Cumhuriyet Dental Journal, 28(2): 278-286, 2025
DOI: https://doi.org/10.7126/cumudj.1613059

Cumhuriyet Dental Journal

| cdj.cumhuriyet.edu.tr | Founded: 1998 Available online, ISSN: 1302-5805 Publisher: Sivas Cumhuriyet Üniversitesi

Diagnosis of Medication-Related Osteonecrosis of the Jaw and Alternative Treatment Methods

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Review Article

History

Received: 04/01/2025
Accepted: 15/01/2025

ABSTRACT

There is currently no specific evidence regarding the pathogenesis of MRONJ and no definitively accepted treatment. Inhibition of bone remodeling is thought to lead to reduced mechanical damage and the resulting accumulation of areas of bone necrosis. When used in therapeutic doses, bisphosphonates inhibit the resorptive activity of osteoclasts, while stimulating the differentiation and bone deposition of osteoblasts. As a result, the bone regeneration mechanism is impaired and the risk of avascular necrosis increases as a result of decreased bone remodeling. Bone resorption markers type I Collagen (Ctx) C-Terminal Telopeptide, Type I Collagen (NTX) N-Telopeptide, Tetrate Resistance Acid Phosphatase Isoform 5b (TRACP 5b), Nuclear Receptor Activator (RANKL) / Osteoprotegerin (OPG), Total Alkaline Phosphatase It has been reported that BRONJ is diagnosed by examining (Talp), Bone Specific Alkaline Phosphatase, Bone Sialoprotein, Pyridnoline, Deoxypyridnoline, Hydroxyproline values. CT is considered a standard method in the evaluation of MRONJ. Treatment of medication-induced osteonecrosis of the jaw basically aims to relieve pain, control secondary infection in soft and hard tissues, and minimize the progression of bone necrosis. Alternative treatment methods for MRONJ such as parathormone, platelet-rich plasma, laser applications, ozone treatment, use of bone morphogenic proteins, pentoxifylline, and surgical debridement guided by fluorescent staining method are also mentioned. The drugs that may be alternatıve to bıphosphonates are Denosumab, Strontıum Ranelate (Sr), Teriparatide, Edta, Stromal Vascular Fractıon Cells (Svf) but further studies are needed to be accepted as a definitive protocol. Despite the complications of bisphosphonate group drugs, their use is widespread and increasing due to their numerous indications. Informing dentists about the mechanism of bisphosphonate-derived drugs, denosumab and anti-angiogenic drugs the treatment of MRONJ and alternative drugs to these group drugs are important for the management of complications that develop due to these drugs.

Keywords: Bronj, Alternative, Treatment, Current, Necrosis.

Çenelerde İlaçlara Bağlı Gelişen Osteonekroz Teşhisi ve Alternatif Tedavi Yöntemleri

Derleme

Süreç

Geliş: 04/01/2025
Kabul: 15/01/2025

ÖZET

MRONJ'ın patogenezine dair kesin kanıtlar bulunmamaktadır ve genel kabul görmüş bir tedavi yöntemi mevcut değildir. Kemik remodelasyonunun baskılanması, mekanik hasarın azalmasına ve nekrotik kemik alanlarının birikmesine neden olur. Terapötik dozlarda kullanılan bifosfonat türevi ilaçlar, osteoklastların rezorptif aktivitesini inhibe ederken osteoblastların farklılaşmasını ve kemik yapımını da etkiler. Bu durum, kemik yenilenmesini bozar ve azalan kemik remodelizasyonu nedeniyle avasküler nekroz riskini artırır. MRONJ tanısında; Tip I Kollajen C-terminal Telopeptid (CTX), N-terminal Telopeptid (NTX), TRACP 5b, RANKL/OPG oranı, Total Alkalen Fosfataz (TALP), Kemik Spesifik Alkalen Fosfataz, Kemik Sialoproteini, Piridinolini, Deoksipiridinolini ve Hidroksiprolin gibi kemik yıkım belirteçleri değerlendirilmektedir. Bilgisayarlı tomografi (BT), MRONJ'nin değerlendirilmesinde standart yöntemlerden biridir. Tedavi ise ağrının giderilmesi, yumuşak ve sert dokulardaki sekonder enfeksiyonun kontrolü ve nekrozun ilerlemesinin önlenmesini hedeflemektedir. Parathormon, PRP, lazer, ozon tedavisi, kemik morfogenetik proteinler, pentoksifilin ve floresan boyama rehberliğinde cerrahi debridman gibi alternatif tedavi yöntemleri araştırılmaktadır. Bifosfonatlara alternatif olabilecek ilaçlar arasında denosumab, stronsiyum ranelat, teriparatid, EDTA ve stromal vasküler fraksiyon hücreleri (SVF) yeralmaktadır. Ancak bunların kesin protokol haline gelmesi için daha fazla çalışmaya ihtiyaç vardır. Diş hekimlerinin bu ilaçların etkileri ve olası komplikasyonları konusunda bilgilendirilmesi önemlidir.

Anahtar Kelimeler: Bronj; Alternatif, Tedavi, Güncel, Nekroz.

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How to Cite: Yılmaz A, Arı I, Samunahmetoğlu E, Hürmüzlü S, Çetiner S. (2025) Diagnosis of Medication-Related Osteonecrosis of the Jaw and Alternative Treatment Methods Diagnosis of Mronj and Alternative Treatments, Cumhuriyet Dental Journal, 28(2): 278-286.

Introduction

MRONJ (Medication-Related Osteonecrosis of the Jaw) is a condition that typically arises as a side effect of medications affecting bone metabolism. The drugs that cause MRONJ can be grouped into three main categories:[1,2]

Bisphosphonates

Bisphosphonates are drugs commonly used for prophylactic or therapeutic purposes during the postmenopausal period. It is known that they increase bone mineral density, reducing bone fractures related to osteoporosis, and prevent mass deformation in the bone due to aging, glucocorticoid use, and the decrease in estrogen.[1]

Bisphosphonates are not only preferred for menopause treatment but also for the treatment of fibrous dysplasia, heterotopic ossifications, Paget's disease, ankylosing spondylitis, hypercalcemia due to malignancies, and multiple myeloma.[2]

Bisphosphonates (BPs) are stable analogs of inorganic pyrophosphate, a by-product of cellular metabolism. Pyrophosphates are easily hydrolyzed and eliminated, but bisphosphonates are resistant to hydrolytic degradation due to the substitution of oxygen with carbon in the bisphosphonate molecule, which explains their accumulation in the bone matrix and their half-life of more than 11 years.[3]

Currently, there is no specific evidence related to the pathogenesis of MRONJ, and there is no universally accepted treatment. The most widely accepted hypothesis is the effect of bisphosphonates on angiogenesis and the inhibition of normal bone remodeling. It is thought that preventing bone remodeling leads to a decrease in mechanical damage and consequently to the accumulation of bone necrosis areas.[1,3,4]

Human Monoclonal Antibody (Denosumab):

Denosumabs were started to be used as an alternative to bisphosphonates, but it is reported that in latest studies like bisphosphonates, it can increase the risk of MRONJ, although its effects subside more quickly after discontinuation. Denosumab suppresses osteoclast activity, thereby reducing bone resorption. Denosumab is used to prevent bone loss in conditions such as osteoporosis (Prolia) and metastatic bone diseases (Xgeva).[5-7]

- Examples: Denosumab (Prolia, Xgeva).

Anti-Angiogenic Drugs:

These drugs are used in cancer treatment to reduce tumor vascularization. They also impair the healing mechanisms of jawbone tissue, thereby increasing the risk of MRONJ.[8]

Examples: Bevacizumab, sunitinib, aflibercept.

Underlying Mechanism

Adequate bone metabolism is ensured by the proper functioning of the osteoblast-osteoclast mechanisms. This mechanism operates through a complex formed by kappa-B ligand (RANKL), osteoprotegerin (OPG), and transforming growth factor β1 (TGF-β1).[3,9] This mechanism can be altered by the application of bisphosphonate derivative drugs. The effects of bisphosphonates on bone metabolism are achieved by inhibiting the osteoclastic activity responsible for bone resorption, but bisphosphonates do not only affect osteoclast cells; they also inhibit osteoblastic activity. They also have antitumor effects, such as preventing tumor invasion and/or inducing apoptosis of tumor cells in the extracellular matrix. Bisphosphonates induce apoptosis in tumoral cells, prevent the passage of tumor cells in the bone to the intercellular matrix, and thus prevent tumor invasion. Their antiangiogenic effects prevent metastasis.[3,9,10]

When used in therapeutic doses, bisphosphonates inhibit the resorptive activity of osteoclasts, while stimulating the differentiation and bone deposition of osteoblasts.[11]

However, the use of bisphosphonates in high doses has a cytotoxic effect on both osteoblasts and osteoclasts. As a result, the bone renewal mechanism is disrupted, and the risk of avascular necrosis increases due to reduced bone remodeling. It has been shown in vitro that bisphosphonates disrupt endothelial cell proliferation, adhesion, and migration. When bisphosphonates reach sufficient concentration in the bone, they create a toxic effect in the soft tissue covering the bone surface adjacent to the bone.[3,10,11]

Bisphosphonates especially bind very easily to hydroxyapatite crystals in areas of active remodeling. They are released from these areas bound on the bone surface and are absorbed by osteoclasts. As a result, the surface properties necessary for osteoclasts to create bone resorption cannot be formed, and osteoclastic activity is suppressed. The most commonly accepted cellular target for bisphosphonates is osteoclasts, and it has been shown that nitrogen-containing bisphosphonates act by inhibiting enzymes of the mevalonate pathway (MVP), a significant regulatory mechanism.[11,12] The inhibition of specific enzymes of the MVP leads to alterations in protein processing. The inhibition of the farnesyl diphosphate synthase enzyme in the mevalonate pathway by bisphosphonates results in inhibited cell proliferation without causing apoptosis in oral keratinocytes in the epithelium. Consequently, the integrity of the oral mucosa is disrupted, and healing is delayed.[11-13]

The effect of Anti-Angiogenic Drugs on bone metabolism is as follows:

Anti-angiogenic drugs work by inhibiting angiogenesis (the formation of new blood vessels) that supply blood to tumors. These drugs typically target VEGF (Vascular Endothelial Growth Factor) or its receptors.[8,14]

VEGF supports blood vessel formation and circulation, and it plays a critical role in bone healing by regulating the function of osteoblasts (bone-forming cells) and osteoclasts. By suppressing VEGF, these drugs reduce blood flow and nutrient delivery to bone tissue, impairing bone healing. This can lead to reduced microvascularization in the jawbone and an increased risk of necrosis.[7,8,14]

Anti-angiogenic drugs are used in cancer treatment (e.g., solid tumors) to inhibit tumor growth and metastasis.

- Examples: Bevacizumab, Sunitinib, Pazopanib.

Classification of Bisphosphonates

Bisphosphonates are classified based on whether they contain nitrogen and their route of oral or intravenous administration: Non-nitrogenous bisphosphonates, also known as first-generation bisphosphonates, are the oldest bisphosphonates. They have short R2 chains. When they reach the bone tissue, they are captured by osteoclasts and exhibit their effects in this way. They are metabolized very quickly in the body.[15,16] Nitrogen-containing bisphosphonates (aminobisphosphonates) have long R2 chains that contain nitrogen. They exhibit a much stronger anti-resorptive effect than non-nitrogenous bisphosphonates. They exhibit their anti-resorptive effects through the mevalonate pathway.[15-17]

Non-nitrogenous bisphosphonates and their trade names include: Etidronate (Didronel®, Osteum®), Tiludronate (Skelid®), Clodronate, etc.

Those administered intravenous bisphosphonates have a stronger and more prolonged effect compared to those taken orally and are used to stabilize bone remnants in metastatic cancers, treat bone resorption defects in multiple myeloma, and treat severe hypercalcemia.[15-17]

Nitrogen-containing bisphosphonates and their trade names include: Alendronate (Fosamax®), Zoledronate (Zometa®), Ibandronate (Boniva®, Roche), Risedronate (Actonel®, Acrel®), Pamidronate (Aredia®), etc.

Didronel (Etidronate): the first bisphosphonate marketed, does not contain nitrogen, is taken orally, and is the least effective in its group, considered an anti-mineralization bisphosphonate. It is used to treat hypertrophic calcification following bone injury and to limit excessive bone formation in Paget's disease.

Fosamax (Alendronate): taken orally, contains nitrogen, and is the most frequently used drug in the treatment of osteopenia and osteoporosis.

Actonel (Risedronate): taken orally, contains nitrogen, and is the second drug prescribed in the treatment of osteopenia and osteoporosis. Both of these drugs have a half-life in the bone of more than 11 years.

Boniva (Ibandronate): a nitrogen-containing bisphosphonate.

Zometa (Zoledronate): a more potent IV bisphosphonate.[15-17]

Bisphosphonates accumulate at a high rate in bones with a high capacity for renewal, such as alveolar bone, and in soft tissues adjacent to bones. The inability to create an aseptic environment due to the oral cavity's wide microflora and its susceptibility to trauma increases the risk of osteonecrosis in the jawbones. Previously, BRONJ was only associated with the jaws, but recent studies have reported cases of femur fractures due to long-term use of bisphosphonate derivative drugs. For a patient to be diagnosed with bisphosphonate-related osteonecrosis, the following criteria must be met.[13,16-18]

1. Past or current treatment with oral or IV bisphosphonates;
2. Presence of exposed, necrotic bone in the maxillofacial region for more than 8 weeks;
3. No radiation therapy applied to the jawbones.

Clinical Findings

Regarding the clinical findings, osteonecrosis of the jaws starts in the alveolar bone and progresses to the basal bone. It can present early subclinical signs such as sclerosis of the lamina dura, loss of lamina dura, and expansion of the periodontal gap. Sclerosis of the lamina dura is the first harbinger of metabolic bone changes. In the clinical examination of patients who develop osteonecrosis due to bisphosphonate use, significant findings include necrosis of the alveolar bone, which can be observed along with foul-smelling discharge.[13,17]

Patients generally complain of severe local pain, discharge, and tooth loss, accompanied by soft tissue swelling. Differential diagnosis includes chronic sclerosing osteomyelitis, metastatic tumors, multiple myeloma, traumatic lesions, Paget's disease, and osteoradionecrosis.[13,15,17]

The most common local predisposing factor for osteonecrosis is tooth extraction, with 52-61% of patients reporting tooth extraction due to periodontal or periapical infection. It has been observed that tooth extraction is a predisposing local factor in 69% of cases, followed by denture use (9.3%), implant placement (4.9%), and spontaneous development or unknown reasons (3.8%). It is known that osteonecrosis occurs more frequently in the mandible (74.3%) than in the maxilla (16.4%). However, a few reported cases have involved both jaws.[4,13,17]

Diagnosis

One of the possible etiologies of MRONJ is destructive bone remodeling triggered by an imbalance between bone resorption and bone formation. Therefore, the diagnosis of MRONJ has been reported through the examination of bone destruction markers such as Type I Collagen (Ctx) C-Terminal Telopeptide, Type I Collagen (NTX) N-Telopeptide, Tartrate-Resistant Acid Phosphatase Isoform 5b (TRACP 5b), Nuclear Receptor Activator (RANKL) / Osteoprotegerin (OPG), Total Alkaline Phosphatase (Talp), Bone-Specific Alkaline Phosphatase, Bone Sialoprotein, Pyridinoline, Deoxypyridinoline, Hydroxyproline values. Valuable markers for diagnosis include[13,18] :

- CTX
- NTX

- TRACP 5b
- RANKL/OPG
- ALP
- Bone sialoprotein
- Pyridinoline
- Deoxypyridinoline
- Hydroxyproline
- Serum Osteocalcin (s-OC)

s-OC (serum osteocalcin) is a biochemical marker of bone formation, and s-CTX is a marker of bone resorption. The assessment of s-CTX is a tool to evaluate the status of anti-resorptive treatment. s-OC measures the function of bone remodeling, thus contributing to the risk assessment for MRONJ.[18] For s-CTX value, having it above 150 is considered safe for us.

The importance of CTX in determining risk factors:

Serum CTX value can identify changes in bone remodeling and renewal from a few days to 2 weeks. CTX measures the serum level of the C-terminal telopeptide fragment of the type 1 collagen counterchain. The CTX test is not valid in cancer patients because the cancer itself leads to collagen degradation, resulting in higher than normal results.[4,18] Additionally, in rheumatologic diseases like Rheumatoid Arthritis, Systemic Lupus Erythematosus, Dermatomyositis, the use of steroids results in inhibited collagen synthesis, leading to falsely low results.[18] Similarly, in patients using methotrexate, it negatively affects bone marrow cells, showing a low CTX level.[4,18] (Table 2)

Table 2: *C-terminal cross-linked telopeptide (ctx) values.*[4]

C-TERMINAL CROSS-LINKED TELOPEPTIDE (CTX) VALUE	RISK OF OSTEONECROSIS
≥ 150 pg/mL	NONE
126-149 pg/mL	MINIMAL
100-125 pg/mL	MODERATE
<100 pg/mL	HIGH

The Role of Mi-RNA in Diagnosis:

Recently, a new approach has been proposed to diagnose diseases using circulating microRNAs in body fluids, which have specificity and stability. The diagnostic performances of circulating microRNAs have been validated in many diseases, including cancers, heart diseases, and osteoporosis.[18,19] In a study, Yang and colleagues investigated whether microRNA could be a biomarker for the detection of MRONJ. They obtained total RNAs of circulating lymphocytes for microRNA analysis from healthy individuals and patients with BRONJ. It has been revealed that most subtypes of microRNAs regulate bone metabolism and affect bone remodeling, suggesting that microRNA could influence specific regulations related to osteoblastogenesis and osteoclastogenesis in MRONJ. In the current study, they evaluated 7 types of circulating microRNA and found significant differences in three of them (miR-21, miR-23a, and miR-145) between the control and MRONJ groups. These three microRNAs have been identified to play a role in the onset and development of MRONJ.[19] The study observed an increase in serum miR-21, miR-23a, and a decrease in serum miR-145 in MRONJ cases. A varying microRNA expression profile in numerous patients with MRONJ was identified, and post-transcriptional regulation could be important for the development of MRONJ, but circulating microRNAs have not yet been accepted as a direct method for MRONJ diagnosis.[19]

Radiological Findings

Common imaging methods to assess MRONJ include panoramic radiography (PR), Computed Tomography (CT), MRI, and Bone Scintigraphy. Compared to panoramic films, computed tomography has a significant advantage in morphological assessment and determining the extent of jaw osteonecrosis.[8,20]

CT is considered the standard method for evaluating MRONJ. However, the CT imaging findings of MRONJ are not specific and may resemble those of ordinary osteomyelitis of the jaw.[8,12]

In both osteomyelitis and MRONJ, findings often include sequestrum, periosteal reaction, cortical perforation, or soft tissue swelling, sometimes appearing as lytic or sclerotic lesions. Other conditions that are difficult to distinguish from MRONJ include osteoradionecrosis, cancer metastasis, and Paget's disease. Although MRI can provide supportive information for diagnosis, this method is not universally available. Conventional dental radiographs help in detecting osteosclerotic, osteolytic, reactive periosteal mixed lesions, and pathological fractures. Bone scintigraphies are among the best screening methods for MRONJ.[8,20]

Treatment Methods

The treatment of medication-related osteonecrosis of the jaw (MRONJ) primarily aims to alleviate pain, control secondary infection in soft and hard tissues, and minimize the progression of bone necrosis. MRONJ treatments are classified into surgical and non-surgical options.[21] Non-surgical treatments include the use of systemic antibiotics and oral antiseptics, variable hyperbaric oxygen therapy, low-level laser therapy, and medical ozone applications.[21,22] Surgical treatments suggested in the literature are more aggressive treatments such as bone debridement, sequestrectomy, or resections of affected bone and jawbone.[22] The treatment of jaw osteonecrosis related to bisphosphonates fundamentally aims to:

- alleviate pain,
- control secondary infection in soft and hard tissues,
- minimize the progression of bone necrosis.[4,21,22]

In the guidelines published by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2022 for cases related to osteonecrosis of jaws, cases are classified according to risk categories, and treatment approaches suitable for these classifications are determined.[14] (Table 1) In the treatment of MRONJ, a combination of penicillin-

based antibiotics and β-lactamase inhibitor is considered the most ideal treatment.[23]

Typically, areas of necrosis are colonized by anaerobic and facultative anaerobic gram-positive and gram-negative bacteria. The most common group of bacteria found in MRONJ-affected areas is Actinomyces, and many types of bacteria and fungi found in oral flora, such as Fusobacterium, Bacillus, Staphylococcus, Streptococcus, Selenomonas, Spirochetes, and Candida, also colonize the area.[24]

Patients with medication-related osteonecrosis of the jaw use generally present to the clinic at Stage 2. Medical treatment should be initiated primarily. To prevent pain, osteomyelitis, and the development of secondary infections, (Penicillin V, Amoxicillin, Quinolones+Metronidazole combination, Erythromycin+Metronidazole combinations) and oral antiseptic solutions (0.12% Chlorhexidine Gluconate) should be used.

Penicillin or second-generation cephalosporins, chlorhexidine mouth rinses, periodic minor debridement, and regular lavage of the wound site form the basis of the treatment. Clindamycin alone is not effective due to its insufficient effect on Actinomyces and Eikenella and similar microorganisms found in the exposed bone.[23,24]

Sensitivities to antibiotics in the MRONJ-affected area are listed as 98% for moxifloxacin, 96% for amoxicillin-clavulanic acid, 85% for levofloxacin, 67% for penicillin, and 60% for clindamycin. Antibiotic treatment for MRONJ serves two purposes[23] :

- Infection Control
- Perioperative Application

Current guidelines related to antibiotic prophylaxis in surgery recommend stopping prophylaxis 24 hours after wound closure. In a study conducted by Akashi and colleagues in 2018, the benefit of preoperative antibiotic use in MRONJ treatment was investigated, and the study found no difference in the risk of wound infection when comparing 1 day to 5 days of systemic antibiotic prophylaxis.[23]

Table 1: *The clinical features and treatment options of medication related osteonecrosis of jaws.*[14]

STAGE	CLINICAL	TREATMENT
Patients at Risk	Cases using bisphosphonates orally or IV without necrotic exposed bone	No treatment required. Patient information.
Stage 0	Cases without clinical evidence of necrotic bone, showing non-specific clinical symptoms and findings	Systemic treatment with analgesics and antibiotics.
Stage 1	Cases with asymptomatic necrotic bone exposure without signs of infection	Antibacterial mouth rinse, clinical monitoring, patient education.
Stage 2	Cases with exposed bone area showing signs of infection such as pain and erythema, with or without purulent drainage	Systemic treatment with oral antibiotics, antibacterial mouth rinse, pain control, superficial debridement to prevent soft tissue irritation.
Stage 3	Cases with pain and infections, with exposed necrotic bone tissue progressing from alveolar bone to the lower border or ramus in the mandible, or to the maxillary sinus or zygomatic bone in the maxilla, resulting in pathological fractures, presence of extraoral fistula, osteolysis reaching to the lower border of the mandible or base of the maxillary sinus due to the formation of oro-antral or oro-nasal connections	Systemic treatment with oral antibiotics, antibacterial mouth rinse, pain control, surgical debridement to alleviate infection and pain.

Alternative Treatment Methods

Alternative treatment methods for MRONJ include the use of parathyroid hormone, platelet-rich plasma, laser applications, ozone therapy, the use of bone morphogenetic proteins, pentoxifylline, and surgical debridement guided by fluorescent staining method.[8,25,26]

Prp and Growth Factors

Autologous platelet concentrates such as platelet-rich plasma (PRP) are increasingly applied in oral surgery as a new approach to tissue regeneration because they release high amounts of growth factors such as platelet-derived growth factor (PDGF), vascular endothelial growth factors (VEGF), and transforming growth factor-beta (TGF-b). They play a role in the healing of hard and soft tissues by stimulating mitogenesis, chemotaxis, and the production of fibronectin. High levels of Vascular Endothelial Growth Factor in wound sockets improve the formation of bone matrix and stimulate neoangiogenesis. Transforming Growth Factor-beta stimulates fibroblast chemotaxis, stimulates the proliferation of gingival fibroblast cells, and produces fibronectin and collagen to repair connective tissues and regenerate bones. PRP accelerates epithelial wound healing, reduces tissue inflammation, speeds up the healing of bone and soft tissues, and promotes tissue vascularization. Considering these benefits, PRP will be effective in releasing growth factors in MRONJ patients and stimulating bone healing and neoangiogenesis, usually suppressed by BPs. Additionally, being an autologous product, PRP is biocompatible and safe, easy to use, and rich in growth factors.[27]

Laser

Several clinical studies have shown promising results for the treatment of MRONJ with ER: Yag laser therapy. The use of ER, Cr: YSGG laser eliminates thermal effects on and around the incision areas during surgery, provides antibacterial and biostimulative effects, reduces postoperative pain, and promotes tissue healing. The

contactless cutting by the laser prevents mechanical trauma caused by friction, thus preventing the prolongation of the healing process. The Er:Yag laser creates microcracks and microplosions, allowing the removal of necrotic tissue without exposing surrounding healthy tissues to any contamination, thus ensuring complete healing for both soft and hard tissues.[28,29] The use of the Er, Cr: YSGG laser has great potential in hard tissue surgery, allowing for effective resection of the maxilla without conventional rotary tools because the laser produces clear and precise cuts with minimal injury to hard and soft tissues. A study found that the combination of Er, Cr: YSGG laser and PRP application enhanced both bone and mucosal healing, with an 80% success rate in MRONJ patients undergoing conservative surgical treatment. The combination of low-level laser therapy (LLLT) with traditional surgical approaches is recommended to biologically stimulate tissue healing.[28,29]

Hyperbaric Oxygen

The angiogenic effect of HBO (Hyperbaric Oxygen) therapy is known. It has been suggested that reducing the anaerobic environment could induce neovascularization. Preliminary studies examining the effectiveness of hyperbaric oxygen therapy in addition to surgical treatment have initially shown that hyperbaric oxygen therapy improves wound healing and long-term pain scores. Recent studies have confirmed the definitive role of HBO therapy in the treatment and prevention of osteoradionecrosis in jawbones, though its utility in BON cases has not been proven. The pathophysiological mechanisms of osteoradionecrosis and bisphosphonate-related jaw osteonecrosis are entirely different. In osteoradionecrosis, the radiation-affected area is hypoxic. In ORN, capillaries die in the radiation-affected area due to a hypocellular effect, while in bisphosphonate-related jaw osteonecrosis, capillaries die secondarily to bone death, and it has been reported that there is no lack of oxygenation in the necrosis area and the simple treatment mechanism of HBO does not work. Additionally, HBO treatment indications may not always be given in oncology patients.[30]

Ozone

In pathologies related to avascular necrosis, it demonstrates its effect through the following mechanisms:

- By stimulating the endogenous antioxidant system,
- By activating blood flow, red blood cells (erythrocytes), and hemoglobin concentration; it increases diapedesis and phagocytosis.
- It acts as a bactericidal agent and stimulates all biological reactions, especially the tissue oxygenation process, as well as calcium, phosphorus, and iron metabolism.[31]
- To enhance the effectiveness of ozone therapy, antimicrobial therapy, namely beta-lactam group antibiotics and antifungal drugs, is required alongside non-invasive surgical interventions.[31]

Alternatives to Bisphosphonates

Denosumab

Denosumab is a human monoclonal antibody (IgG2) that acts by inhibiting the "Receptor activator of nuclear factor kappa-B ligand (RANKL)." Osteoclast-like giant cells contain RANK. Denosumab inhibits the RANK-RANKL interaction, the main driver of osteoclast activity, thereby preventing osteoclast maturation and reducing osteoclast-induced bone destruction.[29,30] It decreases the risk of fractures by reducing the differentiation of bone matrix cells into mature osteoclasts, osteoclast function, and the lifespan of osteoclasts. It is a stronger osteoclast inhibitor than bisphosphonates, has a shorter half-life, and is eliminated from the body a little over 6 months. Due to its relatively short effect duration, it has been used in the treatment of giant cell tumors in growing children, especially in long bones. No effects on epiphyseal or metaphyseal bone growth have been reported yet. In recent studies it is reported that denosumab suppresses osteoclast activity, reducing bone resorption and increasing bone density. However, in areas with high bone turnover, such as the jawbone, this inhibition can impair bone healing, increasing the risk of MRONJ. However, its long-term effects are still unknown.[31,32]

In postmenopausal osteoporosis, the combination of denosumab and teriparatide results in a greater increase in bone mineral density in the hip and spine compared to monotherapy.[33]

Strontium ranelate (sr)

It is suggested as an anti-osteoporosis medication due to its dual effect on bone metabolism. In vitro studies have shown that SR acts by increasing the level of osteoprotegerin and decreasing the level of kappa-b ligand receptor. It is claimed to have effects on promoting bone formation and inhibiting bone resorption. Additionally, SR has been shown to have beneficial effects on both cortical and trabecular bone. A case report published by Pan and colleagues in 2017 demonstrated that Strontium Ranelate supports bone formation by stimulating the differentiation of osteoblasts and blocks bone resorption by inhibiting osteoclast differentiation. However, there is insufficient research to definitively consider it as an alternative to BP.[34]

Teriparatide

Teriparatide is a synthetic polypeptide hormone containing the amino acid fragment 1-34 of the recombinant human parathyroid hormone, i.e., a parathyroid hormone analog. Teriparatide (parathyroid hormone analog) is the only medication shown to stimulate bone formation and potentially reverse osteoporosis to some degree. Teriparatide is recommended only for patients at high risk of fractures who cannot tolerate other medications. Although PTH is considered catabolic because it releases calcium from bone, low doses of teriparatide directly stimulate bone formation by osteoblasts.[35]

Recently, teriparatide has been approved for the management of osteoporosis and has accelerated the healing of vertebral and long bone fractures. Unlike

bisphosphonates, which prevent bone mineral loss from bone tissue, intermittent treatment with teriparatide is well known to activate bone remodeling. It is claimed that teriparatide's enhanced remodeling and bone formation capability facilitate the healing and removal of necrotic or exposed bone. A study investigated whether short-term teriparatide and recombinant bone morphogenetic protein could enhance suppressed bone formation capacity. Recombinant human BMPs are an activation factor for bone repair, now more readily available in larger quantities due to the advent of recombinant DNA technology. The study's results showed significant increases in S-CTX and s-OC levels after treatment with rhBMP-2 and teriparatide, suggesting it could maximize bone regeneration in BRONJ patients and be considered an additional treatment method, potentially shifting treatment from resective to regenerative.[35]

However, teriparatide is contraindicated for patients with hypercalcemic disorders, osteosarcoma, metastatic bone disease, Paget's disease, pregnancy, and those receiving radiation therapy to the skeleton or soft tissue, and those with severe kidney or liver failure.[35,36]

When discussing alternatives to bisphosphonate derivative drugs, it is also necessary to mention EDTA and SVF from studies conducted on animals but not yet approved for use in humans.

Ethylenediaminetetraacetic acid (EDTA)

Ethylenediaminetetraacetic acid (EDTA) is widely used in medical applications as well as in dentistry. It is FDA-approved and regularly used worldwide to treat heavy metal poisonings in patients. In dentistry, it is routinely used to improve the smear layer, root canal treatment, and root surface during periodontal treatments; 17% EDTA is the most commonly used concentration in clinical dentistry and dental research. A study investigated whether ex-vivo EDTA decalcification would significantly reduce the bisphosphonate content in bone. Since EDTA's affinity for Ca ions is greater than that of the bisphosphonate group drug, it has been shown that EDTA binds to Ca in bone, inhibiting the formation of indigestible BP-Ca complexes. Additionally, adding EDTA to oral bisphosphonates has been shown to increase their bioavailability in the gastrointestinal (GI) system due to competitive EDTA-Ca chelation, thus reporting that it could reduce the binding of bisphosphonates to osteoclasts, preserving the normal function of osteoclasts.[37]

Stromal Vascular Fraction Cells (Svf)

Stromal Vascular Fraction (SVF) cells are mesenchymal stem cells derived from adipose tissue. A study conducted in Japan in 2017 investigated the transplantation effects of stromal vascular fraction cells on bone and soft tissue wound healing in tooth extraction sockets in mice treated with chemotherapeutic bisphosphonate combination therapy.[38] Although bone marrow stem cell therapy has been shown to reduce MRONJ-like lesions in mice, the approval of stem cell therapy for MRONJ is strictly limited due to various issues. The study showed that treatment with stromal vascular fraction (SVF) cells significantly increased blood vessel and vascular surface area, accelerating bone and soft tissue wound healing in tooth extraction sockets. Systemic transplantation of uncultured Stromal Vascular Fraction cells has been shown to reduce MRONJ-like lesions induced by tooth extraction in mice treated with bisphosphonates. Therefore, SVF therapy has been reported as a potentially more suitable treatment strategy for MRONJ.[38]

Conclusions

Despite the complications associated with bisphosphonate group drugs, their use is widespread and increasing due to their numerous indications. Although there are many studies investigating the changes these drugs create in hard and soft tissues aimed at preventing osteonecrosis, which is of great interest to dentistry and difficult to treat, the pathogenesis has not yet been fully explained. The development of alternative drugs is promising for the management of MRONJ, but further studies are needed for regular use indications. Informing physicians about the mechanism of bisphosphonate derivative drugs, anti-angiogenic drugs and denosumab the treatment of MRONJ and alternative drugs to these groups are important for managing the complications associated with these drugs.

Acknowledgements

None.

Conflicts of Interest Statement

There is no conflict of interest between the authors.

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