International Journal of Scientific Research and Engineering Development-– Volume 3 - Issue 4, July - Aug 2020
Available at www.ijsred.com

RESEARCH ARTICLE OPEN ACCESS

MRONJ: From A Dentist's Perspective

Priyada.C*,Bindu R Nayar,** Babitha Babu***
*Senior Resident -Dept of Periodontics, Govt Dental College,Alappuzha
** Prof & HOD - Dept of Periodontics, Govt Dental College,Alappuzha
*** Intern - Govt Dental College,Alappuzha
Email: priyadac14@gmail.com

----------**********----------

Abstract:

Medication-related osteonecrosis of the jaw (MRONJ) is a potentially serious complication, following treatment with antiresorptive drugsused to reduce the risk of skeletal complications in patients with bone loss, resulting from osteoporosis or in patients withmalignant bone disease. It is very important for dentists to be aware of ways to identify and treat patients at risk, of this rare condition. The following article reviews on clinical features,drugs causing,prevention and management of MRONJ.

Keywords **— medication related osteonecrosis of jaws,bisphosphonates related osteonecrosis of jaws.**

I.INTRODUCTION

Medication related to osteonecrosis of the jaw (MRONJ) is an uncommon oral condition that occurs after exposure to therapeutic agents used to prevent bone complications such as bisphosphonates (BPs), denosumab and angiogenesis inhibitors [1]. At present the majority of MRONJ cases are observed in patients who have received intravenously administered bisphosphonates or antiresorptivetherapy for skeletal malignancy and osteoporosis.Alveolar bone turnover is more rapid in the mandible and maxilla than in long bones, hence the jaws are a better target for MRONJ [2].

II.HISTORICAL BACKGROUND

It was in 19 th century that phosphorus necrosis of jaw or "Phossy jaw" was first reported among workers of match making factories, following chronic exposure to yellow phosphorus. Bern convention in 1906 put a ban on the use of yellow phosphorus for match making.(1) Medication related ONJ and phosphorus necrosis (phossy jaw) were similar clinical entities.Robert Marx in 2003 described first modern bisphosphonate related oseonecrosis of jaw. Novaritis (2004) manufacturer of IV bisphosphonates first notified healthcare profesionals of the risk of ONJ associated with bisphosphonate medication.

III.DEFINITION

The earlier terminology "Bisphosphonate related osteonecrosis of jaw" (BRONJ has been replaced by "Medicated related osteonecrosis of jaw" (MRONJ) as certain other drugs like denosumab has been associated with ONJ, apart from bisphosphonates.

The diagnosis of BRONJ is made by following criteria *(**American association of Oral and Maxillofacial surgeon**: special committee on medication related osteonecrosis of the jaws)*[1]

- *Presents of exposed bone (or bone that can be probed through an intraoral or extra oral fistula) in the maxillofacial region over a period of 8 weeks.*
- *Current or previous treatment with antiresorptive (bisphosphonates or denosumab) or antiangiogenic agents.*
- *No history of radiation therapy to the jaws or obvious metastatic disease to the jaws.*

IV.CLINICAL FEATURES

Exposed necrotic bone in the oral cavity is the hallmark feature of the disease.(Fig no :1)Soft tissue swelling, suppuration, intra or extraoral draining sinus tracts and even local abscess are present when infection occurs. In severe cases infection spread into deep spaces of head and neck. A rare classical symptom only in the mandible is "Vincent or numb chin syndrome" following the impairment of inferior alveolar nerve.Depending on the affected area; local inflammatory process, sequestration or pathologic fracture of mandible might induce numbness in parts of chin, lower lip, gingiva and teeth.

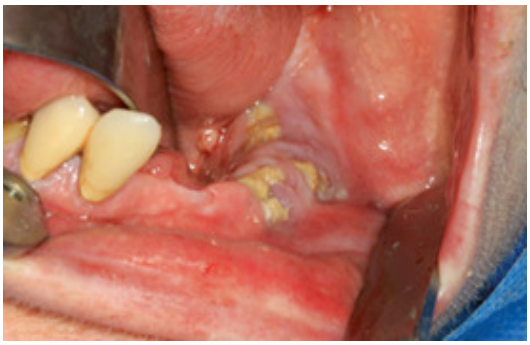


Fig 1:64-year-old female breast cancer patient, receiving IV zoledronate for 92 months. Photograph shows affected necrotic area in left mandible.

Staging of BRONJ/MRONJ according to AAOMS 2009 and 2014 update –Table 1

TABLE -1 [Adapted from 2,3]

	2009 AAOMS Staging	2014 AAMOS Staging
At Risk	No apparent necrotic bone in patient who have been treated with either oral or I.V BP.	No changes
Stage 0	No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms.	No changes
Stage 1	Exposed and necrotic bone in asymptomatic patients without evidence of infection.	Exposed and necrotic bone, or fistula that probes to bone, in patients who are asymptomatic and have no evidence of infection.
Stage 2	Exposed and necrotic bone associated with infection as evidenced by pain and erythema in regions of exposed bones with or without purulent discharge.	Exposed and necrotic bone and fistula that probes to bone, associated with infection as evidenced by pain and erythema in regions of exposed bones with or without purulent discharge.
Stage 3	Exposed and necrotic bone in patients with pain, infection which is extending beyond the alveolar bone resulting in pathological fracture, fistula etc.	Exposed and necrotic bone and fistula that probes to bone, in patients with pain, infection which is extending beyond the alveolar bone resulting in pathological fracture, fistula etc.

In maxilla which is involved approximately one third of the ONJ came under bisphosphonates treatment. The disease can be complicated by occurrence of maxillary sinusitis and rarelyoroantral communication. Further symptoms are loosening of teeth due to necrosis of bone and halitosis due to inflammation. Other complications are disfigurement of facial contour due to extensive boneloss, deviation of mandible following surgical resection[1].

V.DRUGS RELATED TO MRONJ & PATHOPHYSIOLOGY

Bisphosphonate molecules dock into the hydroxyapatite-binding sites on bone surfaces. As resorption of this bone begins by the osteoclasts, liberated bisphosphonates bind to farnesyl pyrophosphate synthase complexinside the osteoclasts, leading to their apoptosis. Denosumab, a human monoclonal antibodyshows a different mode of action.Denosumab targets and binds toreceptor activator of nuclear factor k-B (RANK) ligand(RANKL); thus preventing the activation of RANK on the surface of osteoclasts and their precursors. Inhibition of the RANKL-RANK interaction affect osteoclast formation, function, and survival, thereby reducing bone resorption[4]MRONJ is more prevalent among patients receiving high cumulative doses of intravenous bisphosphonates or denosumab than in patients who receive lower doses or oral administration.(Table 2,3)

The pathophysiology of MRONJ has not been fully understood.Though pathological findings were commonin many cases of MRONJ,no definitive pathogenesis was identified in clinical studies. Proposed hypothesis are the following[1]

- ***Inhibition of osteoclastic bone resorption & remodeling:***

Bisphosphonates and other antiresorptives such as denosumab, inhibit osteoclast differentiation,function and increase apoptosis leading to decreased bone resorption and remodeling.

- ***Inflammation or infection:***

Early studies identified bacteria speciallyactinomyces species in biopsied specimen of necrotic bone removed in patients with ONJ.

- ***Inhibition of angiogenesis:***

Clinical studies in cancer patients treated with zoledronic acid shows that interruption in vascular supply or avascular necrosis predisposes to ONJ.

TABLE 2

Drugs causing MRONJ			
Bisphosphonate	**Antiangiogenic Agents**	**RANKL Inhibitor**	**M-TOR Inhibitor**
Zoledronate Alendronate Pamidronate Risedronate Ibandronate Clodronate Etidronate	Bevacizumab Sunitinib Sorafenib Pazopanib Axitinib	Denosumab	Everolimus Temsirolimus

TABLE3

Bone Modifying agents and Risk of MRONJ

Drug	Indication	Route	Dose, mg	Schedule	Frequency of MRONJ
Pamidronate	Bone metastases of solid tumors, Multiple myeloma	IV	90	Every 3-4 weeks	3.2-5.0 %
Zoledronic acid	Bone metastases of solid tumors, Multiple myeloma. Adjuvant treatment	IV	4	Every 3-4 weeks or 12 weeks Every 3-6months	1.0-8.0 % 0-1.8%
Denosumab	Bone metastases of solid tumors. Adjuvant treatment	SC	120 60	Every 4 weeks Every 6 months	0.7-6.9% 0%

VI.LOCAL RISK FACTORS FOR MRONJ

1) Operative treatment :Dento alveolar surgery is a major risk factor for the occurrence of MRONJ.A retrospective review revealed that the risk of BRONJ is very high, twelve months after oral uptake in patients who had dental extractions, prosthetic injuries,irrecoverable teeth-foci and surgical procedures[5].

2)Anatomic factors: MRONJ is more likely to appear in the mandible than the maxilla but can appear in both jaws.

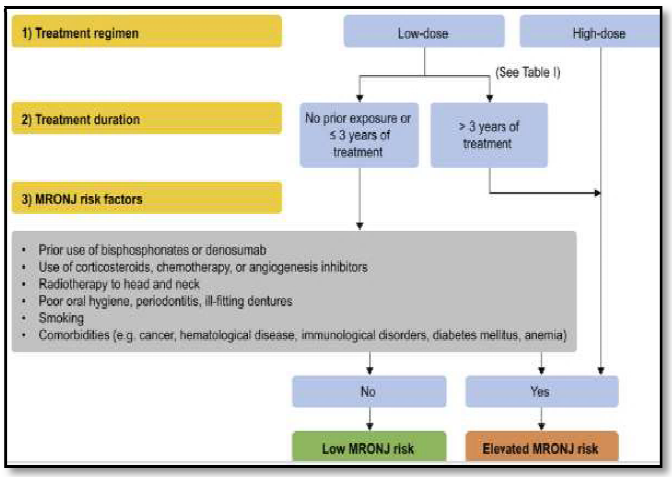
3)Concomitant oral disease: Preexisting inflammatory dental disease such as periapical pathology or periodontitis are accepted risk factors. (Fig no 2)

The precise aetiology of MRONJ is still unknown.Lately, theoriesregarding role of local inflammation and consecutive pH changes have been proposed. More evidences are upcoming on the role of local inflammation and dento-alveolar infections.It is now widely accepted that MRONJ has multifactorial aetiology.

VII.IMAGING MODALITIES & CHARACTERISTICS OF MRONJ

Panoramic radiographs are the primary modality for MRONJ imaging. Radiographic signs include sclerosis, persisting alveolar sockets and lack of bone filling in extraction sites, osteolysis and sequestration. CT and CBCT may be used to gain further 3-D information of the extent of osteonecrosis. Radiographic findings in MRONJ [1](Table 4)

Fig 2: Risk Factors ([Adapted from [3])



VIII.HISTOPATHOLOGY

- Necrotic bony trabeculae demonstrating empty osteocyte lacunae
- Necrotic bone usually surrounded by bacterial colonies and shows irregular periapical resorption and prominent reversal line.
- Actinomyces in contact with vital bone is consistent histologic findingempty howship lacunae at the periphery of bone
- Intertrabecular spaces infiltrated by inflammatory cells
- Pseudoepitheliomatous hyperplasia of the overlying mucosa observed in BRONJ.

IX.TREATMENT

The diagnosis of an osteonecrosis should be confirmed by histopathological investigations. The medications related osteonecrosis of the jaw (MRONJ) is considered a therapy resistant osteonecrosis entity. Both conservative and surgical treatment regiments are recommended.[1]. Treatment is recommended as following (Table 5)

TABLE 4

Radio opacity	**Radiolucency**	**Finding in advanced Diseases/complications.**
Sclerosis, focal/diffuse	Impaired healing of extraction sites, lack of bone filling, persisting alveolar sockets	Sequestra
Thickening of the lamina dura	Osteolysis of cortical bone/ Spongious bone.	Pathological fracture
Prominent mandibular canal	Focal cortical disruption.	Signs of sinusitis
Periosteal reaction	Periradicularlucency	

TABLE 5

Stage	Description	Treatment strategies
0	No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms.	Systemic management, including use of pain medication and antibiotics.
1	Exposed and necrotic bone in asymptomatic patients without evidence of infection.	Antibacterial mouthrinse, clinical follow up, patient education.
2	Exposed and necrotic bone associated with infection as evidenced by pain and erythema in regions of exposed bones with or without purulent discharge.	Symptomatic treatment with oral antibiotics, antibacterial mouth rinse,pain control, superficial debridement
3	Exposed and necrotic bone in patients with pain, infection which is extending beyond the alveolar bone resulting in pathological fracture, fistulaetc.	oral antibiotics, antibacterial mouth rinse,pain control, surgical debridement

1.SURGICAL THERAPY

The success rate of surgical approaches is significantly higher compared toconservative treatmentregimens.Conservative therapy usually takes months or years, with weeklyor biweeklyreviews for conservative wound management,that is an additional burden for patients. Surgical treatment is usually completed by 3-4 weeks.

LOCAL FLAPS

- ***Mucosalflap***

Mucosal flap is a local flap providing tissue closure to the area of exposed bone.Buccal mucosalflap, Buccal fat padflap,Mylohyoidflap and Nasolabial flap could be used.

- ***Microvascular free flaps***

Microvasular free flaps from distant donor sites such as radial fore arm flap and osteocutaneous fibular flap are used.

Aggressive surgical treatment interventions may be used if MRONJ results in persistent symptoms or impacts function despite initial conservative treatment.

2.ADJUVANT TREATMENT

1.Hyperbaric Ozone Therpy- HBO has significant angiogenic potential so it helps hypervascularity of the osteomyelitis part of the jaw bone.

2.Ozone therapy-It improves reparative process, increase inorganic matrix of bone and stimulate lymphatic and capillary growth.

3.Mini invasive laser surgery- Combined treatment with antibiotics, minimally invasive surgery (Er:YAG laser), and low-level laser therapy in the early stages of the disease could be the gold standard for bisphosphonate-related osteonecrosis of the jaw management[6].

4.Teriparatide- Recombinant human parathyroid hormone, with stimulatory effects on osteoblasts and osteoclasts, increasing bone turnover and bone formation, has shown encouraging results in MRONJ patients.[7]

5.BoneMorphogenic Protein-BMP-2 & BMP-7placed incleaned bone cavities, induces a successful healing of the necrotic area and new bone formation but with some side effects.[7]

6.Platelet concentrates: the use of autologous platelet concentrate rich in PGF,IGF,TGF-$\mathcal{B}$, as a local agent during bone resection has evolved as a promising

therapeutic strategy.[7]

7.Cell based therapy in craniofacial tissue engineering- This new and innovative treatment is also in the trial phase for management of MRONJ.

X. ROLE OF DENTIST IN PREVENTION OF MRONJ

Dental professionals are usually the first personnelsinvolved in diagnosis and treatment of the unexpected side effect of bisphosphonates.A complete dental examination should be performed includingradiographics(panoramic radiograph and/or full mouth IOPAs) before commencing treatment with bone modifying agents.[8]European Society for Medical Oncology recommends that "before zoledronic acid or denosumab therapy is initiated, patients should undergo an oral examination and appropriate preventive dentistry and be advised on maintaining good oral hygiene."[9] Different views exist regarding the benefit of "drug holidays", temporarily pausing treatment with bisphosphonates or denosumab in patients who are about to receive invasive dental treatments[10]

The role of dentists is to:

1.Be aware of risk of dentoalveolar surgical procedure in development of ONJ.

2.Recognise the clinical and radiological features of osteonecrosis.

3.Identify the local and systemic risk factors on NBP's that place them into the low or high risk group for BRONJ.

4.Adopt preventive strategies in patients on NBP's and especially in those who require dentoalveolar surgical procedure.

5.Consider the predictive role of biochemical markers of metabolic bone activity in determining the risk of MRONJ.

DENTAL REHABILITAION IN PATIENTS RECEIVING ANTI RESORPTIVE DRUG

- Surgical extraction of teeth is regarded to be the most frequent event for MRONJ.
- Sore spots of denture base are important prosthodontic risk factors for MRONJ.
- Removable prosthesis may be considered in patients with severe disease on anti resorptive medication.

RECOMMENDATIONS

1.Include a comprehensive dental, periodontal, and oral radiographic exam when feasible before initiating therapy.Dentistsfollow-up should be performed on a regular basis, every 6 months once treatment with a bone modifying agent has begun.

2.Address modifiable risk factors at the earliest,such as poor oral health, invasive dental procedures, ill-fitting dental prosthesis or systemic factors such as uncontrolled diabetes mellitus and tobaccouse.

3.Electivedentoalveolar surgical treatments such as nonmedically necessary extractions, alveoloplasties and dental implants, should not be performed while on active therapy with anoncologic dose of bone modifying agent.

4.If essential dentoalveolar surgery has been performed, the dental specialistshould evaluate thepatient on a systematic and regular basis (eg, every 6 to 8 weeks) until complete mucosal coverage of the surgical site has occurred.

5.Temporary discontinuation of bone modifying agents before dentoalveolar

surgery for patients receiving these at an oncologic dose,but there is insufficient evidence to support this.[2]

XI.FUTURE PROSPECTIVES OF BISPHOSPHONATES IN DENTISTRY

Bisphosphonates are in trial phase for use in dentistry as anticalculus agents&anticariesagent,reduce bone loss in periodontitis &periimplantitis,socket preservation ,reimplantation and for coating implant surface.

REFERENCES

[1] Medication related osteonecrosis of the jaws. Svenotto.Springer-Verlag Berlin Heidelberg 2015

[2] Bisphosphonates and Osteonecrosis of the Jaw: A Multidisciplinary Approach.Francesco Saverio De Ponte,Giorgio Lannetti.Springer-VerlagMailand 2012

[3] Salvatore.L.Ruggiero et al Medication Related Osteonecrosis of the Jaw.Position Paper

American Association of Oral and Maxillofacial Surgeon. 2014 update

[4] NicolatouGalitis et al Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. Vol. 127 No. 2 February 2019

[5] CoskunBenlidayi, Ilke, and RenginGuzel. “Oral bisphosphonate related osteonecrosis of the jaw: a challenging adverse effect.” ISRN rheumatology vol. 2013 215034. 16 May. 2013, doi:10.1155/2013/215034

[6] Weber JB, Camilotti RS, Ponte ME. Efficacy of laser therapy in the management of bisphosphonate-related osteonecrosis of the jaw (BRONJ): a systematic review Lasers Med Sci. 2016 Aug;31(6):1261-72.

[7] Thomas Lombard,VirginieNeirinckx,BernardRogister , Yves Gilon and Sabine Wislet.Medication-Related Osteonecrosis of the Jaw: New Insights into Molecular Mechanisms and Cellular Therapeutic Approaches. Stems cell international.2016https://doi.org/10.1155/2016/8768162

[8] Noam Yarom, Charles L. Shapiro, Douglas E. Peterson, Catherine H. Van Poznak,KariBohlke, Salvatore L. Ruggiero. Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO, Clinical Practice Guideline.Journal of Clinical Oncology.2019; 37(25): 2270-2290

[9] Almasan HA, Baciuţ M, Rotaru H, et al. Osteonecrosis of the jaws associated with the use of bisphosphonates. Discussion over 52 cases.Romanian Journal of Morphology and Embryology. 2011;52(4):1233–1241.

[10] RamagliaL,Guida A, Iorio-Siciliano V, Cuozzo A, BlasiA,Sculean A. Stage-specific therapeutic strategies of medicationrelated osteonecrosis of the jaws: a systematic review and meta-analysis of the drug suspension protocol. Clin Oral Investig. 2018:Mar;22(2):597-615.doi: 10.1007/s00784-017-2325-6

