Yu-Jen, L. (2023) Effectiveness of the different treatments for medication-related osteonecrosis of the jaws. Revista Internacional de Medicina y Ciencias de la Actividad Física y el Deporte vol. 23 (89) pp. 282-303
DOI: https://doi.org/10.15366/rimcafd2022.87.020

ORIGINAL

EFFECTIVENESS OF THE DIFFERENT TREATMENTS FOR MEDICATION-RELATED OSTEONECROSIS OF THE JAWS IN YOUNG PLAYERS

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Spanish-English translators:

UNESCO Code / UNESCO Code:
Council of Europe classification / Council of Europe classification:

Recibido 30 de abril de 2020 **Received** April 30, 2020
Aceptado 26 de junio de 2020 **Accepted** June 26, 2020

ABSTRACT

Medication-related-osteonecrosis of the jaw, MRONJ, is a severe iatrogenic condition. Patients receiving certain types of medications related to the inhibition of osteoclast function may have an increased risk of developing bone necrosis. The overall prevalence of MRONJ is low, and the current treatment methods include antibiotics and surgical intervention. **Objective**: The main purpose is to compare the effectiveness of different contemporary treatment modalities in relation to MRONJ. **Material and methods:** A systematic electronic search was performed mainly using Pubmed. After adjustment of the exclusion criteria, a total of 21 articles were selected for this review. **Result**: The overall success rate for conservative treatment ranged from 0% to 33%, whereas surgical therapy had an overall success rate of 88.57% to 100%. Success rate for adjunctive treatment, including teriparatide, fluorescence guided surgery, low-level laser therapy, and leukocyte- and platelet-rich-fibrine ranged from 5.17% to 99.4%. **Conclusion**: The chances of achieving complete healing with purely conservative treatments are low. Regardless of MRONJ stage, early surgical treatment can achieve better success rates and prevent disease deterioration. The recent introduction of adjunctive treatments can accelerate bone healing and improve patient morbidity, although more evidence is still needed to confirm which treatment achieves the highest success rates.

Keywords: Bisphosphonate-associatedtherapy; Medication-related Jaw Treatment of osteonecrosis treatment; Osteonecrosis Jaws.

1.INTRODUCTION

Medication-related-osteonecrosis of the jaw, abbreviated as MRONJ, also known as avascular necrosis, is a severe and rare iatrogenic condition. Patients

that require intragenic activity, which, at the same time, also receive certain types of medications that are related to the inhibition of the action of osteoclast, may have an increased risk to develop irreversible bone necrosis. The signs and symptoms were initially reported in 2003 by a maxillofacial surgeon observing patients under Pamidronate (Aredia) and Zoledronate (Zometa).

General Concepts of necrosis and osteonecrosis

Necrosis is derived from the Greek term meaning “death.” It is an irreversible process where cells undergo, after a pathological injury that leads to the premature death of cells in the living organism (Bezzerra, 2019; Proskuryakov, Konoplyannikov, & Gabai, 2003). To differentiate cell apoptosis from cell necrosis, firstly, the cause of cell necrosis is stimulated by an external factor such as infection or heat, which ultimately induces cell death. On the other hand, apoptosis is the elimination mechanism of the cell itself. Furthermore, apoptosis of the cell benefits the organism, while necrosis leads to several disadvantages. (Table 1)

After exposure to an external stimulus, for instance, heat, radiation, UV light, swelling of cell organelle and plasmatic membrane rupture, and eventually lysis of the cell is observed. Common factors that generate necrosis (Aryal, 2022) Hypoxia: The cell is unable to carry out respiration due to lack of oxygen which leads to the inability to produce ATP. This condition could happen due to ischemia, shock, or respiratory failure.Physical agents: Includes external injuries such as trauma, extremetemperature, exposure to radiation, or electric shock.

Chemical agents: contaminants,pesticides,metals,tobaccos, alcohol, and drugs. Biological agents: Includes bacteria, viruses, or fungi Immunologic reactions: autoimmune response.

Table 1. Main differences between necrosis and apoptosis.

	Necrosis	**Apoptosis**
Cause	Hypoxia (hypoxia),changes in pH, changes in temperature	Program cell death,DNA damage, lackof growth factors
Characteristic	Pathological,non-specific	Physiological or pathological, specific
Induce by	Strong stimulus, random occurrence	Weak motivation, non-random occurrence
biochemistry	Passive process, no new protein synthesis,no energy consumption	Active process, newprotein will become,energy consumption
Cell number	Mass cell death	Single-cell loss
DNA electrophoresis	Random degradationof DNA, showing diffuse bands on electrophoresis	DNA fragmentation(80-200bp) electrophoresis shows ladder-like bands
Inflammationreaction	Lysosome rupture,local inflammation reaction	The lysosome is relatively intact, nolocal inflammation reaction

Common mechanisms of action leading to necrosis

ATP Depletion

Depletion of ATP due to the lack of oxygen inside the cell causes the inability of respiration. Lack of ATP results in the failure of the sodium pumpin

the plasma membrane, which causes an influx of calcium and water, leading to swelling of the cell (Lieberthal, Menza, & Levine, 1998). It then explodes and causes necrosis.

Oxygen derived free radical

Increase of free radicals inside the body caused by oxygen and toxic radiation. Free radicals destroy lipid, protein, and nuclear acid, causing necrosis of the cell.

Loss of intracellular calcium hemostasis

Toxicant or ischemia causes an increase in the concentration of calcium inside the cell. Active phospholipase and proteases break down membrane and protein, leading to distortion of protein inside the cell. Rising Ca (2+) concentration in the cytoplasm causes Ca (2+) influx into mitochondria and nuclei. In mitochondria, Ca (2+) accelerates and disrupts normal metabolism leading to cell death. In nuclei, Ca (2+) modulates gene transcription and nucleases that control cell apoptosis.

Mitochondrial damage

Damage to mitochondria causes the inability of the cell to produce energy. Under stress, mitochondria are often the target, leading to necrotic and apoptotic cell death (Lemasters et al., 1999).

Classification of necrosis

Under the microscope, there are different forms for necrosis; the most common are:

a. Coagulation necrosis: proteins inside the cell are frozen, which maintains the size and contours of the cell, but eventually, the cellswill be eliminated by the body itself (Marunouchi & Tanonaka, 2015).
b. Caseous necrosis: This pattern is almost unique to tuberculosis. Certain fungi can also exhibit caseous necrosis. In tuberculosis, theorganism is partially resistant to digestion and phagocytosis by tissue macrophages, and this leads to activation of the macrophages to form giant cells and epithelioid cells.
c. Liquefaction necrosis: most commonly found in the central nervoussystem, hydrolytic enzymes lead to loss of cell structural integrity, which turn into a dense mass (Wang et al., 2019).
d: Fibrinoid necrosis: Accumulation of fiber in blood vessels causes necrosis.

History and Definition

The definition and the criteria for diagnosis of MRONJ have changed throughout the decades. The early terminology used by the AAOMS, American Association of Oral and Maxillofacial Surgeons, was BRONJ (Bisphosphonate-related osteonecrosis of the jaw), which is specifically related to Bisphosphonates. Distinct exposure of necrotized bone in the

maxillofacial region that sustained for more than eight weeks; current or previous treatment with bisphosphonate medication, and no history of radiation therapy of the jaws were characteristics that were ruledout to suggest the possibility of a patient with BRONJ.

However, recent research suggests not only bisphosphonates cause the necrosis of the jaw but also other medication, such as Denosumab, has a firm and distinct relationship to the onset of osteonecrosis of the Jaw. Hence, as a result, AAOMS had suggested to modify the original term of BROJN to MRONJ (Medication-related osteonecrosis of the jaw) in the year 2014 (Chung et al., 2018).

Current concepts that were widely accepted for the population for MRONJare patient with the exposure of the following characteristics:

1.Current or previous treatment with anti-resorptive or anti-angiogenicagents.
2.Exposed bone or bone that can be probed through an intraoral orextraoral fistula in the maxillofacial region that exceeded eight weeks.
3. No history of radiation therapy of the jaws or prominent metastaticdisease to the jaw.

Recently, the Italian Society of Oral Pathology and Medicine (SIPMO) introduced a new concept for MRONJ. In the year 2018, the meeting claimed that MRONJ is an “adverse drug reaction described as the

progressive destruction and death of bone that affects the mandible and maxilla of patients exposed to the treatment with medications known to increase the risk of disease, in the absence of a previous radiation treatment” (Di Fede et al., 2018). According to the conference, it had been reported that not only anti-resorptive medication showed a positive relationship but also the adverse effect from the treatment of anti-angiogenic had a significant association with MRONJ (Campisi et al., 2020).

The concept, diagnosis, and treatment of this particular disease has been updated frequently in the last 20 years. Therefore, medical and dental practitioners, especially the oral surgeons and dentists who carry out dental extraction surgery on a routine basis, should be continuously updated to provide a favorable treatment.

Epidemiology

On the basis of Sweden’s 4-year prospective study in 2018, the overall prevalence of MRONJ is low (Hallmer et al., 2018). The prevalence of Alendronate (oral bisphosphonate) 70mg per month is about 0.043%, which is relatively lower than intravenous bisphosphonate (1.03%). The prevalence of Denosumab, anti-RANKL, is about 3.64%.

In terms of gender, the mean age for males to manifest the symptoms of MRONJ is approximately 63.6 years, while the female is 73.1years. The most common underlying disease was osteoporosis, 56%, followed by breast cancer, 20%, prostate cancer, 11%, multiple myeloma,9%, lung carcinoma, 2%, and giant cell carcinoma, 2%.

Average dose and duration

The time and dosage required to develop MRONJ for the three types of medication, oral bisphosphate, IV bisphosphate, and Denosumab, were analyzed and summarized.The establishment lesion of MRONJ notonly varies from drug to drug but also the medical history of the patient.

For instance, patients receiving intravenous bisphosphate have a worse condition than those under oral bisphosphate.

1.1.1 Oral bisphosphonate: an average dosage of 4503mg Alendronic acid, 156,000mg ibandronate acid, and 3395mg Risedronic acidleads to the development of MRONJ

1.1.2 Intravenous bisphosphate: an average dose of 150mg Zoledronicacid leads to the development of MRONJ. In other words, 30 months of treatment has a high possibility to develop MRONJ. Onthe other hand, the average dose for Pamidronic acid is about 1620mg, which is about 18 months of treatment.

1.1.3 Anti-RANKL: subcutaneous injection of Denosumab per month with the dose of 120mg. Around 15.8 months with the dosage of1740mg leads to the possible development of MRONJ.

Site: The occurrence of MRONJ is relatively higher in the mandible, 75%, and maxilla 25%. Moreover, it has a higher probability of being located in the posterior mandible (78%), compared to 6% in the anterior mandible, and the remaining 6% were found in more than one segment of the mandible. No significant differences in healing of necrosis lesions when located eitherin the mandible or maxilla (n=55).

Stage:18% of MRONJ were recognized as stage 1, while 65% were stage 2 and17% were in stage 3.

The unbearable symptoms revealed in stage 2, such as pain, bring the patient to seek medical support urgently. This could be one of the reasons that there is a greater percentage for the discovering of MRONJ at the second stage.

Precipitating factors: The most common factor that induces MRONJ is tooth extraction, taking up around 70% (n=55). The remaining factors were marginal periodontitis,18% spontaneously occurring, 5%, apical periodontitis, 3.6%, denture,trauma, at 1.8%. An interesting finding pointed out that previous to dental extraction surgery,around 91% of the patient (29 individuals) have had severe marginal periodontitis, which could be detected through intraoral radiographs.

Pathophysiology of the MRONJ

The research and study of MRONJ has been carried out for several years. Nonetheless, the exact cause of the pathophysiology of MRONJ remains unknown. Currently, there are two theories that are widely accepted by the

clinician: (Figure 1)

Inside-outside theory

The idea of the inside-outside theory refers to the cause of osteonecrosis is formed primarily by internal factors, such as inflammation of the bone, secondary to distortion of the external structures, which in advance give rise to necrosis of the bone tissue. Anti-resorptive agents inhibit not only the activity of the osteoclast but also the ability of bone metabolism. Due to exposure to the high concentration of various pathogenic microorganisms in our daily life and routine activity as such chewing which leads to mandible microdamage, could lead to the same outcome. (Lombard, Neirinckx, Rogister, Gilon, & Wislet, 2016) According to other histological studies, data have shown that patients who had complete integral epithelium had histological osteonecrosis underneath in a microscopic view. Only a few patients had symptoms of the exposure of bone. In summary, bone exposure is not a necessary requirement for osteonecrosis (Kang et al., 2013).

Outside-inside theory

This theory suggests that bone necrosis happens from the external region, for example, mucosal or dental lesion, and progresses to the internal osseous tissue. In numerous investigations, dental extraction seemed to be related to MRONJ, being considered as a major risk of MRONJ. Infact, if the tooth or oral mucosa are the source of infection, a significant relationship with the development of MRONJ is suggested. (Aghaloo et al., 2011)

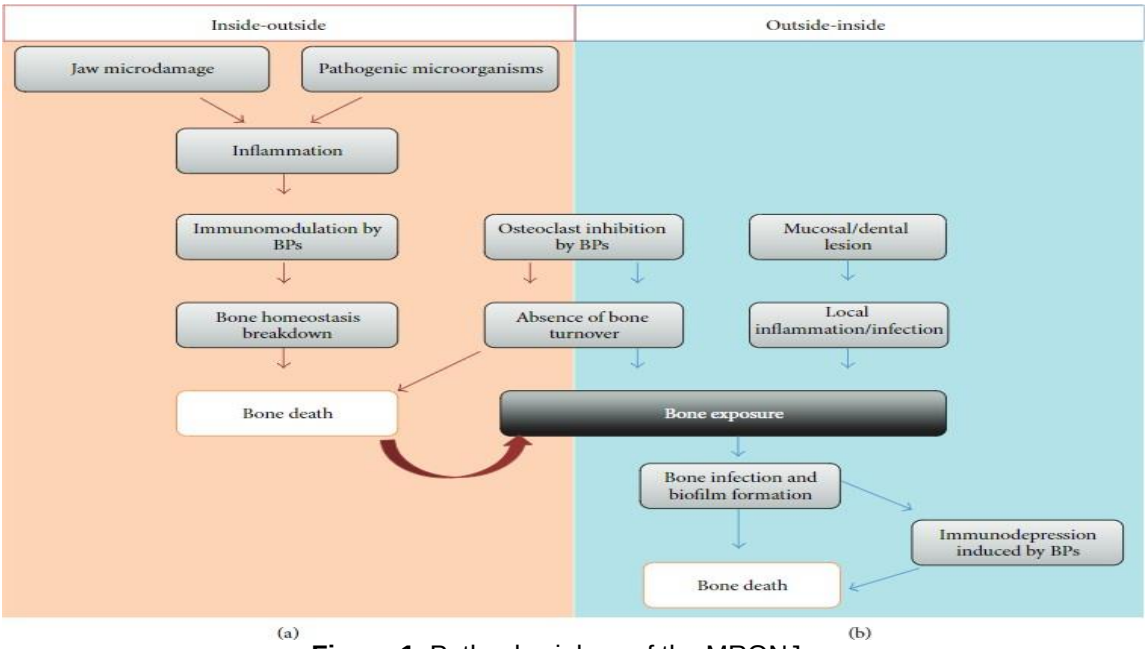

Figure 1: Pathophysiology of the MRONJ

Medications related to MRONJ

Three drugs have been found to be related to the symptoms of MRONJ. The indication, pharmacological mechanism with MRONJ will be introduced for each specific medication. (Figure 2)

Bisphosphonate (BPS)

Bisphosphonates are a type of drug used to treat osteoporosis in both men and women. They have been widely accepted since the 1990s. The effectiveness of BPS in treating osteoporosis is related to its ability to inhibit bone resorption (Lesclous et al., 2009). Bisphosphonates are very efficacious in the prevention of fractures in a patient with osteoporosis. On the other hand, although it is a relatively safe drug there are still several rare and serious adverse effects that should be monitored. It is decisive to educate the patient for effective treatment of osteoporosis. At the same time, the patient should also be notified to eliminate other risk factors that could lead to a higher risk of osteoporotic fractures, activities such as smoking, weight- bearing exercises. Examples:

Mechanism of action

Similar to the structure of native pyrophosphate, Bisphosphonate could be divided into two groups: Nitrogen-containing bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid) and non-nitrogen-containing bisphosphonates (etidronate, clodronate, and tiludronate). The mechanism of action of all bisphosphonate is by attaching to hydroxyapatite binding site on the bone which leads to inhibition of bone resorption. Deposition of bisphosphonate in the bone impairs the activity of osteoclasts, inhibiting bone resorption.Nitrogen-containing bisphosphonate inhibits farnesyl pyrophosphate synthase, which is essential in the attachment of the osteoclast to the bone. It detaches osteoclast from the bone giving a result of inhibition of bone resorption.Non-nitrogen-containing bisphosphonate is metabolized within the cell forming a nonfunctional molecule that competes with adenosine triphosphate in the energy metabolism of the cell. These nonhydrolyzable ATP analogs are cytotoxic to osteoclasts. This situation initiates osteoclast apoptosis.Oral biphosphates were developed prior to IV biphosphates. However, due to the low bioavailability and diverse side effects of oral biphosphates, it encouraged the development of IV biphosphates. (Table 2)In the year 2015, a study performed in Japan (Harris et al., 1999) compared IV and oral biphosphates in the treatment of osteoporosis. IV biphosphates had a better bioavailability of 0.7% versus oral biphosphate. However, no significant differences between the result of oral and IV bisphosphonates to bone marrow density (BMD) of the femur were seen. Thus, it can be concluded the bioavailability of the particular drug does not have a major

influence in recovering bone density. Another study in the year 2012 showed similar results as the above mentioned in 2015 (Black et al., 2007).

Table 2: Characteristics of Oral and IV Bisphosphonates

	IV Bisphosphonates	**Oral Bisphosphonates**
Bioavailability	Good	Poor due to GI resorption
Potency	High	Low
GI side effects	Less, well-tolerated	more
Indications	Bone metastasis Osteoporosis	Osteoporosis
Adverse effect	Fever and flu-like symptoms Bone and joint pain	Esophagus irritation
Prevalence to induce MRONJ	High	Low

Bisphosphates and MRONJ

The major adverse effect of bisphosphate corresponds to MRONJ. In patient with multiple myeloma and breast cancer high dosages of bisphosphonates are prescribed which leads to the possible onset of MRONJ. According to the study of 2015, the prevalence of BRONJ is between 1 in 10,000 to 1 in 100,000 (Lyles et al., 2007), especially with those individuals that are exposed to the following risk factors:

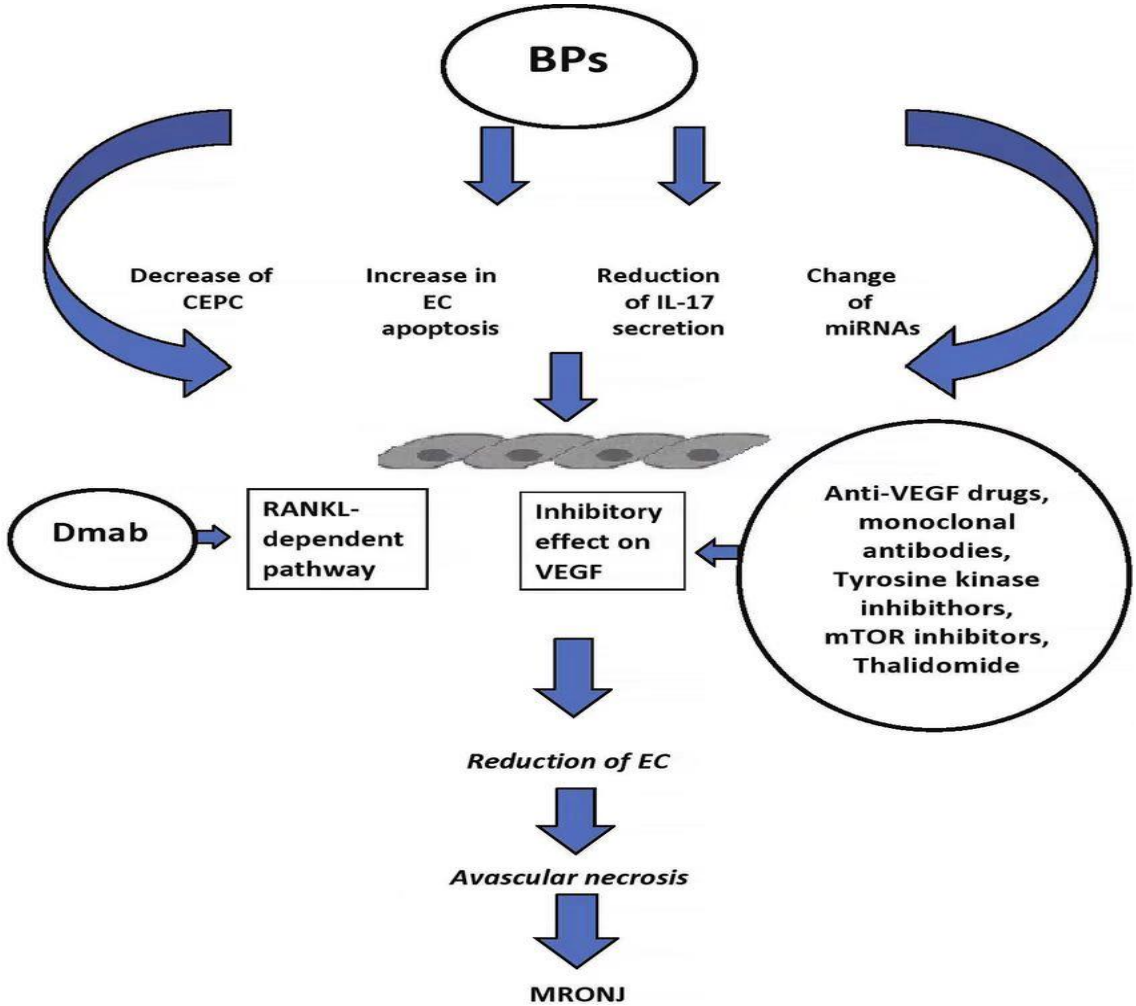

Figure 2. Antiresorptive medications

RANK Ligand Inhibitor

RANK ligand inhibitor (Denosumab), is an anti-resorptive agent made by human IgG2 monoclonal antibody against RANK ligand (RANK-L) and inhibits osteoclast function. At present, it is the most commonly used agentagainst the activity of osteoclast differentiation due to its effectiveness.

Indication

1.Prevention of skeletal-related events (e.g., bone pain and fractures) 2. Giant cell tumor of the bone]3. Hypercalcemia of malignancy. This drug is indicated when hypercalcemia is refractory to bisphosphonate therapy.4.Osteoporosis where bisphosphonates have not been

successful.5.Glucocorticoid-induced osteoporosis 6.Bone loss (Chesnut III et al., 2004).

Mechanism of Action

RANK ligand inhibitor binds to receptor activator of NF kappa B ligand (RANKL) and competitively inhibits its binding to receptor activator of NF kappa B (RANK). When bound to RANK, RANKL potentiates osteoclast differentiation from hematopoietic stem cells and activates and prolongs the survival of mature osteoclasts. osteoclasts' primary function then is to promote bone resorption. Denosumab binds to RANKL with high affinity and blocks it from binding to and oligomerizing its receptor RANK, thus inhibiting osteoclast maturation and bone resorption.

RANKL inhibitors and Osteonecrosis of the Jaw

The relation of RANKL and MRONJ is more contemporary compared to Bisphosphates. In consequence, more evidence is required to support the statements that were declared. In a mice experience (Horikawa, Miyakoshi, Shimada, Sugimura, & Kodama, 2015) that was performed in the year 2015, the authors discovered that patients under theprescription of RANKL inhibitor and periapical pathology (dental infections)had a relatively higher risk of MRONJ. The result of the finding was not onlysupported by radiography examinations but also histologically.

Angiogenesis Inhibitors

Angiogenesis inhibitors are a group of drugs that inhibit the formation of blood vessels. They are used for the treatment of gastrointestinal tumors, renal cell carcinomas, neuroendocrine tumors, and others.Based on the mechanism of action of angiogenesis inhibitors, they can be categorized into three major groups:1.Anti-VEGF- monoclonal antibody (e.g., Bevacizumab)2.VEGF decoy receptors or VEGF-Trap (e.g., Aflibercept)3.Small molecule tyrosine kinase inhibitors (TKI) that block the VEGF receptors signaling pathways (e.g., Sunitinib, Cabozantinib, and Sorafebin)

Angiogenesis Inhibitors and Osteonecrosis of the Jaw

According to the Comprehensive Review of the Literature made in 2018 (Shiraki et al., 2012), the final consequence and possibility of MRONJ for the patient with advanced breast cancer after receiving the medication of angiogenesis inhibitor was 0.2%, which is significantly lower compared to patientsreceiving other antiresorptive agents (7%). [35] Angiogenesis inhibitors have a lower prevalence in MRONJ not onlybecause it is a safer drug but also there are fewer people under this medicalprescription.MRONJ secondary to angiogenesis inhibitors, patients were mostly diagnosed with metastatic renal cell cancer, followed by metastatic colorectal cancer and metastatic breast cancer.The following table is a summary of the most commonly prescribed drugs.(Table 3)

Table 3. Most common drugs, active substance and brand name

Category	Active ingredient	Brand name	Indication
Bisphosphonates	Alendronate	Fosamax	Osteoporosis
	Ibandronate	Boniva	Osteoporosis
	Neridronate	Nerixia	Osteoporosis imperfectaPaget disease
	Pamidronate	Aredia	Bone metastases
	Risedronate	Actonel	Osteoporosis
	Zolendronate	ZometaReclast	Bone metastasesOsteoporosis
RANK ligand inhibitor	Denosumab	ProliaXgeva	OsteoporosisCancer
Angiogenesis inhibitors	Bevacizumab	Avastin	Metastatic colorectal cancernon-small-cell lung cancer Glioblastoma multiforme Metastatic renal cell cancer
	Aflibercept	Eylea Zaltrap	Metastatic colorectal cancer
	Sorafenib	Nexavar	Metastatic renal cell cancer Hepatic carcinoma
	Sunitinib	Sutent	Metastatic renal cell carcinoma Gastrointestinal stromal tumor Pancreatic neuroendocrine tumor
	Cabozantinib	Cabometyx	Medullary thyroid cancer

Stages of MRONJ

There are various classifications proposed for MRONJ, however, theAAOMS 2014, [8] remains the most widely used and accepted. An adapted

version based on the readership is present below with corresponding recommended management

At-risk

In this stage, patients receiving certain antiresorptive drugs where no apparent necrotic bone is present. No active treatment is needed, only health education for those patients.

Stage 0

No clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms are featured. Treatment would be systemic management, including use of pain medication and antibiotics.

Stage 1

Asymptomatic exposed and necrotic bone or fistulas that probe to bone without evidence of infection. The patient should be prescribed antiseptic mouth rinse (e.g., Chlorhexidine 0.2%) and the medication that causes the MRONJ may be disrupted.

Stage 2

Exposed and necrotic bone with the presence of the infection including pain and erythema in the region with or without purulent discharge. The treatment includes:

1.Symptomatic treatment with oral antibiotics,
2.Oral antibacterial mouth rinse.
3.Pain control
4.Debridement to relieve soft tissue irritation and infection control

Stage 3

The patient presents the following:
1.Exposed and necrotic bone or a fistula that probes to the bone inpatients with pain, infection.
2.Exposed and necrotic bone extending beyond the region of alveolar bone resulting in pathologic fracture, extraoral fistula,oroantral or oral-nasal communication, or osteolysis extending tothe inferior border of the mandible or sinus floor.
The treatment strategy would be:
3.Antibacterial mouth rinse
4.Antibiotic therapy
5.Pain control
6.Debridement/resection for longer term palliation of infection andpain

2. OBJECTIVES

Aim: The main purpose is to compare the effectiveness of the different contemporary treatment modalities of the medication-related osteonecrosis of the jaws.

Specific objectives

1. To summarize the indications, contraindications, and adverseeffects of contemporary protocols in the management of MRONJ.
2. To compare each treatment modality including success rates and recurrence rates.

3. MATERIAL AND METHODS

An electronic website research for the article reading of the syndrome of MRONJ was carried out. To conduct the exploration, PubMed, which is a site for the usage of a free full-text search engine that is accessible for theprimary MEDLINE database, was the first choice for relevant articles that were published in English.The medical search term was initially limited to “medication-related osteonecrosis” then a time limitation of the declaration of the article was set, which narrowed the total results from the 2009 articles to 1660. After inserting the keywords, the remaining result was reduced to 757. Within the 757 results that were obtained from the previous instructions, 47 paperswere extracted for the systemic review while the remaining results were ruled out. To finalize the search, 7 articles were excluded for the topicof femur head necrosis and another 8 were discarded due to the irrelevanttopic to osteonecrosis of the jaw. As a final result, 21 articles were includedfor the review of MRONJ. (Figure 3)

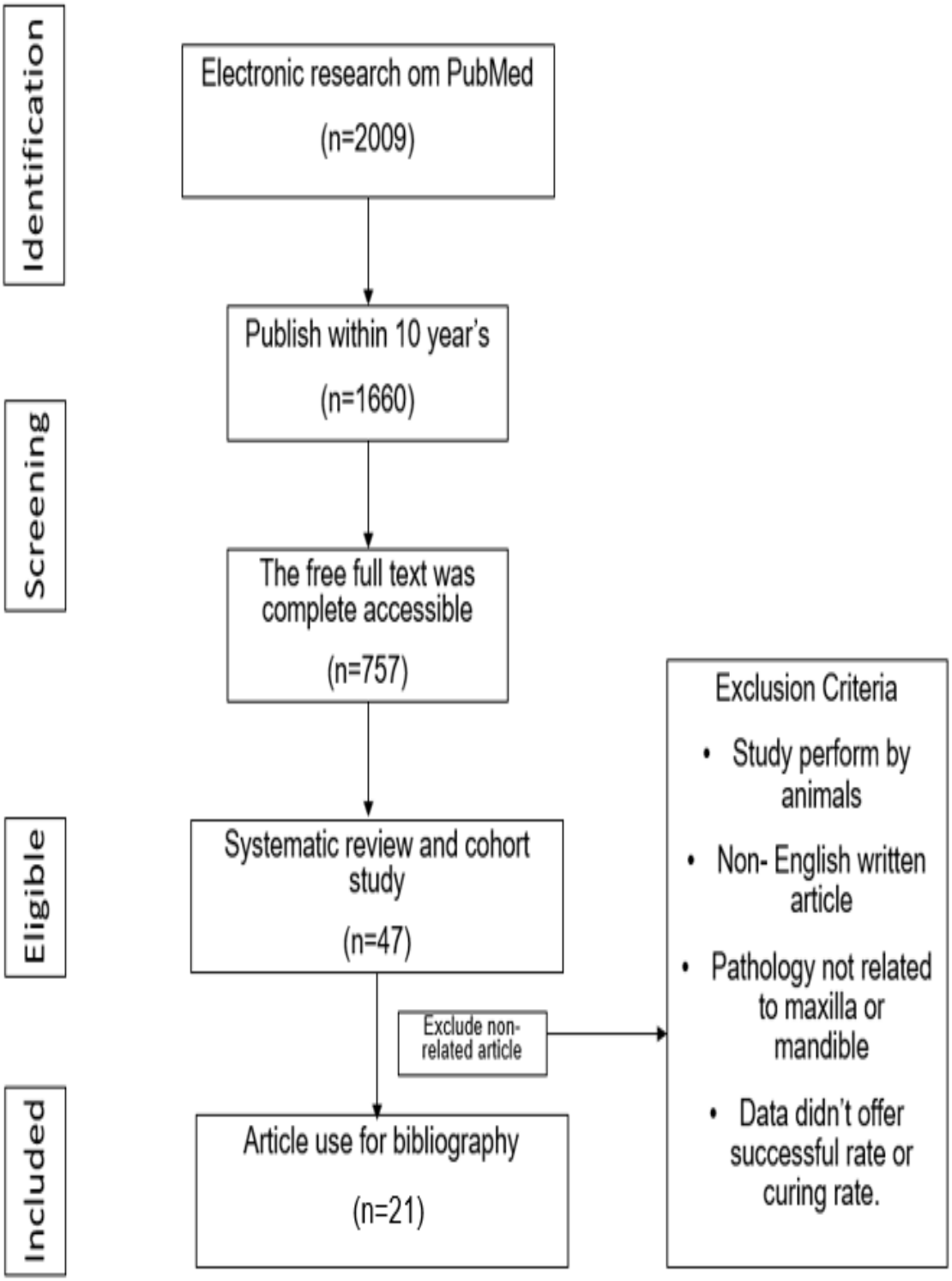

Fig. 3 Flow chart of the search strategy and the results obtained

4. RESULTS

This literature reviews the effectiveness of contemporary treatments for MRONJ, so we will first list the current therapies for MRONJ according to the AAOMS and then compare the differences between them. The final selection is shown in Table 4.

Table 4. Articles included in the review.

Author	Year	Simple size	Conclusions
Conservative treatment			
Oliver Ristow et al.	2019	75 patients	Stage 1 conservative treatment led to healing in rare cases.
Massimo Albanese et al.	2020	12 patients	Patients who cannot have surgery, non-surgical treatment may be effective
Elena-Beatriz Bermúdez-Bejarano et al.	2017	18 articles	Antibiotic is essential for treating the MRONJ in order to reduce the symptoms and avoid deterioration. Difficult to choose the most optimal treatment due to lack of randomized control trials.
Surgery and conservative treatment			
Kai Alons et al.	2008	7 patients	Surgical treatment plus non-surgical treatment might lead to predictable outcome in mail and moderated BRONJ.
David C Stanton et al.	2008	33 patients	Combination was successful in treating MRONJ.
P. Vescovi et al.	2012	151 patients	Medical treatment only improve the symptoms, the complete healing can only be achieved by medication+ surgery and laser treatment.
A.W.Eckert	2007	24 patients	Management of patients with BRONJ remains extremely difficult and includes surgical procedures
Antonia Marcianó,	2020	103 patients	Combination of radical necrotic bone surgery, in stage 1 and 2 patients show complete healing; for stage 3 patients that are not eligible for surgery, palliative treatment was effective to reduce symptoms.
Na Rae Choi et al.	2020	116 patients	Surgical treatment had a high success rate.
Elena M. Varoni et al.	2021	35 patients	Combination modality, had a high healing rate and a low recurrence rate.
Takanori Eguchi et al.	2017	52 patients	Stage 2 patients: surgical treatment was more effective than non- surgical treatment.
G Favia et al.	2018	106 patients	Non-surgical therapy never completely healed the lesions. Surgery should be considered.
Aida Comas-Calonge et al.	2017	13 studies	Surgical treatment such as sequestrectomy, surgical debridement and bone osteotomies had a 58%-100% success outcome.
Adjuvant treatment			
Dries Govaerts et al.	2020	30 articles	Adjuvant therapies are beneficial for mucosal healing. Lack of scientific evidence.
A Agrillo et al.	2012	131 patients	In 90% of the cases, positive effect of adjuvant therapy.
F Goker et al.	2021	118 articles	More studies with large sample are needed when evaluating the possible benefit of these modalities.
Roberto Sacco et al.	2019	13 studies	Difficult to determine whether ozone is better than hyperbaric oxygen due to low quality of studies.
Ie-Wen Sim et al.	2020	34 patients	Teriparatide is a safe treatment for MRONJ, and it improves the outcome.
S. Otto et al.	2016	54 patients	Fluorescence-guided surgery is a safe and successful method for all MRONJ stages.
Elen de Souza Tolentino et a.l	2019	41 patients	Adjunct therapies are safe and effective, however better designed studies are needed.
Freiberger et al.	2012	56 patients	HBO shows to be a useful adjunct treatment in severe cases. Not enough evidence for clear conclusions.

Contemporary protocols in the management of MRONJ.

According to the AAOMS guidelines, treatment can be divided into oral hygiene recommendations, use of antibiotics or analgesics, and surgery. In addition, supplementary innovative therapies such as laser or oxygen therapy have gained popularity in the past few years may also become useful.

Oral Hygiene Recommendations

Since MRONJ is a disease that involves bone infections caused by microbes, maintaining oral health plays a crucial role in preventing and treating MRONJ. Recommendations for maintaining oral health involve two aspects: implementing basic oral hygiene education and informing risks of developing MRONJ.

Basic Oral Hygiene Education

There are no differences between oral hygiene education for people at risk of developing MRONJ and people who are not at risk, including regular tooth brushing, use of floss and mouthwash, and regular visits to dentists. The AAOMS recommends patients diagnosed with stages 1, 2, and 3 MRONJ the use of antiseptic mouthwash, such as chlorhexidine 0.12%.

Education of possible risks of developing MRONJ

Patients taking medications that could cause MRONJ should be informed of the risks of developing MRONJ after oral surgical interventions. They should also notify their dentists of the medications they are taking during their dental visits, which allow preventive measures such as extractions of teeth with poor prognosis before the use of such medicines. Indications: Prevention and treatment in all stages of MRONJ.Contraindications: Patients allergic to chlorhexidine (CHX-incidence of 0.78 per 100,000) and breastfeeding women. Adverse effects: For chlorhexidine (CHX) 0.12%, xerostomia, hypogeusia, or tooth staining

Antibiotics

The most common antibiotic used to treat MRONJ are penicillin, amoxicillin, amoxicillin/clavulanic acid and metronidazole. Indications: Both for prevention and treatment of Stage 2 and Stage 3. Contraindications and adverse effects as [Table 5].

Table 5 Contraindications and adverse effects of common antibiotics used for the treatment of MRONJ.

	Contraindications	Adverse effects
Penicillin [40]	Severe allergic reactions or penicillin and its derivatives.	Nausea, Vomiting, Diarrhea, Rash, Abdominal pain, and Urticaria
Amoxicillin [41]	Patients were allergic to any beta-lactam antibiotic or served skin reactions such as Stevens-Johnson syndrome.	Nausea, Vomiting, Diarrhea, Elevations in AST and ALT, Crystalluria, interstitial nephritis, Mucocutaneous candidiasis
Amoxicillin/clavulanic acid [42]	Patients on hemodialysis or with severe renal impairment with creatinine clearance less than 30 mL/minute. Patients with previous hypersensitivity reactions to amoxicillin, clavulanic acid, or other beta-lactam antimicrobials are also contraindicated.	Diarrhea, Nausea, Vomiting, Loose stools, and abdominal discomfort
Metronidazole [43]	First-trimester pregnancy. Avoid consuming alcohol or products containing propylene glycol. Hypersensitivity to metronidazole.	Headache, Vaginitis, and Nausea Maybe carcinogenic and neurological disturbances

Surgery

The purpose of surgical interventions is to eliminate the necrotic bone and preserve the remaining amount of bone. However, in stage 3, the patient might be indicated for palliative surgery to improve the symptoms for a better quality of life. Surgery strategy may be modified by the location of necrotic bone, stage, and risk/benefit assessment of the patient's condition. The surgeon should perform a mucoperiosteal flap with enough visualization of the lesion, follow up with the superficial debridement, saucerization, and marginal bone resection, depending on the severity of the lesion. The use of platelet-rich plasma (PRP) may also be indicated. In case of insufficient soft tissue, the advanced mucoperiosteal, or even mylohyoid flap or pedicled buccal fat pad may be necessary. Indications: Certain stage 2 cases and Stage 3 of MRONJ cases with exposed bone and possible presence of fistula, communication, and pathological fracture , however, some authors refer to broader indication (stage 2) for a better prognosis for the patient.Contraindications: Systemic conditions which preclude surgery.

Adjuvant treatment

Govaerts et al. (2020) summarized the most common adjuvant therapies for patients who suffer from MRONJ in a systemic review [48], which include oxygen therapy (HBO and Ozone), teriparatide, fluorescence guide surgery, laser, LLLT, and L-PRF.

Oxygen therapy

Oxygen therapy includes ozone therapy and hyperbaric oxygen therapy. Oxygen therapy is a form of treatment in which the patient is placed in a hyperbaric chamber and allowed to breathe 1.4 to 3 absolute atmospheric pressures of pure oxygen in the same way, as usual, natural breathing. It not only increases partial oxygen pressure in the diseased area but also improves the blood circulation of the affected area and relieves the phenomenon of oxygen deficiency and edema, and promotes normal wound healing so that the phagocytic white blood cells can effectively carry out the task of bactericide and accelerate the recovery of the affected area.

Indications: pre and postoperative treatment of bone debridement on stage 3 patient.

Contraindications: Patients with a significant deficit of G-6PD, pregnancy patients**,** particularly the early phase, hyperthyroidism, thrombocytopenia, and cardio-vascular severe instability, and patients who treat with ACE inhibitors. Adverse effects: Middle ear barotrauma, Sinus/paranasal barotrauma, Dental barotrauma, Pulmonary barotrauma, CNS oxygen toxicity

Teriparatide

Teriparatide is an endogenous parathyroid hormone usually injected subcutaneously to stimulate osteoblasts and promote osteogenesis in trabecular and cortical bones.Indications: Bone healing after surgical MRONJ treatment.Contraindications: Patients allergic to Teriparatide or its excipients.

Adverse effects: Headache, weakness, nausea, joint pain, dizziness, rhinitis, temporary hypercalcemia 4-6 hours after drug administration.

Fluorescence guided surgery (FGS)

Fluorescence-guided surgery injects tetracycline or doxycycline before the surgery and introduces the VEL scope system (VEL scope fluorescence lamp; LED Dental, White Rock, British Columbia, Canada) making debridement more efficient.

Indications: MRONJ surgery aid.

Contraindications and adverse effects: None have been specified in the research.

Low-Level Laser Therapy (LLLT)

The principle of LLLT is not yet completely understood. Still, it may be related to the electron transport chain, where light irritates, promoting photoreceptors to induce cell proliferation and division. In animal studies, post-extracted teeth after laser treatment can promote faster alveolar bone repair and reduce symptoms. The commonly used lasers include Er: YAG, Nd: YAG, and diode laser.

Indications: Treatment of MRONJ, reducing MRONJ pain, or combining surgery with L-PRF treatment in Stage 3.Contraindications and adverse effects: In 2010, The North American Association for Laser Therapy conference recommended the use of LLLT under the following conditions:1.The laser beam should not be directed into the eye, and patients should wear safety glasses appropriately.2.Do not use LLLT on any primary and secondary carcinoma except in patients undergoing chemotherapy. 3.Do not treat pregnancy or epileptics patients.

Leukocyte- and platelet-rich-fibrine (L-PRF)

L-PRF has been used in dental and orthopedic surgery for post-operative wound healing in recent years. L-PRF contains many growth factors and cytokines to accelerate healing, relieve pain and prevent infection. [55] Indications: Direct application during the surgery in patients diagnosed with stage 3 MRONJ.Contraindications: Patients with coagulation and hematological disorders.

Adverse effects: L-PRF is an autologous product with no known adverse effects (Chen, 2017).

Comparison between the effectiveness of different treatments protocols of the MRONJ

Surgical versus non-surgical treatment

To compare the effectiveness of the conservative treatment, 5 cohort studies have been selected in this section and is shown in [Table 6]. Two articles divided patients into two groups: conservative (including antibiotic

treatment, oral hygiene education, and CHX mouth wash) and surgical resection. Regardless of the stage, the success rates for the surgery group ranged from 86.5% to 100%, while with conservative treatments, the success rates varied from 0% to 33%. Another article suggested conventional treatment first and then surgery when the sequestered bone is not spontaneously exfoliated. With this treatment strategy, a short-term success rate of 88.57%, and the long term increased to 92%. Although conservative treatment did not cure the necrotic bone of the MRONJ, it significantly improved patient morbidity (p value< 0.05).

The effectiveness of adjunctive treatment of the MRONJ

Oxygen therapy

Sacco et al. published a systemic review of ozone treatment and Hyperbaric oxygen therapy. The healing rate of the ozone therapy showed a 44.58% improvement, while hyperbaric oxygen therapy had 5.17%. However, Freiberger et al. reported that hyperbaric oxygen has 52% of the complete healing rate compared to medical and conservative surgery, with only 33% of the total healing rate.

Teriparatide

Sim et al. prescribed eight weeks of subcutaneous teriparatide (20 µg/day) versus no treatment in the placebo group. Teriparatide showed two significant effects: greater resolution of the MRONJ lesion (p value= 0.013) and reduction of bony defects (p value= 0.017).

Fluorescence guide surgery

Otto et al. used visually enhanced lesion scope and 100mg doxycycline twice a day before surgery. In those 54 patients who received fluorescence guide surgery, 94.4% of the complete mucosal healing was achieved after surgery.

Low-Level Laser Therapy (LLLT)

In 2019, Souza Tolentino et al. published a systematic review in relation to LLLT treatment outcome. LLLT and conservative treatment, achieved only 19% of complete healing of lesions. However, when the LLLT was combined with surgery and conventional treatment, the success rate increased to 71.6%. Moreover, 64.2% of the patients reported improvements of the symptoms.

Leukocyte-and platelet-rich-fibrine (L-PRF)

Souza Tolentino et al. (2019) also summarized in their review outcomes involving treatment with L-PRF. Overall, the complete healing rate ranges from 80%~94%.

5. DISCUSSION

Oral health education

Before discussing the efficacy of various MRONJ treatments, it is important to mention that patients need to understand and recognize the symptoms of MRONJ as well as how to prevent MRONJ. Before and during treatment with certain drugs, patients need to be aware of the risk of osteonecrosis after oral and periodontal surgery, along with dental extractions. According to a study performed in Saudi Arabia in 2020, focusing on patients who were going to initiate bisphosphonate and/or Denosumab along with anti-Angiogenic drugs compared with patients who were currently on those medications, only 33.82% were aware of the risks of MRONJ. This shows that patients, in general, are not aware of the serious adverse effects. Although the chances of developing MRONJ are relatively low (0.043%~3%), patients should still understand their medications' potential risks and notify their dentists during their dental visits.

Not only there is a lack of awareness among patients, but there is also a lack of awareness among dentists. According to a study done in the UK in 2017, more than 90% of general dental practitioners were unaware that other medications could cause MRONJ other than bisphosphonate. Dentists who regularly perform periodontal surgery, extractions, and implant surgery need to be aware of the patient demographics that can be affected by, for example, osteoporosis and could taking these drugs.

Antibiotic treatment

The AAOMS recommends prescribing antibiotics for patients in stage 2 although no specifications on dosage and antibiotic preference is suggested. Meanwhile many articles emphasize the importance of antibiotics, there is no consensus on the duration of antibiotic prescription. There are no clinical trials comparing the efficacy of different antibiotics regimes. Some authors recommend prefer 1 week while other defend 15 days; other clinicians recommend using antibiotics for the entire duration before completion of wound healing. All of those publications suggest antibiotic treatment for a long period and until remission of symptoms in cases of stage 2 and 3 MRONJ.

Surgery

In the retrospective cohort Study published by Elena M. Varoni et al. in 2021, in 80% of Stage 2 patients, after an average follow-up of 23 months, and after treatment with Amoxicillin 3g, four patients had complete healing of necrotic bone lesion. The remaining patients had both short-term and long-term success rates of 90% after sequestrectomy. The recurrence rate of 30% was not due to surgical failure but because patients failed to followed up. This study illustrates that early drug treatment may allow patients to be successfully managed without surgery, and subsequent surgical treatment revealed a high success rate (important to mention the small sample size in this study)

Eguchi et al. divided 52 Stage 2 patients into surgical and conservative groups and reported that patients treated with surgery had a higher success

rate (89.3%) during a 6-month follow-up. The authors believeds that the AAOMS classification strategy does not consider treatment effectiveness. The article also mentions that many stage 3 patients are in poor physical condition due to cancer and may not withstand segmental resection and bone block reconstruction. The authors suggest an early-attitude in performing surgery on patients at Stage 2 to prevent deterioration of their condition. The same result was also mentioned in the article by Favia et al. Even in stage 1 surgical treatment could achieve 100% complete healing, whereas, in patients treated only with medication, no patients recovered completely even using LLLT as adjuvant therapy. For Stage 1 patients, Oliver Ristow et al. found in 2018 that up to 91.3% of patients still had bone exposure after conservative treatment, which means that regardless of the stage, early surgical treatment should be considered the treatment of choice.

Recommendation for early surgery at any stage has been mentioned in systematic reviews by Goker et al. and Aida Comas-Calonge et al. although the level of evidence is insufficient to make a clear recommendation. Both authors suggest more controlled randomized clinical trials with larger sample sizes are needed to support the conclusion that surgery is better than conservative treatment..Albanese et al. showed a significant improvement in MRONJ symptoms, including mucosal edema, halitosis, and pain, after treatment with antibiotics and analgesics alone in 12 SICMF-SIPMO stage 2 and stage 3 (p value<0.05), however medication and conservative treatment can only provide about 70% of temporary healing including symptom relief, indicating that medication cannot completely resolve the problem of MRONJ.

Adjunctive treatment

Since the treatment of MRONJ lacks specific and consensual guidelines, several non-traditional adjunctive treatments have been introduced as additional treatments for MRONJ. Moreover, there is no recognized success rate for conventional treatment and surgery treatment which makes this review article challenging to compare whether the adjunctive treatment has a significantly better effect on patient healing condition. Although these adjunctive treatments cannot replace conservative and surgical treatments, they have shown to improve patients' symptoms. Nonetheless, better designed randomized clinical trials are needed to confirm the beneficial effect of these treatments, including success rates and establishing protocols and guidelines.

6. CONCLUSIONS

Nowadays, treatment of MRONJ include oral hygiene recommendations, antibiotic therapy, and surgical removal of the necrotic bone. The chances of achieving complete healing with purely conservative treatments are low. Regardless of the MRONJ stage, early surgical treatment can achieve better success rates and prevent disease deterioration. The recent introduction of adjunctive treatments can accelerate bone healing and improve patient morbidity, although more evidence is still needed to confirm which treatment achieves the highest success rates.

Table 6. Overview of the studies comparing surgery and conservative treatment.

Author, year,	Type of study	Sample size/ Mean age	Stage n (%)	Treatment	Success rate	S
Elena M. Varoni et al. [60] 2021	Retrospective Cohort Study	35/73.46 y	Stage 1: 6(17.1%) Stage 2: 28(80%) Stage 3: 1(2.9%)	Patients treated with Amoxicillin 3g/day. If no response, add 500mg metronidazole for a maximum of 14 days, + 0.2 CHX mouthwash. If the no bone exfoliation perform surgical treatment.	Conservative treatment: 11% Surgery: Short term success rate: 88.57% Long term success rate 92% Recurrence: 30.4%	N/A
Takanori Eguchi et al. [61] 2017	Retrospective Cohort Study	52/74y	Stage 2: 100%	Conservative treatment: Antibiotic Surgical treatment of Necrotic bone resection.	Conservative treatment: 33.3% Surgical treatment 89.3%	P< 0.01
G Favia et al. [63], 2018	Retrospective study	106/ 72y	Stage 1: 8% Stage 2: 49% Stage 3: 42%	Conservative treatment: Antibiotic + LLLT+ CHX Surgery treatment: Simple surgical debridement to extensive bone resection	Conservative treatment: 0% Surgical treatment Stage 1 and 2: 100% Stage 3: 86.5%	N/A

Author, year,	Type of study	Sample size/Mean age	Stage n (%)	Treatment	Success rate	S
Massimo Albanese et al. [62], 2020	Retrospective Cohort Study	12/81.5y	SICMF-SIPMO Stage 2 and 3	Dental hygiene each four-month for a year CHX 0.12% mouthwash two times a day Amoxicillin + clavulanic acid (875 mg + 125 mg) three times per day and metronidazole (500 mg) three times per day	Improvement of signs and symptoms of the disease were observed in the population	N/A
Oliver Ristow et al. [64], 2018	cohort study	75/ 68y	Stage 1	Conservative antibiotic	8.7%	N/A

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