and those with Stage 2 and 3 disease received Chlorhexidine, systemic antibiotics, and analgesic medications. Sixty-five lesions were Stage 1, 46 lesions were Stage 2, and six lesions were Stage 3. Seventy-one percent of lesions resolved completely and 22% showed some degree of disease improvement with local wound care. Seventy-two percent of all Stage 1 lesions, 70% of Stage 2 lesions, and 67% of Stage 3 lesions showed complete resolution with the treatment regimen outlined above. The authors determined that the success illustrated in their study was linked to the physical debridement of biofilm, plaque, and debris on exposed bone. Of note, the treatment period for patients using local wound care was up to two years or greater until disease resolution was noted with some patients remaining with disease beyond two years of a palliative management protocol. Additionally, only six patients presented with Stage 3 disease during the study period so results may not be applicable to this group. Another recent study by Albanese et. al., analyzed the outcomes of non-surgical treatment on 12 patients with Stage 2 and 3 MRONJ lesions (based on the SIPMO/SICMF staging system) for one year. These patients were treated with professional dental hygiene visits every four months, Chlorhexidine 0.12% rinses the first seven days of each month, two times a day, and antibiotic treatment for seven days every month whenever signs of infection (purulence) or pain was present (Amoxicillin/Clavulanic acid 875mg/125mg TID and Metronidazole 500mg TID). The authors noted statistically significant improvement in outcome symptoms (erythema, edema, halitosis, mucus and cutaneous fistulas, pain) at interval follow up visits during the study period. The results of these studies suggest that non-surgical symptom management is an option for patients who elect to not pursue surgery and are compliant with a frequent wound care regimen over the course of months to years with the caveat that a risk factor for Stage 3 disease is long standing Stage 1 or 2 disease.

Contrary to the studies above, a recent review by AlDhalaan et. al., concluded that a non-surgical approach should only be used in patients in the at risk or early, asymptomatic stages – this method of treatment may only provide temporary relief of symptoms, rather than a cure. Another retrospective study analyzed the effectiveness of non-surgical management of 75 patients with 92 AAOMS Stage 1 MRONJ lesions with 0.2% Chlorhexidine mouth rinse and 1% Chlorhexidine gel. Only if Stage 1 lesions advanced to Stage 2 did the study subjects receive systemic antibiotics, until the lesions resolved to Stage 1. 91.3% of lesions in this study had persistent exposed bone through the follow up period (not specified), 79.8% of lesions progressed to Stage 2 or 3 lesions, and 68% of lesions required eventual surgical intervention given the worsening of disease. Although there are some studies that support the utility of palliative or non-surgical treatment of MRONJ lesions, the literature in general presents a mixed picture of success in favor of surgical intervention. Symptoms can be managed temporarily with palliative, non-surgical treatment in patients.
who may be in the process of preparing for surgery (undergoing medical optimization, arranging for post-operative care, etc.) or who elect to defer surgery despite risk of progression, but palliative care is not a route to a cure. If MRONJ is suspected by a dental or medical specialist not equipped to definitively treat MRONJ, it is appropriate to initiate care with topical antimicrobials (e.g., Chlorhexidine rinses) and systemic antibiotics (e.g., Amoxicillin/Clavulanic acid) while also referring the patient to a specialist.26

A systematic review by Vanpocke et. al., analyzed 13 studies with a total of 223 patients with Stage 3 MRONJ (per AAOMS staging guidelines) treated with one of three methods: 1) Non-surgically with Chlorhexidine mouth rinses, systemic antibiotics, regular follow ups and low-level laser therapy, 2) Conservative surgical management with superficial sequestrectomy with or without platelet rich fibrin, 3) Aggressive surgical management with full resection of necrotic bone to bleeding margins with or without microvascular reconstruction. This review concluded that treatment of Stage 3 lesions with conservative therapy did not positively or negatively affect Stage 3 lesions and was not effective in promoting mucosal healing. In the conservative surgical management group 75% of patients showed clinical improvement, of which 54% had full mucosal healing. Among the patients treated with aggressive surgical management without microvascular reconstruction, 85% healed with full mucosal coverage, and 97% treated with both aggressive surgery and microvascular reconstruction healed with full mucosal coverage.51 In addition to previously discussed evidence, it is the ability to clear all necrotic and compromised bone from the patient that is the best predictor of treatment success.

**Therapeutic Adjuncts**

Platelet rich fibrin (PRF) in oral and maxillofacial surgery has long been touted for its ability to promote wound healing – most notably as an adjunct to bone regeneration, maxillary sinus lifting, and soft tissue grafting.80 It is only logical that this technique be applied as an adjunctive measure to surgical debridement and soft tissue closure of MRONJ lesions. While the mechanism by which PRF aids in the healing of MRONJ lesions is not fully understood, studies have shown statistically significant improvements in clinical staging of disease, clinical soft and hard tissue healing, and decreased relapse rates as compared to traditional surgical debridement and soft tissue closure.81,82 Decreased post-operative pain and infections are additional benefits that have been supported in recent literature.83-85

In addition to surgical and non-surgical methods of treatment, there have been studies that investigated the use of oral medications such as Teriparatide, and Pentoxifylline with Tocopherol. A recent randomized clinical trial conducted by Sim et. al., concluded that eight weeks of 20 µg Teriparatide administered subcutaneously once daily with 600mg Calcium Carbonate once daily, and 1000 IU Vitamin D once daily in addition to a standardized treatment pathway for MRONJ (i.e., antimicrobial mouth rinse, systemic antibiotic therapy, and surgical debridement), improved the rate of healing of MRONJ lesions. Among the patients in the treatment group of the study, seven were Stage 0/1, nine were Stage 2, and three were Stage 3 (AAOMS classification system).86 Liu et. al., conducted an investigation of the effects of Icariin and Teriparatide on MRONJ in a rat model and found that both provide some benefit when it comes to healing of MRONJ lesions.87 Icariin has been investigated for
use in glucocorticoid induced osteonecrosis of the femoral head and similar conditions, but has not been studied for use in MRONJ prior to the study by Liu et. al. A literature review by Chopra and Malhan found positive evidence to support the effectiveness of Teriparatide use in MRONJ Stage 2 and 3 lesions. The studies included in their review had a mean duration of treatment of 22 weeks (range 12-48 weeks).\textsuperscript{88} Alarmingingly, these findings were contradicted by a literature review by Anabtawi et. al., who concluded that the quality of evidence available is weak and insufficient to justify the use of Teriparatide for MRONJ.\textsuperscript{89} It is clear that further studies are warranted before the use of Teriparatide can be considered as a reliable adjunct in the treatment of MRONJ.\textsuperscript{90,91}

The use of Pentoxifylline and Tocopherol is known for its use in osteoradionecrosis and currently is being investigated in the PENTO clinical trial (NCT03040778). Studies on the use of these medications in MRONJ are very limited and insufficiently powered. Recent systematic reviews do not contain enough evidence to advocate for their use.\textsuperscript{90,92,93} Perhaps there may be benefit to the use of Pentoxifylline and Tocopherol in MRONJ, however, this has yet to be proven in the literature.

A recently published case report is the first to describe the adjunctive use of Cilostazol and Tocopherol in the management of MRONJ. The authors describe a case in which a 77-year-old female with Stage 3 MRONJ was started on Pentoxifylline and Tocopherol, but due to epigastric pain and nausea, Pentoxifylline was switched to Cilostazol 100mg twice daily (in addition to Tocopherol 500 IU twice daily). After one month on this adjusted regimen, the patient’s osteocutaneous fistula resolved and continued to show clinical improvements over the next nine months while on the regimen.\textsuperscript{94} While this is the first report of this combination of drugs for MRONJ, it may be a catalyst for a new method of adjunctive medical management of MRONJ. Similarly, there have been case reports emerging describing the use of photodynamic therapy as an adjunctive treatment for MRONJ. The theory behind this method of treatment is the production of reactive oxygen species that then reduces the population of bacteria present on an area of exposed bone.\textsuperscript{95} More studies are necessary before this method of treatment can be validated and used on a widespread basis.

Despite some encouraging results described in the literature regarding the adjuncts defined above, studies still are limited with small study populations and insufficient power. Caution should be taken before considering the use of adjuncts to proven surgical and non-surgical treatment of MRONJ.

**CONCLUSION**

This review aims to provide a brief recap of current understanding of MRONJ with updates from recent literature. Oral and maxillofacial surgeons are trained and equipped to provide a single stage surgical cure for MRONJ with a high rate of success. In doing so, one avoids potentially years of exposed bone prone to infections, pain, and risk of disease progression. Surgical treatment of MRONJ has also been shown to significantly improve patients’ overall quality of life.\textsuperscript{71,96} Due to the rarity of this disease, much of the research in alternative MRONJ treatment is retrospective in nature, is limited to small patient population sizes, or is based on expert opinion. Results of current studies, systematic reviews, and meta-analyses should be interpreted with caution. Furthermore, it is difficult to interpret research that uses different systems to classify extent of disease. Recent
guideline articles rely on insufficient evidence or studies with lower than adequate number of study subjects. As newer medications for metastatic disease and osteoporosis are created, the incidence of MRONJ may continue to increase. This may allow studies with larger populations and provide clinicians with more concrete evidence for optimizing treatment modalities in affected patients.

REFERENCES


