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Medication-Related Osteonecrosis of the Jaw: An Overview

Marko Blašković and Dorotea Blašković

Abstract

Medication-related osteonecrosis of the jaw (MRONJ) is a rare side effect of medications belonging to the antiresorptive (AR) and antiangiogenic (AA) groups. The first cases were described in the literature in 2003, and more than 1300 publications and 15,000 cases have been published since then. The incidence of MRONJ among cancer patients treated with bisphosphonates is 0–6.7%, with denosumab is 0.7–1.7% and with bevacizumab is 0.2%. Patients treated for osteoporosis have a lower risk of developing MRONJ at 0.02 and 0.04% with bisphosphonates and 0.2% with denosumab. In more than 50% of cases, tooth extraction was considered the causative factor responsible for the onset of the MRONJ. Treatment strategies include preventive, medical and surgical interventions.

Keywords: medication-related osteonecrosis of the jaw, bisphosphonate-related osteonecrosis of the jaw, antiresorptive-associated osteonecrosis of the jaw, denosumab, antiangiogenic medicamentations

1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a side effect of some medications belonging to the antiresorptive (AR), such as bisphosphonates and denosumab, and antiangiogenic (AA) groups. The disease is present as an exposed necrotic bone in the maxilla or mandible persisting for more than 8 weeks in patients taking the aforementioned medical therapy but without a past history of radiotherapy [1, 2]. The first cases described in 2003 were thought to be a side effect of bisphosphonates (BP) alone and was termed bisphosphonate-related osteonecrosis of the jaws [3, 4]. More than 1300 publications with more than 15,000 cases have been published since then, with two new names indicating that medications other than BPs could help trigger osteonecrosis of the jaws [5].

Reports of denosumab-associated osteonecrosis began surfacing in 2010, which led the American Dental Association to revise the term ‘MRONJ’ to antiresorptive-related osteonecrosis of the jaws (ARONJ) to stress the fact that other antiresorptive compounds could lead to osteonecrosis of the jaws [6–11].

Recently published literature has, however, demonstrated the implication of both antiresorptive and antiangiogenic medications in osteonecrosis of the jaws. It was known previously that the antiangiogenic medications could increase the incidence of osteonecrosis of the jaws when they were administered together with BP [12, 13]. New evidence indicates that antiangiogenic therapy can cause osteonecrosis of the jaws in patients naive to BP therapy [12]. Consequently, the American Association of Oral and Maxillofacial Surgeons (AAOMS) published an update in

2014 establishing the new moniker ‘MRONJ’ to better reflect the variety of medications known to induce jaw osteonecrosis [14].

From a historical stand point, the first cases of the jaw osteonecrosis were described in the nineteenth century in matchmaking industry workers who were exposed to phosphorous compounds. The condition was known as ‘phossy jaw’, a painful jaw bone exposure associated with sequestration and infection. It was a very progressive condition with high mortality rate because of the absence of antibiotic therapy. The incidence of the condition “phossy jaw” decreased significantly due to the improvement of the working conditions in the matchmaking industry [15].

In the literature, this condition is known under several names and acronyms:

MRONJ—medication-related osteonecrosis of the jaw

BRONJ—bisphosphonate-related osteonecrosis of the jaw

BAONJ—bisphosphonate-associated osteonecrosis of the jaw

ARONJ—antiresorptive-associated osteonecrosis of the jaw

BON—bisphosphonate osteonecrosis

ONJ—osteonecrosis of the jaw [5]

1.1 Antiresorptive medicaments: bisphosphonates (BPs)

Bisphosphonates belong to a group of antiresorptive medications often used to treat osteoporosis. Other members of the AR group are monoclonal antibodies against receptor activator of nuclear factor- κ denosumab (RANKL), selective oestrogen receptor modulators, estrogens and calcitonin. Only the first two members, BP and denosumab, are associated with MRONJ. Unfortunately, these are also the most commonly utilised medications for the treatment of osteoporosis. BPs are in fact considered the first-choice treatment for osteoporosis worldwide [16, 17].

The first biological use of BP dates back to the 1960s, when etidronate was used to treat heterotopic ossification. Soon after, further research led to the use of BP in the treatment of osteoporosis [18, 19]. BPs are also used to treat non-malignant diseases affecting the bone tissue such as Paget’s disease of bone, fibrous dysplasia, cystic fibrosis, primary hyperparathyroidism and osteogenesis imperfecta [19–23].

They are also used to treat osseous malignant conditions such as metastases of solid tumours, malignant hypercalcemia and multiple myeloma. The literature shows that BPs have significant positive effects on the quality of life in cancer patients by reducing complications such as bone fractures, pain and serum calcium imbalances. Furthermore, some members of the BP family such as zoledronate also present antiangiogenic and antitumour features by inhibiting human endothelial cell proliferation and changes in endothelial cell migration and adhesion. Zoledronate’s antitumour effects include induction of apoptosis as well as inhibition of cell invasion and adhesion. These aforementioned features are beneficial in delaying tumour growth [17, 24–29].

BPs can be divided into two groups based on the presence or absence of nitrogen atom in the side chain. The presence of nitrogen is related to the higher potency of the BP, which will clinically translate to a better antiresorptive effect and higher binding affinity to hydroxyapatite within bones. It is estimated that BPs have half lives in bone of approximately 11 years [30, 31]. Unfortunately, higher potency of the medication is also linked to a higher incidence of MRONJ. Bone resorption is achieved by two mechanisms. Non-nitrogen BPs are linked to osteoclast apoptosis. Nitrogen-containing BPs have a much more complex working mechanism that inhibits mevalonate signalling to impact osteoclastogenesis, apoptosis and cytoskeletal dynamics [32].

1.2 Antiresorptive medicaments: denosumab

Denosumab is a human monoclonal antibody that inhibits receptor-activated nuclear factor- κ B ligand (RANKL). Denosumab prevents the RANKL activation, which is crucial for osteoclast activation, function and differentiation resulting in decreased bone resorption and cancer-induced bone destruction [33–37]. It is available under two names: Prolia, which is used for treating osteoporosis, and Xgeva, which is used for treating complications in patients with bone metastases and solid tumours. The dosing used in the treatment of osteoporosis is 60 mg subcutaneous injection every 6 months. The treatment of patients with bone metastasis is 120 mg subcutaneous injection every 4 weeks [37]. Although the incidence of MRONJ is similar in patients treated with BPs and denosumab, there are some advantages of denosumab over bisphosphonates such as improved efficacy and better tolerability. Furthermore, denosumab creates no nephrotoxic effects and may be used in patients with renal insufficiency [36, 38, 39].

2. Antiangiogenic medications

Antiangiogenic medicines are used to treat patients with different types of tumours such as gastrointestinal stromal tumour, glioblastoma, hepatocellular carcinoma, hormone receptor-positive breast carcinoma, mantle cell lymphoma, metastatic colorectal carcinoma, multiple myeloma, metastatic renal cell carcinoma, non-squamous non-small cell lung carcinoma, pancreatic neuroendocrine tumour, renal cell carcinoma, subependymal giant cell astrocytoma and soft tissue sarcoma. They are used to inhibit or decrease neoangiogenesis which is crucial for the expansive tumour growth. It was known previously that antiangiogenic medications could increase the incidence of osteonecrosis of the jaws when administered concurrently with BP or denosumab [12, 40–43]. New evidence indicates that antiangiogenic therapy can also cause osteonecrosis of the jaws in patients naive to BP therapy [12, 41, 42, 44–49]. Many AA-associated cases of MRONJ were reported after the use of sunitinib and sorafenib, both of which are members of tyrosine kinase inhibitors [37].

3. Diagnosis of the MRONJ

In order to diagnose MRONJ, three diagnostic factors must be met:

1. Current or previous treatment with antiresorptive and/or antiangiogenic agents
2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than 8 weeks
3. No history of radiation therapy to the jaws or obvious metastatic disease to the jaws [1, 7, 14, 50]

Radiation therapy of the jaws must be excluded since the clinical presentation of the osteoradionecrosis and MRONJ may be impossible to distinguish. A diagnosis of osteoradionecrosis should be considered in patients with the aforementioned symptoms as well as a history of head or neck radiotherapy [7].

MRONJ diagnosis is established mainly via oral examination and review of medical history. Other more complex diagnostic tools such as imaging modalities

or histopathological examinations are not specific enough and should be used as adjunctive tools to assess the stage and extent of the disease. The initial diagnosis of MRONJ can be made by any dentist or physician with a basic understanding of MRONJ [7, 50].

Consultations with the patient's physician are critical because many patients remain confused or forgetful regarding their current or previous antiresorptive/antiangiogenic therapy. Furthermore, cancer patients may receive a complex therapy consisting of different medications used at different time sequences, which contributes to the overall confusion.

3.1 Clinical picture of MRONJ

A defining feature of MRONJ is the exposure of necrotic bone or fistulation that can be probed to the osseous surface which fails to heal for more than 8 weeks. This clinical finding can be anticipated by mild pain and discomfort in the affected site. As the disease progresses, the adjacent soft tissue becomes inflamed, appearing erythematous and swollen. Purulent exudate may be present as a consequence of a secondary infection. In the later stages of the disease, oroantral fistula, oronasal fistula, oral cutaneous fistula or pathological fractures may be present [1, 7, 14, 51].

3.2 Imaging

Radiographic features of MRONJ are not pathognomonic and depend on the stage and development of the disease.

In the early stages of the disease, zones of higher and diffused radiopacity and thickening of the lamina dura can be present within the affected bone. Previous extraction sites may demonstrate minimal or complete absence of bone healing, which results in radiolucent radiographic appearance with a prominent residual lamina dura.

In more developed stages of MRONJ, the exposed bone becomes colonised by bacteria which induce focal bone demineralisation. Radiography shows a poorly circumscribed mixture of radiolucent and radiopaque zones. Other osteolytic processes with similar radiographic findings include osteomyelitis, multiple myeloma, metastatic disease and primary lymphoma of the bone [7, 52].

Further advancement of the disease can result in the formation of bony sequestra, which is visible on radiographic image as radiopaque or mottled fragments surrounded by a radiolucent border. Additionally, in some cancer patients treated with BP, a periosteal thickening (mimicking a second layer of compact bone surrounding the cortical bone) and new bone formation on the Schneiderian mucous membrane were described [7, 52, 53].

MRI and Technetium-99m imaging modalities may be more useful in detecting the presence of inflammation in patients with established MRONJ [7].

Scintigraphy may show additional benefits in cancer patients undergoing intravenous (IV) BP therapy. There exists evidence that many of those who presented with an increased tracer uptake in the jaws subsequently developed necrosis, though further research is needed to confirm these findings [54, 55].

PET imaging has low diagnostic values in MRONJ because of a low level of sensitivity and accuracy [7].

3.3 Histopathology

MRONJ specimens are composed of grey coloured hard tissue and, occasionally, friable soft tissue. Decalcification of the larger specimens can be prolonged as a result of bone sclerosis. In contrast, smaller bone specimens may have soft

consistency as a result of bacterial colonisation. While the necrotic fragments are devoid of osteocytes and osteoclasts, they may have bacterial debris adherent to their surfaces from bone exposure. The adjacent soft tissue consists of granulation tissue with or without abscess formation [7, 52].

Although infrequently, metastatic cancer was identified in bone specimens clinically diagnosed as MRONJ in cancer patients exposed to BP therapy. Thus, all the bone specimens obtained from MRONJ cancer patients either by biopsy, sequestrectomy or segmental osteotomy should be sent for histopathological analysis [56].

3.4 Microbiology

Microbiological culture assessment of exposed bone has previously failed to identify a definite, specific microbial aetiology behind MRONJ. The samples demonstrated a polymicrobial infection caused by pathogens present in the normal oral flora [7, 52].

4. Frequency of MRONJ

MRONJ is an uncommon disease whose frequency is generally low regardless of the type of antiresorptive or antiangiogenic medications administered. According to one study, an average general dentist can expect one new case of MRONJ every 62 years of his work among patients on oral BP [57]. The overall risk of MRONJ among patients with cancer diagnosis (primary or metastatic) is 0–6.7% if treated with IV BPs [58–60], 0.7–1.7% if treated with denosumab [58, 61, 62] and 0.2% if treated with the AA agent bevacizumab [12, 58, 63]. The risk range of MRONJ among patients who are exposed to both zoledronate (intravenous BP) and bevacizumab (antiangiogenic) is 0.9% [12]. The risk among patients treated for osteoporosis who are exposed to oral zoledronate alone is 0.02% [58, 64], while the risk for patients treated with denosumab alone is 0.04–0.2% [58, 65, 66].

5. Risk factors of MRONJ

5.1 Risk factors connected with AR medications

- Route of administration of AR medications

Patients with intraosseous malignancies are treated intravenously with BP or subcutaneously with denosumab, while patients affected with osteoporosis can be treated with oral or intravenous BP medications or subcutaneously with denosumab.

Oral BPs are associated with lower occurrence risk of MRONJ than intravenous BPs or denosumab. The incidence of AR therapy-associated MRONJ is significantly lower for osteoporosis patients than for cancer patients [58].

- Duration of BP therapy

The prevalence of MRONJ increases over time, from 0.5 to 0.6% after 1 year of therapy, 0.9 to 1.1% after 2 years and 1.3 to 1.1% after 3 years [67]. For patients with osteoporosis who are exposed to oral BPs, the prevalence of MRONJ increases over time from 0 to 0.2% after 4 years. The average duration of BP

therapy in patients who developed MRONJ is 4.4 years [58]. Some authors found that there were no significant increases in risk between the third and fourth years of BP therapy [59].

- Dose and potency

Zoledronic acid is considered the most potent BP medication. Its potency is estimated to be 10 times higher compared to ibandronate and 20 times higher than pamidronate [68].

5.2 Local factors

- Dental treatment

Dentoalveolar surgery with bone manipulation (tooth extraction, implant placement and periodontal or endodontic surgical procedures) is the most common local risk factor for patients exposed to AR/AA with MRONJ. Tooth extraction was considered a precipitating factor in 52–61% of cases of MRONJ. In addition, exposure to zoledronate prior to tooth extraction incurred a 16- to 33-fold increase in risk of MRONJ [13, 69, 70]. The risk for patients treated with oral BPs is 0.5% or less [71, 72]. The same risk for the cancer patients treated with intravenous BPs is within the range of 1.6–14.8% [73, 74] or 1.7–4.7% [72] depending on the investigation.

Though they are considered risk factors, the exact rate of MRONJ in patients treated with AA/AR medications after periodontal, implant or endodontic surgeries is not yet certain. Anecdotal experience stipulates that they nonetheless demonstrate similar risks when compared to dental extractions [14].

- Dental or implant inflammation

The inflammatory processes associated with dentoalveolar surgery are considered a causative factor in developing MRONJ. The periodontal or periapical pathology were considered a risk factor for 50% of the cases of MRONJ [13, 14, 73, 75, 76]. Since many dental inflammatory diseases are treated via extraction, the exact degree to which surgical trauma or inflammatory changes actually contribute to the development of osteonecrosis is not yet clear [27].

5.3 Anatomic factors

MRONJ appears in the mandible more often than in the maxilla. Instance in the lower jaw is 73%, in upper jaw is 22.5% and in both jaws is 4.5% [13, 14].

Denture use increases the risk of MRONJ. This is especially true in cases of cancer patients with dentures exposed to ibandronate, zoledronate or pamidronate. These patients experience a two-fold increase in risk of osteonecrosis [69, 70].

5.4 Demographic risk factors

Higher prevalence of MRONJ in the female population may be associated with the prevalence of osteolytic conditions in women [14]. Women over 50 have a 50 and 12% lifetime risk of developing osteoporosis and breast cancer, respectively.

On the other hand, men in the same age group have a 20% risk of developing osteoporosis and a 17% risk of prostate cancer [16].

Few studies have been conducted exploring MRONJ risk in the paediatric population. However, a recent survey of the literature revealed no significant rate of MRONJ despite the fact that a number of patients were exposed to long-lasting BP therapies and invasive dental treatments [77, 78].

5.5 Systemic risk factors

Corticosteroids [13, 75] and antiangiogenic [12, 13, 37, 40–43, 45–49, 69] medications may increase the risk of MRONJ when administered concurrently with a bisphosphonate.

Other comorbidities were inconsistently linked to elevated risk of developing MRONJ, such as anaemia, diabetes [13, 75] and the type of cancer [15, 16].

6. Staging of MRONJ

The staging system was developed primarily to guide the clinician with specific treatment strategies according to clinical presentation. Furthermore, it helped introduce homogeneity to MRONJ literature, allowing for new advancements in the diagnosis and treatment of the disease.

The guidelines were first published in 2006 then updated in 2009 and 2014 as a result of new findings relevant for treatment of the disease [2, 7, 14].

6.1 Stage 0

The initial stage includes patients exposed to AR/AA therapy with no clinical evidence of exposed or necrotic bone. Only non-specific symptoms are present which cannot be attributed to other pathological entities. Recent literature suggests that up to 50% of patients at stage 0 will progress to the subsequent stage.

1. **Symptoms present during stage 0:** odontalgia not explained by dental cause, dull pain in the body of the mandible, sinus pain and altered neurosensory function.
2. **Clinical findings present during stage 0:** increased tooth mobility not explained by periodontal disease and fistula that is not associated with endodontic pathology.
3. **Radiographic findings present during stage 0:** alveolar bone resorption not associated with periodontal disease, thickening of the maxillary sinus walls, irregular trabecular patterns, absence of bone healing and persistent lamina dura in extraction sites, thickening of the lamina dura and a decrease in the size of the periodontal ligament space.

6.2 Stage 1

The clinical picture of stage 1 consists of exposed necrotic bone or a fistula that can be probed to the bone. Since there is no infection, the patients typically do not experience additional symptoms. Radiographic findings mentioned in the stage 0 may also be present.

6.3 Stage 2

In the second stage, the exposed necrotic bone is infected and the patients experience pain. Second stage patients can present with abscess and fistulation as well. Radiographic findings mentioned in the stage 0 may also be present. The adjacent soft tissues may be swollen or secondarily infected.

6.4 Stage 3

All of the symptoms and clinical findings characteristic of the second stage are also present in the third stage: infection, pain and exposed necrotic bone or fistulation that probes to bone. Furthermore, one or more of the following symptoms manifest as a result of disease progression beyond the anatomical borders of the alveolar bone:

- Exposed necrotic bone reaching the inferior border of the mandible or the floor of the maxillary sinuses
- Pathological fracture
- Extra-oral fistula
- Oroantral or oronasal communication
- Bone resorption extending to the inferior border of the mandible or the sinus floor [7, 14, 52]

7. Treatment of MRONJ

Three different types of treatment strategies have been developed for the MRONJ: preventive, [79, 80] medical and surgical treatments [14, 81]. Preventive measures are indicated for patients who are slated for AA/AR therapy or have undergone treatment without notable symptoms of MRONJ. The latter two treatment modalities are used to treat patients with an established diagnosis of MRONJ.

7.1 Preventing MRONJ

Preventive measures are undertaken to reduce risk factors and preserve oral health of the patient at risk of developing MRONJ. The incidence of MRONJ can be reduced by up to one third if preventive measures are applied. These measures differ depending on the indications of the AR/AA therapy as well as the nature of the triggering dental treatment.

Preventive measures fundamentally rely on proper communication and collaboration between the oncologist, the primary care physician, the dentist and the patient. The healthcare professionals must inform the patient of the possibility of developing MRONJ and of the importance of oral health in its prevention. Prior to initiating AR/AA treatment, the patient should be referred to a dentist for a complete clinical and radiological oral examination. It is the dentist's responsibility to evaluate the risk factors (such as dental decay, periodontal diseases and ill-fitting prostheses) for each individual patient, eliminate or decrease the risk factors, restore oral health and maintain oral health throughout and after the AA/AR treatment [79, 80].

According to some studies, only 30% of the patients taking BP are referred to a dentist because of a lack of AR/AA prescriber awareness. In addition, approximately 40–50% of dentists expressed a low-to-moderate level of knowledge of MRONJ, sometimes requesting discontinuation of medications not associated with osteonecrosis of the jaw [82, 83].

7.1.1 Cancer patients with AR/AA therapy

Before initiating AA/AR treatment, the oncologist should inform the patient about possible oral side effects and refer the patient to a dentist for comprehensive dental examination [79, 80]. Dentoalveolar surgery remains the major risk factor for developing MRONJ and extraction increases this risk, as do periodontal or periapical pathology [13, 69, 70]. As estimated above, pre-existing dental inflammatory disease is a risk factor for more than 50% of cases [13, 14, 73, 75, 76]. Thus, in accordance with the oncologists, the onset of the AR/AA therapy should be postponed until dental health is established. All extractions and dentoalveolar surgery should be performed and the surgical sites should be allowed to heal completely. Some studies advise at least 2–3 weeks of mucosal healing, while others recommend up to 45–60 days prior to initiation of AA/AR therapy [14, 79]. In the case of patients with total or partial dentures, intraoral examination for decubital areas should be performed. Old or ill-fitting dentures should be relined or replaced [69, 70].

If a cancer patient has already been exposed to AR/AA compounds, preventive therapy is directed towards preventing infections and avoiding dentoalveolar surgery. Consequently, good oral hygiene and frequent recalls are of paramount importance. All infected dentition should be addressed via endodontic therapy. If surgery cannot be avoided, chlorhexidine (CHX) mouth wash 0.12% should be started 7 days before the surgical procedure 2–3 times per day and should be continued for the next 2 weeks after the extraction. Antibiotic treatment should also be initiated before the extraction and continued afterwards, though there exists no current consensus [79] on the type, duration, onset and route of administration of the antibiotic therapy [84]. Some authors also recommend deep scaling of the remaining teeth prior to surgical interventions [72].

Again, proper communication must be established between the oncologist, the dentist and the patient to reduce the rate of complications.

7.1.2 Osteoporosis patients with AR/AA therapy

The risk of MRONJ in osteoporosis patients on oral bisphosphonate therapy increases significantly when the duration of therapy exceeds 4 years. During the first 4 years of oral BP therapy, minor surgical procedures can typically be performed without therapy modification. Thus, prophylactic dentoalveolar surgery is not critical to the degree it is in cancer patients and/or those undergoing IV AR/AA therapies. The patient should nonetheless be monitored regularly and given proper oral hygiene instruction [14, 79].

Patients who have been prescribed with a combination of BP, AA or corticosteroids demonstrate an additive risk of developing MRONJ [12, 13, 37, 40–43, 45–49, 69]. There exists much discussion in the literature regarding discontinuation (drug holiday) of BP therapy prior to surgical procedures. The purpose of a ‘drug holiday’ is to reduce the risk of MRONJ and complications with wound healing. However, suspension of BPs may increase the risk of complications including fractures. Furthermore, BPs have long half-lives when bound to hydroxyapatite, and the efficacy of a temporary discontinuation has been questioned. The clinician must weigh the risk of MRONJ

with the risk of complications in partnership with the physician who prescribed the BP therapy [1, 11, 14, 79, 84].

According to the guidelines from the AAOMS, a pre-operative drug holiday of 2 months may be considered regardless of the total duration of BP therapy. This should also be done in partnership with the physician who has prescribed the BP therapy. All BP therapy should be resumed once all appropriate post-operative healing has occurred [14].

7.2 Medical management of MRONJ

The aim of medical management is to prevent infection of the exposed bone using topical or systemic antibiotics. The use of analgesics is indicated if the patient complains of odontalgia or dull pain located in the affected areas. Since more than 50% of patients diagnosed with stage 0 progress to a higher stage, frequent recalls with oral health instructions and preventive measure can be beneficial in the long term [54, 81, 85].

Patients presenting with stage 0 and 1 of MRONJ may be treated with medical modalities only. Adjunctive therapy is used to enhance healing of the exposed bone by decreasing inflammation, improving vascularization and stimulating bone turnover.

- Typically, the topical antibiotic of choice is chlorhexidine gluconate 0.12%
- Systemic antibiotics

The first line antibiotic is a penicillin-class antibiotic such as amoxicillin. In case of allergy, clindamycin, fluoroquinolones and/or metronidazole may be used. Currently, there exists no scientific consensus on the duration of antibiotic therapy, though an empiric proposition recommends a 2-week course for patients with a persistent stage 1 disease and 4–6 weeks course therapy for more advanced stages of the disease.

- Pentoxifylline and vitamin E

The combinations of these drugs have already found some success in the treatment of osteoradionecrosis. Their specific mechanism of action in the treatment of MRONJ is not completely understood. It is believed that their ability to decrease inflammation and promote vascularization can contribute to positive outcomes. Though the duration of the treatment has not been established, some studies recommend suspension of this therapy after 3 years. Patients with all stages of osteonecrosis may benefit from pentoxifylline and vitamin E. The recommended dose of pentoxifylline is 400 mg twice daily and 1000 IU vitamin E daily.

- Teriparatide

This drug is used primarily in the treatment of osteoporosis. It may improve bone remodelling by stimulating osteoblasts, increasing bone cell signalling and activating osteoclasts. The safety, side effects, dosing and duration of the therapy for MRONJ are currently not known and additional research is warranted.

- Hyperbaric oxygen therapy

Hyperbaric oxygen therapy is used in the treatment of osteoradionecrosis because of its purported beneficial effects on wound healing. This treatment may help provide greater oxygenation to tissues with reduced vascular

supplies, accelerating wound healing and increasing bone turnover. Currently, the clinical utility of hyperbaric oxygen therapy in the treatment of MRONJ remains unclear. Higher costs and extended therapy duration could prevent routine use in MRONJ therapy [81].

7.3 Surgical treatment of MRONJ

Surgical treatment is typically indicated for the second and third stages of the disease. The degree of surgical intervention can vary from simple sequestrectomy to marginal or segmental osteotomies depending on disease dissemination, patient comorbidities, medical status and treatment expectations.

Mobile bone sequestra should always be removed regardless of the disease stage.

The term 'marginal resection' refers to surgical removal of the necrotic alveolar bone, preserving the inferior border of the mandible. On the other hand, segmental resection osteotomy includes removal of the inferior border of the mandible and results in a continuity defect. The former intervention may be used in the treatment of second stage MRONJ since the disease is limited to the alveolar bone. Consequently, the latter is reserved for the third stage of the disease as it is characterised by progression beyond the anatomical borders of the alveolar bone.

During surgical extractions or alveoplasties, the soft tissue over the bone defect should be sutured in multiple layers to ensure primary intention healing. Pre- and post-op systemic antibiotics should also be considered especially if the patient already has an established diagnosis of MRONJ [81].

Other adjunctive treatment modalities include platelet-rich fibrin (PRF) or other platelet concentrates as well as low level laser therapy. Platelet concentrates may aid soft tissue healing while low level laser therapy is linked to increased vascularity and osteoblastic differentiation, resulting in better bone healing [72, 86, 87, 89, 90].

Benefits of adjunctive treatments nonetheless remain controversial. Conflicting rates of healing have been reported when additional treatments were combined with surgical treatment compared to surgical treatments alone [86, 88–90].

8. Conclusion

MRONJ is an uncommon disease that can cause significant impairments and reductions in a patient's quality of life. Additional investments should be made to raise awareness and increase collaboration among patients, AR/AA prescribers and dentists. Issues that require further investigation include the exact number of medications associated with MRONJ, the role of drug holidays in its prevention and the choice of modalities (such as antibiotics, pentoxifylline, teriparatide and surgery) in its treatment.

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