Volume 2 • Issue 3 • September-December 2021

ISSN 2667-0720

Journal of MEDICAL EVIDENCE

The Official Publication of the All India Institute of Medical Sciences (AIIMS), Rishikesh

www.journaljme.org

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Review Article

Medication-Related Osteonecrosis of Jaw and Rheumatoid Arthritis: Revisiting the Concepts

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Abstract

Medication-related osteonecrosis of the jaw (MRONJ) is one of the most challenging condition that clinicians come across owing to its varied degree of presentation defined in literature. In rheumatoid arthritis (RA), individuals are under the influence of varied medications which might impact the bone turnover. Hence, this narrative review has been undertaken to specifically discuss development of MRONJ in RA, to study the associated risk factors, to highlight the importance of oral health care and to revisit the concepts of medications related to the above said condition. PubMed and Cochrane database search was done in English language literature using the term "Medication-related osteonecrosis of jaw and rheumatoid arthritis" and "bisphosphonate induced osteonecrosis of jaw and rheumatoid arthritis", which resulted in 45 articles. It was concluded that MRONJ is a multifactorial condition, seen concomitantly with various medical co morbidities like thromphophilia, hypertension, kidney disorders, osteoporotic conditions, arthritis, and various medications like steroids, bisphosphonates and other drugs affecting metabolism of bone. Literature has often tried to prove the association of RA in MRONJ causation, however there is no uniform agreement on the same. Though various risk factors have been delineated, but multiple evidences suggest that RA may prove to be a major risk factor. Present review supports the same and also highlights the growing evidence on the role of emerging new drugs in MRONJ development. Also utmost dental care, appropriate patient education, reduction of infective foci prior to initiation of medical therapy, patient compliance and regular follow up is required for reduction of number of patients presenting with MRONJ.

Keywords: Bisphosphonates, immunosuppressants, medication-related osteonecrosis of jaw, methotrexate, osteonecrosis of jaw

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is one of the most challenging condition that clinicians come across owing to its varied degree of presentation and protocols of treatment defined in literature.[1] This clinical entity has been given a series of nomenclature in order to attain standardisation so as to address the growing number of under-reported cases.[2] The exact pathogenesis is controversial in exiting literature, although a number of risk factors have been implicated. Exposure to anti-resorptive and anti-angiogenic therapeutic agents are the main culprits consistent with this disease process.[3] Accurate history and examination facilitates rapid diagnosis and early treatment.

In rheumatoid arthritis (RA), individuals are under the influence of varied medications which might impact the bone turnover leading to jaw osteonecrosis (ON). Literature has often proven the association of bisphosphonate (BP) use in RA for causation of MRONJ, but there is no uniform consensus on whether other drugs used in RA can also cause the same.[4] The advent of latest biologic medications for RA warrants monitoring for their suspected side effects. Furthermore, there are various risk factors associated with MRONJ such as prior dental intervention, concomitant medical conditions, age, tobacco use and infection; but RA in itself may prove to be a major risk factor for such bony impairment in near future. Although there are many medical conditions in which patients are predisposed to such clinical development, this narrative review has been undertaken to specifically discuss development of ON of

Received: 30-05-2020 **Revised:** 02-02-2021 **Accepted:** 01-04-2021 **Available Online:** 04-06-2021

Access this article online

Quick Response Code:

Website: www.journaljme.org

DOI: 10.4103/JME.JME_7_20

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How to cite this article: Bansal A, Reddy GS, Chug A. Medication-related osteonecrosis of jaw and rheumatoid arthritis: Revisiting the concepts. J Med Evid 2021:2:228-33.

jaw (ONJ) in patients with RA, to study the associated risk factors, to highlight the importance of oral health care and to revisit the concepts of medications related to the above said condition.[5]

Methodology

This is a narrative review of literature, where PubMed and Cochrane database search was done in English language literature using the term 'Medication-related osteonecrosis of jaw and rheumatoid arthritis' and 'bisphosphonate induced osteonecrosis of jaw and rheumatoid arthritis' with no limitation of time. The articles were excluded if there were no clearly stated cases of jaw ON in RA patients, or if ONJ was seen in medical conditions other than RA. All articles were checked thoroughly to avoid including same patients for review.

Results

This equation for search identified 45 articles in PubMed database search. No data was found in Cochrane library for the similar search. Out of these, three articles were based on clinical radiology, three other articles considered the development of MRONJ in cancer patients and one case report was in Spanish language; hence, these seven articles were excluded. Out of 38 articles, 13 were retrospective studies, case reports were found to be 11; 8 were review of literature; case series and systematic review were two each; one was observational cohort study and there was a single prospective controlled animal study. Table 1 enlists the articles considering MRONJ in RA patients. About 120 cases of RA were seen associated with MRONJ. Furthermore, among the medications, bisphosphontes were associated with maximum number of cases, followed by other drugs such as tumour

Table 1: Enlisting the articles considering medication-related osteonecrosis of the jaw development in rheumatoid arthritis patients

Author	Year of publication	Article type (SR, PS, OS, RA, RS, CS, CR, CC)	MRONJ cases in RA	Associated drugs (BP, TNF-α in, steroids, MTX, IS, other anti-rheumatic drugs, AG)
Hess *et al*.[5]	2008	SR	2	BP
Sacco *et al*.[6]	2020	SR	1	TNF-α in
De Molon *et al*.[7]	2016	PS	13	BP
Furuya *et al*.[8]	2017	OS	5	BP, steroids
Compain *et al*.[9]	2018	RA	50	BP, IS, steroids
Palaska *et al*.[10]	2009	RA	12	BP
Furukawa *et al*.[11]	2018	RA	19	MTX, BP
O'Ryan and Lo[12]	2012	RS	5	BP, TNF-α in
Hayashi *et al*.[13]	2018	RS	1	Steroids, other anti-rheumatic drugs
McGowan *et al*.[14]	2018	RS	3	BP
Guo *et al*.[15]	2014	RS	3	BP
Schwaneck *et al*.[16]	2020	RS	3	Steroids, other anti-rheumatic drugs, BP
Chiu *et al*.[17]	2014	RS	5	BP
Longato *et al*.[18]	2013	RS	8	BP, steroids
Manfredi *et al*.[19]	2011	RS	5	BP
Junquera *et al*.[20]	2009	RS	1	BP
Otto *et al*.[1]	2012	RS	9	BP, steroids, AG (thalidomide)
Nisi *et al*.[21]	2018	RS	5	BP
Aghaloo and Tetradis[22]	2017	CS	3	BP, steroids
Park *et al*.[23]	2010	CS	3	Steroids
Alsalleeh *et al*.[24]	2014	CR	1	MTX
Favia *et al*.[25]	2017	CR	1	TNF-α in (infliximab)
Javelot *et al*.[26]	2019	CR	1	TNF-α in (rituximab)
Horie *et al*.[27]	2015	CR	1	MTX
Mori *et al*.[28]	2015	CR	1	BP, steroids, MTX
Longato *et al*.[18]	2013	CR	1	BP
Chiu *et al*.[17]	2013	CR	1	BP
Grana *et al*.[29]	2008	CR	1	BP
Mathai *et al*.[4]	2018	CR	3	MTX, BP
Conte Neto *et al*.[30]	2011	CR	2	BP (alendronate)
Tolstunov *et al*.[31]	2012	CR	1	BP
Bejhed *et al*.[32]	2016	CC	24	BP

MRONJ: Medication-related osteonecrosis of the jaw, RA: Rheumatoid arthritis, SR: Systematic review, PS: Prospective study, OS: Observational study, RA: Review article, RS: Retrospective study, CS: Case series, CR: Case report, CC: Case control, BP: Bisphosphonate, TNF-α in: Tumor necrosis factor-alpha inhibitors, MTX: Methotrexate, IS: Immunosuprressants, AG: Anti-angiogenic

necrosis factor-α inhibitors, methotrexate (MTX) and other immune-suppressive and anti-angiogenic drugs.

Discussion

ON affects about 20,000 persons per year involving bones such as jaw, knee and hips.[5] ON carries a multitude of risk factors including infection, age, inactivity, thrombophilia, hypertension, kidney disorders, osteoporotic conditions, arthritis and various medications like steroids, BPs and other drugs affecting metabolism of bone.[5]

Nomenclature

Since its first description in 2003, ONJ used to be known as BRONJ.[3] Position paper of AAOMS (The American Association of Oral and Maxillofacial Surgeons) stated three conditions for consideration of drug related ONJ which included: if the patient had a history of treatment with or is currently under anti-resorptive or anti-angiogenic drugs; if there is persistence of exposed bone or bone which can be probed through fistula (either intra-oral or extra-oral) in the maxillofacial region, which has persisted for more than 8 weeks; and no therapeutic radiation history to the jaw or any jaw metastasis.[2] Hence, they changed the nomenclature to MRONJ to give consideration to drugs other than anti-resorptive and anti-angiogenic therapies.

Bisphosphonates

BPs are pyrophosphates with a tendency for resorption. Their impact on bone remodelling is due to the osteoclast inhibition. A number of under-reported cases of ONJ have come into picture due to establishment of its association with BPs; and their intake in RA has been well known in literature. Intake of BPs along with the presence of concomitant RA can increase the risk of bony fractures. Estimate of overall prevalence of ONJ in patients taking BPs is 0.03% to 0.1%.[12]

Hess *et al*. did a systematic review to evaluate the development of ONJ in patients taking BPs for conditions other than malignancy. Ninety-nine such cases were identified, out of which two were known cases of RA.[5] However, they concluded that ONJ is not solely attributed to BP use and is associated with risk factors. Similarly, study by Guo *et al*. clinically analysed 24 MRONJ cases taking BPs. Three of the cases reported history of RA.[15] This is equivalent to a retrospective analysis done by Chiu *et al*. of 7332 patients over age of 50 years receiving alendronate for a mean duration of 4 years and concluded that out of 40 cases of ONJ, five cases were of RA. In addition, ONJ has a higher incidence in cases taking alendronate as compared to raloxifene.[17] Manfredi *et al*. also retrospectively reviewed 135 patients of ONJ, of which five were RA patients under the influence of BPs.[19]

There has been various studies reporting ONJ in patients taking intravenous BPs like pamidronate and zoledronic acid. However, no much data is available on association with its oral form. Literature has suggested that minimum dosage of oral BPs (risedronate or alendronate) required for ONJ causation is 13,870 mg; with a range of 900–72,000 mg.[10] A retrospective cohort study was done by O'Ryan *et al*. to study ONJ development in patients taking oral BPs. Thirty such cases were identified and around 57% of these patients had concomitant comorbidities, with RA in five patients.[12] The mean duration of drug exposure was 4.4 years and prior dental intervention was positive in three RA cases, concluding that bisphoshonates along with newer anti-rheumatoid drugs like tumour necrotic factor-alpha (TNF-α) inhibitors might interfere with bone healing and can explain ONJ in such cases. Study by Conte-Neto *et al*.[33] also concluded that oral BPs like alendronate and etidronate increase the risk of jaw inflammation.

Tumour necrotic factor-alpha inhibitors

BPs, i.e., bone-modifying agents or monoclonal antibodies like denosumab, who work against receptor activator of nuclear factor kappa-B ligand have often been highlighted for their role in MRONJ. However, other drugs used in RA like tumour TNF-α inhibitors has been rarely studied or reported. TNF-α inhibitors are immunomodulators which targets inflammatory conditions such as RA, inflammatory bowel disease, psoriasis and spondyloarthritis through binding with TNF receptors specifically and hence reducing their inflammatory response.

A systematic review by Sacco *et al*. to studied the association of TNF-α inhibitors with MRONJ.[6] It stated that currently there are only five approved treatments to interfere with the activity of TNF-α; which are etanercept, infliximab, adalimumab, golimumab and certolizumab pegol. Monoclonal antibodies of them include adalimumab, infliximab and golimumab, and all have shown to be effective in RA. Their common adverse effects described in literature are tuberculosis, invasive fungal infections; bacterial and viral infections. However, no study ever evaluated their association with MRONJ. A total of six studies (involving six patients) were included in this review out of which four patients developed ONJ; and only one out of them was affected with RA. Infliximab was most found to be maximally responsible for ONJ, hence suggesting that MRONJ might develop even in the absence of anti-angiogenic and anti-resorptive medications. Report by Favia *et al*.[25] and Javelot *et al*.[26] also considered intake of infliximab and rituximab in RA respectively as the major trigger factor for ONJ.

Immunosuppressants

Hayashi *et al*. did a retrospective cohort study to examine the effect of immunosuppressive drugs on wound healing and development of ONJ following tooth extraction.[13] This study included one hundred and one patients. Nine patients had RA as an underlying disease. Immunosuppressants such as cyclosporine, azathioprine, tacrolimus, mycophenolate motefil, everolimus and mizoribine; corticosteroids like dexamthasone and prednisolone; and biological agents and disease modifying anti-rheumatoid drugs like infliximab, golimumab, tocilizumab, MTX and adalimumab were included. Corticosteroid dosage used was kept equivalent to

prednisolone and a drug-free period of 3 months was taken prior to dental procedure. ONJ was shown to develop in one of the cases of RA undertaking prednisolone and MTX.[13]

Lymphoproliferative disorders

RA is often associated with lymphoproliferative disorder (LPD), whose risk is 2.0-5.5 times greater in RA than other individuals with an unclear aetiology.[34] Cases of RA under MTX influence in LPD cases are referred to as MTX-related LPD. Furukawa *et al*. reported three such oral cases with a mean age of 71.1 years, where only MTX discontinuation led to the resolution of 80% cases, hence its role in MRONJ development.[11] This is equivalent to a report by Horie *et al*. where a 60-year-old man with RA presented with MTX-related LPD, and withdrawal of drug caused remission.[27] Mathai *et al*.[4] also proposed use of MTX in low dose in RA as a potential risk factor for MRONJ, similar to case reported by Alsalleeb *et al*.[24] A study by Park *et al*. also considered steroids as a reliable risk factor for MRONJ.[23]

Other risk factors

MRONJ is associated with a multitude of risk factors and requires meticulous reviewing of their signs and symptoms for its appropriate treatment. A case report by Tolstunov *et al*. stressed on the above said fact, especially in RA patients, where an accurate medical history including their systemic conditions and medications is necessary for its early diagnosis.[31] In this report, MRONJ was difficult to diagnose as patient suffered from multiple comorbidities. An observational cohort study by Furuya *et al*. studied oral health of RA patients.[8] Of the data collected form 5695 RA patients, dental treatment/extraction was done in 46.7% patients. Only five RA patients were confirmed having ONJ and were taking BPs and steroids at the time of diagnosis. All patients had concomitant medical condition, and it showed that there was only 0.094% prevalence of ONJ in RA patients.[8] Mori *et al*. reported MRONJ in RA patient with hypertension and osteoporosis who was under BPs, steroids and MTX influence.[28]

Majority of MRONJ cases have been seen associated with old age and female gender, equivalent to a survey done by McGowan *et al*., which showed predominance of females over males and mean age being 67 years.[14] Park *et al*. also supported similar results.[23] The reason for female predominance can be attributed to the decreased oestrogen levels in post or peri-menopausal phase which can alter bony homeostasis.

Oral health

The role of dental interventions and oral health in MRONJ causation has often been proven. A study by Hess *et al*.[5] and Sacco *et al*.[6] confirmed that recent dental procedure including extraction of tooth, any oral surgical procedure has been considered consistent with ONJ in RA patients. A 73-year-old female affected by ONJ due to BPs use was reported by Longato *et al*. where she characteristically had periodontitis.[18]

Duration of drug exposure

Drug exposure duration often acts as an ONJ risk factor in RA. More than 5 years of drug use is associated with a higher risk,[13] equivalent to a study by Furukawa *et al*. where mean MTX exposure was 6.6 years,[11] and Hugo *et al*. who found mean duration of BP treatment to be 46.8 months for MRONJ in RA.[9] Palaska *et al*.[10] calculated mean time of 1.8 years with a minimum of 10 months after zoledronic acid treatment (intravenous BPs), while it was 2.8 years in case of pamidronate. For oral BPs, mean therapy time was found to be 4.6 years while 3 years was found to be minimum.[10]

Rheumatoid arthritis: A risk factor

Apart from the factors aforementioned for MRONJ, RA in itself may be ascertained to be a major risk factor. Schwaneck *et al*. did a retrospective study on 198 patients to identify MRONJ prevalence in inflammatory rheumatic diseases undergoing osteoporosis therapy.[16] Three cases of MRONJ were identified and all these cases had RA, and hence indicated that rheumatic diseases, especially RA may be a major risk factor for the development of ONJ.[16] Case–control study by Bejhed *et al*. gave further evidence in support of RA being a risk factor.[32]

Conte Neto *et al*.[30] tried to establish and identify the link of RA as a risk factor for MRONJ, and commented that Gamma-delta T-cells (GDTC) has a role in pathogenesis of RA as they are raised in patients affected with ONJ. Also, cases of Vitamin-D deficiency leading to BRONJ has been linked to activation of GDTC.[30] RA also show an increase in pro-inflammatory cytokines which can reach the jaw bone leading to MRONJ, especially in infected cases and in older age group. Also, oxidative stress has always been implicated both in RA and MRONJ.

de Molon *et al*. demonstrated that there was increased degree of bone exposure if zoledronic acid was administered in cases affected with arthritis.[7] In a study done by Movila *et al*., it was presented that MRONJ tissue of humans express elevated γδT cell infiltration leading to Sema4D (class 4 semaphorin which is membrane bound) expression, which is associated with RA as it then results in TNF-α production in MRONJ lesion.[35] Also, a case report of multiple ON of the jaw in a patient diagnosed with refractory RA who was under BP use was given by Grana *et al*.[29]

Bone predilection

MRONJ usually shows predilection towards mandible, which is supported by Sacco *et al*.,[6] Junquera *et al*.[20] and Otto *et al*.[1] This may be attributed to the greater content of collagen and lower content of hydroxylysine in mandible as compared to long bones. However, Aghaloo *et al*. reported the most common site to be posterior maxilla.[22]

The management of MRONJ has been considered standard based on its defined stage-wise classification in literature.[2] However, there are various studies which support minimal intervention in such cases. Nisi *et al*.[21] concluded that sequestrectomy and debridement of soft tissues represents a valid treatment option for this condition, which is supported by Junquera *et al*.[20] in which patients responded well to the surgical debridement conservatively.

Study limitations

The limitations of the study included lack of randomised controlled trials, and long-term follow-up. Literature has often tried to prove the association of rheumatic disease like RA in ONJ causation, however there is no uniform agreement on the same. Although various risk factors have been delineated for this clinical entity, multiple evidences have suggested that RA may prove to be a major risk factor for the development of MRONJ.

Conclusion

MRONJ is a multifactorial condition which is seen concomitantly with various medical comorbidities. The present review supports RA being a causative factor for MRONJ, and also highlights on the growing evidence on the role of emerging new drugs in MRONJ development. Also, utmost dental care and prophylaxis, appropriate education to patients at risk, reduction of infective foci prior to the initiation of medical therapy, patient compliance and regular follow-up is required for reduction of number of patients presenting with MRONJ.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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