Review Article

The role of antiresorptive drugs and medication-related osteonecrosis of the jaw in nononcologic immunosuppressed patients: A systematic review

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Medication related osteonecrosis of the jaw (MRONJ) is a severe condition affecting the jaws of patients exposed to specific drugs, and is primarily described in patients receiving bisphosphonate (BP) therapy. However, more recently it has been observed in patients taking other medications, such as the RANK ligand inhibitor (denosumab) and antiangiogenic drugs. It has been proposed that the existence of other concomitant medical conditions may increase the incidence of MRONJ. The primary aim of this research was to analyze all available evidence and evaluate the reported outcomes of osteonecrosis of the jaws (ONJ) due to antiresorptive drugs in immunosuppressed patients. A multi-database (PubMed, MEDLINE, EMBASE and CINAHL) systematic search was performed. The search generated twenty-seven studies eligible for the analysis. The total number of patients included in the analysis was two hundred and six. All patients were deemed to have some form of immunosuppression, with some patients having more than one disorder contributing to their immunosuppression. Within this cohort the commonest trigger for MRONJ was a dental extraction (n=197). MRONJ complications and recurrence after treatment was sparsely reported in the literature, however a total of fourteen cases were observed. The data reviewed have confirmed that an invasive procedure is the commonest trigger of MRONJ with relatively high frequency of post-operative complications or recurrence following management. However, due to low-quality research available in the literature it is difficult to draw a definitive conclusion on the outcomes analysed in this systematic review.

Key words: Antiresorptive drugs, immunosuppress, intervention, medication-related osteonecrosis of the jaw, osteonecrosis, patients

How to cite this article: Sacco R, Woolley J, Yates J, Calasans-Maia MD, Akintola O, Patel V. The role of antiresorptive drugs and medication-related osteonecrosis of the jaw in nononcologic immunosuppressed patients: A systematic review. J Res Med Sci 2021;26:23.

INTRODUCTION

The medical term medication-related osteonecrosis of the jaws (MRONJ) defines a potentially severe condition that is a result of using specific medications, such as antiresorptive or antiangiogenic drugs. These medications are used for the treatment of the skeletal manifestation of malignancies and/or bone metastases, and in the management of osteoporosis, Paget's disease, and hypercalcemia.[1,2]

Since the first clinical study of bisphosphonate-related ONJ (BRONJ) in 2003, a growing number of scientific articles have been published demonstrating similar complications connected with other medications, such as the RANK ligand inhibitor (denosumab) and monoclonal antibodies. Monoclonal antibodies have been shown to contribute toward the development of similar lesions by binding and selectively inhibiting vascular endothelial growth factor-A, specifically the mammalian target of rapamycin inhibitors.[3-5] Due to the number of medications linked with the development of

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_794_20

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Submitted: 04-Jul-2020; **Revised:** 05-Aug-2020; **Accepted:** 28-Jan-2021; **Published:** 31-Mar-2021

ONJ, in a 2014 positional paper, the American Association of Oral and Maxillofacial Surgeons (AAOMS) developed and defined the medical term MRONJ.[6] The medications most commonly reported to be associated with MRONJ are listed in Table 1.[6,7]

The AAOMS position paper states that patients should be considered to have MRONJ if all of the following characteristics are present:

1. Current or previous treatment with antiresorptive 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 longer than 8 weeks
3. No history of radiation therapy to the jaws or obvious metastatic disease to the jaws.

Following a diagnosis of MRONJ, the AAOMS classification and staging system can then be used to guide the management strategy [Table 2]. Furthermore, it is currently accepted that some patients may present with nonspecific symptoms and may not have evidence of exposed bone. In the most recent AAOMS positional paper, this category of patients has been classified as Stage 0.[8]

The staging of MRONJ is based entirely on clinical signs. This has been heavily criticized in some literature, which have emphasized the importance of radiological findings as a necessity for accurate MRONJ staging, and consequently in providing specific management strategies.[6,8,9]

A major risk factor for the development of MRONJ is dentoalveolar surgery. A history of tooth extraction or oral surgery procedure (apicectomy or cystectomy) has been reported in 52%–80% of patients with MRONJ.[10,11]

Moreover, studies have also suggested that the risk of ONJ may be dependent on the potency of the antiresorptive agent and duration of treatment.[7,10,12,13] For instance, MRONJ is more common in patients receiving intravenous bisphosphonates (BPs) compared to oral BPs.[14] The incidence of MRONJ can also vary based on the prior medical history of the patient and their indication for treatment with MRONJ-specific medication.

Table 1: Antiresorptive drugs used in oncologic and nononcologic patients

Pharmacologic active ingredient	Formulation	Route of administration	Target therapy	Indication and frequency
Alendronic acid (sodium salt)	Tab 70 mg Tab 10 mg	PO	Osteoclast inhibition	Treatment of postmenopausal osteoporosis (70 mg/week) Treatment of osteoporosis in men (70 mg/week) Treatment and prevention of osteoporosis induced by glucocorticoids (70 mg/week)
Alendronic acid + cholecalciferol	Tab 70 mg/5600 UI	PO	Osteoclast inhibition	Treatment of postmenopausal osteoporosis in patients with unsupplemented vitamin D deficit (70 mg/week)
Ibandronic acid (monosodium salt monohydrate)	Tab 50 mg Btl 6 mg/6 ml Tab 150 mg Btl 3 mg/3 ml	PO IV PO IV	Osteoclast inhibition	Prevention of SREs in breast cancer patients with bone metastases (50 mg/day p.o. or 6 mg every 3-4 weeks iv.) Treatment of hypercalcemia of malignancy Treatment of postmenopausal osteoporosis in patients at high risk of fracture (150 mg/4 weeks p.o. or 3 mg every 3 months iv.)
Neridronate acid (sodium salt)	Btl 25 mg/2 ml Btl 100 mg/8 ml	IV/IM IV	Osteoclast inhibition	Osteogenesis imperfecta (2 mg/kg/3 months) Paget's bone disease (different schedules)
Pamidronic acid (disodium salt)	Btl 15 mg/5 ml Btl 30 mg/10 ml Btl 60 mg/10 ml Btl 90 mg/10 ml	IV	Osteoclast inhibition	Prevention of SREs in breast cancer patients with bone metastases or MM with bone lesions (60-90 mg every 3-4 weeks) Treatment of hypercalcemia of malignancy
Risedronic acid	Tab 35 mg Tab 5 mg	PO	Osteoclast inhibition	Treatment of postmenopausal osteoporosis (35 mg weekly or 5 mg daily) Treatment and prevention of osteoporosis induced by glucocorticoids (35 mg weekly or 5 mg daily) Treatment of Paget's disease
Zoledronic acid (monohydrate)	Btl 4 mg/5 ml Btl 5 mg/100 ml	IV IV	Osteoclast inhibition	Prevention of SREs in cancer patients with bone metastases or MM (4 mg every 3-4 weeks). Treatment of hypercalcemia of malignancy Treatment of osteoporosis in postmenopausal women, in men at increased risk of fracture, including those with a recent hip fracture from minor trauma (5 mg once per year) Treatment of bone Paget's disease
Denosumab	Btl 120 mg Btl 60 mg	SC SC	Monoclonal antibodies	Prevention of SREs in cancer patients with bone metastases (120 mg every 4 weeks) Treatment of hypercalcemia of malignancy. Osteoporosis (60 mg every 6 months)

Btl=Bottle; IM=Intramuscular; IV=Intravenous; MM=Multiple myeloma; PO=Peri-oral; SC=Subcutaneous; SRE=Skeletal-related event; Tab=Tablet

Table 2: Medication related of osteonecrosis of the jaw staging according to the American Association of Oral and Maxillofacial Surgeons 2014[7]

Stage	MRONJ clinical findings
At-risk category	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates
Stage 0	No clinical evidence of necrotic bone, but nonspecific clinical findings, radiographic changes, and symptoms
Stage 1	Exposed and necrotic bone, or fistulae that probes to the bone, in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed and necrotic bone, or fistulae that probes to the bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage
Stage 3	Exposed and necrotic bone or a fistula that probes to the bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone,(i.e., inferior border and ramus in the mandible, maxillary sinus, and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral-nasal communication, or osteolysis extending to the inferior border of the mandible

MRONJ=Medication related of osteonecrosis of the jaw; IV=Intravenous

Researches have reported that for patients treated with intravenous BP or denosumab, the incidence of MRONJ following the tooth extraction ranges from 1.6%–14.8% to 1.3%–15.6%, respectively, while the incidence is reported at only 0.5% for patients taking oral BP.[7,15,16]

In addition to the signs, symptoms, and incidence of MRONJ, clinicians and surgeons need to be aware of the risk factors that can contribute to the development and severity of the condition. Exposure to antiresorptive and antiangiogenic therapy represents the primary risk factor for MRONJ; however, it has been established that MRONJ can be affected by other local and systemic factors. In the current literature, ONJ has been associated with and accelerated by certain medical conditions. For example, the presence of anemia, diabetes-mellitus, diseases of immunosuppression, and renal failure have all been reported to increase the incidence of MRONJ.[10,17,18] However, it remains unclear whether these concomitant diseases or conditions are distinct contributing factors.[7,10,17,18]

Although MRONJ is debatably the most severe oral disease associated with antiresorptive medication, other side effects have been associated with and reported in patients undergoing antiresorptive drug therapy. These range from osseous and extraosseous adverse effects, upper gastrointestinal tract adverse effects, ocular adverse effects, renal toxicity, and hypocalcemia.[7,10]

The aim of this review is to analyze all available evidence and evaluate the reported outcomes in the development of MRONJ in immunosuppressed patients resulting from treatment with antiresorptive medications.

MATERIALS AND METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[19]

The protocol of this review was registered in the international platform of registered systematic review and meta-analysis protocols (INPLASY) under number INPLASY202050114 (https://inplasy.com/inplasy-2020-5-0114/).

The following four databases were explored: PubMed, MEDLINE, EMBASE, and CINAHL. A three-stage screening approach was used to ensure precision and safeguard the quality of the search. The screening of titles and abstracts was carried out independently by three authors (RS, JW, and OA) to eliminate any irrelevant material (i.e., reviews, animal studies, nonclinical studies, studies including oncology patients, and studies that did not report patients affected by immunosuppressed disease or therapy inducing immunosuppression). Disagreements were resolved by discussion until a consensus was reached.

A data screening and abstraction form was used to:

- Verify the study eligibility derived from the inclusion/exclusion criteria
- Carry out the methodological quality assessment
- Extract data on study characteristics and outcomes for the included studies [Figure 1].

The authors of any studies eligible for inclusion in the review with insufficient information were contacted directly to provide further information.

Focused question and Population Intervention Comparison Outcome strategy

Is there any sufficient evidence that nononcological immunosuppressed patients are at higher risk of developing ONJ due to antiresorptive drug therapy?

- Population (P): Any nononcological immunosuppressed patients previously or under treatment with antiresorptive drugs
- Interventions (I): Any type of intervention performed to treat MRONJ
- Comparison (C): Not applicable
- Outcome (O): State of knowledge regarding the risk of MRONJ as it relates to the type of drug, dose,

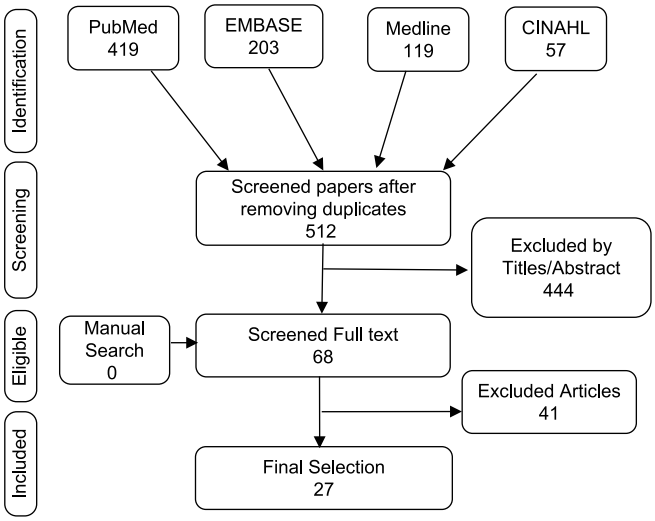

Figure 1: Study flow diagram

time-to-event, and rate of recurrence/progression after treatment in the immunosuppressed category of patients.

A search strategy for all databases was developed as follows:

1. Bisphosphonate [MeSH Terms] OR diphosphonate [MeSH Terms] OR Antiresorptive [MeSH Terms] OR Denosumab [MeSH Terms] OR Alendronic acid [MeSH Terms] OR Zoledronic acid [MeSH Terms] OR Pamidronate [MeSH Terms] OR Etidronate [MeSH Terms] OR Clodronate [MeSH Terms] OR Ibandronate [MeSH Terms] OR Risedronate [MeSH Terms] OR Tiludronate [MeSH Terms] OR Romosozumab [MeSH Terms]
2. Osteonecrosis [MeSH Terms] OR Avascular osteonecrosis [MeSH Terms] OR Osteonecrosis of the jaw [MeSH Terms] OR MRONJ [MeSH Terms] OR ONJ [MeSH Terms] OR BONJ [MeSH Terms] OR ARONJ [MeSH Terms] OR BRONJ [MeSH Terms]
3. HIV [MeSH Terms] OR AIDS [MeSH Terms] OR Transplant [MeSH Terms] OR Immunosuppress [MeSH Terms] OR Common variable immunodeficiency [MeSH Terms] OR CVID [MeSH Terms] OR alcoholism [MeSH Terms] OR diabetes [MeSH Terms] OR Selective immunoglobulin A deficiency [MeSH Terms] OR SIgAD [MeSH Terms] OR Immunologic deficiency [MeSH Terms] OR Adenosine deaminase deficiency [MeSH Terms] OR ADA [MeSH Terms] OR purine nucleoside phosphorylase (pnp) deficiency [MeSH Terms] OR PNP [MeSH Terms] OR Transcobalamin II deficiency [MeSH Terms] OR Thymic hypoplasia [MeSH Terms] OR X-linked agammaglobulinemia [MeSH Terms] OR Ataxia telangiectasia [MeSH Terms]
4. 1 and 2 and 3.

The search strategy included appropriate changes in the keywords and followed the syntax rules of each database.

Criteria for inclusion in this review

Types of studies

The search strategy considered published randomized controlled trials, case–controlled studies, case series, retrospective observational studies, and case reports. Papers were obtained from January 2003 to April 2020. Animal studies, reviews, and those studies which included patients with a previous history of radiation therapy to the head and/or neck regions were excluded. No language restrictions were imposed to the search.

Types of participants

The review considered studies involving nononcological immunosuppressed patients who developed MRONJ [Table 3]. No restriction of age, gender, or ethnic origin was applied. There was also no restriction on the minimum number of patients included in the studies.

Types of outcome measures

Disease definition

The disease definition, as proposed by AAOMS, includes the persistence of exposed necrotic bone in the oral cavity for 8 weeks, despite adequate treatment, in a patient with current or a previous history of antiresorptive and antiangiogenic drugs, without local evidence of malignancy, and no prior radiotherapy to the affected region. A clinical staging system has been proposed to classify patients with established MRONJ, with appropriate treatment for each severity of the condition.

Outcomes measured

- Primary outcomes: Evaluate the current state of knowledge regarding the risk of MRONJ as it relates to the type of drug, dose, time-to-event, and rate of recurrence/progression after treatment in the immunosuppressed category of patients
- Secondary outcomes: Evaluate the contributing factors to the MRONJ:
    - Invasive dental procedures
    - Unfit dental prosthesis
    - Spontaneous event
    - Site of the necrosis (maxilla, mandible, and anterior or posterior of the jaws)
    - Rate of complications related to the disease (fracture of the jaws, sepsis, etc.) and to the treatment of the disease (intra- or postoperative complications).

For the "complications" outcome measure, any intra- and postoperative surgical and nonsurgical complications

Table 3: List of the most common immune disorders according to the WHO

Disease	Definition	Diagnosis	Treatment associated with the disease (e.g., drugs)
HIV	Virus targets the immune system and weakens defense systems against infections and some types of cancer	Blood or saliva testing. Staged using CD4 T cell count and viral load (HIV RNA)	NRTIs, NNRTIs PIs, fusion inhibitors, CCR5 antagonists, integrase inhibitors, postattachment inhibitors, pharmacokinetic enhancers[b]
AIDS	Most advanced stage of HIV infection, defined by the development of certain cancers, infections, or other severe clinical manifestations	Blood or saliva testing and CD4 T cell count below 200	NRTIs, NNRTIs, PIs, fusion inhibitors, CCR5 antagonists, integrase inhibitors, postattachment inhibitors, pharmacokinetic enhancers[b]
Transplant	Organ is removed from the donor site and placed in the body of a recipient, to replace a damaged or missing organ		Immunosuppressants Induction drugs Maintenance drugs (calcineurin inhibitors, antiproliferative agents, mTOR inhibitor steroids)[c]
CVID	A heterogeneous group of diseases characterized by a significant hypogammaglobulinemia of unknown cause, failure to produce specific antibodies after immunizations, and susceptibility to bacterial infections[ϕ]	Testing for low serum IgG immunoglobulin concentrations and on exclusion of other causes of hypogammaglobulinemia[f]	Immunoglobulin replacement therapy[f]
Alcoholism	Harmful use of alcohol with physical dependency	Screening	Moderation, abstinence, therapy, detox or medications (Acamprosate, Disulfiram, Naltrexone, and Nalmefene)[d]
Diabetes	Chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces	Testing of blood sugar using glycated hemoglobin (A1C) test	Diet, exercise, medications (insulin, metformin, sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors)[a]
Selective immunoglobulin A deficiency	Genetic immunodeficiency lacking IgA, which protects against infections of the mucous membranes[f]	Blood tests demonstrate undetectable levels of IgA with normal levels of the other major classes of immunoglobulins[f]	Mostly untreated unless infections, which may be treated with antibiotics[e]
Severe combined immunodeficiency due to adenosine deaminase deficiency	A form of SCID characterized by profound lymphopenia and very low immunoglobulin levels of all isotypes resulting in severe and recurrent opportunistic infections[f]	Diagnosis is based on evidence of low or undetectable ADA activity in erythrocytes in combination with evidence of a marked reduction of T, B, and NK cell counts when compared to age-matched healthy controls[f]	ERT, allogeneic HSCT, and autologous GT[f]
PNP deficiency	A rare immune disease characterized by progressive immunodeficiency leading to recurrent and opportunistic infections, autoimmunity and malignancy as well as neurologic manifestations[f]	Clinical examination and laboratory findings showing leukopenia, severe lymphopenia with low CD3, CD4, and CD8 counts, and variable B cell function and immunoglobulin levels[f]	Hematopoietic stem cell transplantation[f]
Transcobalamin II deficiency	Disorder of cobalamin transport that usually presents during the first few months of life and is characterized by megaloblastic anemia, failure to thrive, vomiting, weakness, and pancytopenia[f]	Laboratory findings showing pancytopenia and accumulation of homocysteine and methylmalonic acid[f]	Intramuscular administration of hydroxocobalamin. Or oral treatment or treatment with cyanocobalamin[f]
Thymic hypoplasia	The thymus is underdeveloped or involutedf associated with 22q11.2 deletion syndrome and Ataxia telangiectasia[f]	Molecular genetic testing[f]	Specific medical management of immunodeficiencies and sinopulmonary infections, neurologic dysfunction, and malignancy[f]
X-linked agammaglobulinemia	Clinically variable form of isolated agammaglobulinemia, an inherited immunodeficiency disorder, characterized in affected males by recurrent bacterial infections during infancy[f]	Molecular genetic testing[f]	Gamma globulin therapy[f]

Contd...

Table 3: Contd...

Disease	Definition	Diagnosis	Treatment associated with the disease (e.g., drugs)
Sarcoidosis	Multisystemic, autoinflammatory disorder of unknown etiology characterized by the formation of immune, noncaseating granulomas in any organ(s), leading to variable clinical symptoms and severity[f]	Compatible clinical and radiographic manifestations, biopsy showing noncaseating granulomas, and exclusion of all other causes of granulomatous disease[f]	Corticosteroids if severe[f]
Amyloidosis	A group of diseases defined by the presence of insoluble protein deposits in tissues[f]	Histological findings[f]	symptomatic when irreversible kidney failure occurs (dialysis or transplant), chemotherapy to reduce the levels of monoclonal Ig, liver transplant has been suggested to stop the production of the causative protein[f]
Familial Mediterranean fever	Autoinflammatory disorder characterized by recurrent short episodes of fever and serositis resulting in pain in the abdomen, chest, joints, and muscles[f]	Genetic testing or using Tel-Hashomer criteria[f]	Colchicine
Polyarteritis nodosa	A rare, clinically heterogeneous, rheumatologic disease characterized by necrotizing inflammatory lesions affecting small- and medium-sized blood vessels[f]	Biopsy showing pathologic changes in medium-sized arteries[f]	Corticosteroidsf
Ulcerative colitis	A long-term condition where the colon and rectum become inflamed[d]	Blood tests, stool tests, imaging tests, colonoscopy, sigmoidoscopy, or tissue biopsies[d]	ASAs, corticosteroids Immunosuppressants[d]
Crohn's disease	Parts of the digestive system become inflamed[d]	Blood tests, stool tests, imaging tests, colonoscopy, sigmoidoscopy, or tissue biopsies[d]	ASAs, corticosteroids, immunosuppressants, azathioprine, methotrexate, cytokine modulators, nutritional therapies, surgical treatment[d]
Lupus erythematosus	Long-term condition causing inflammation to the joints, skin, and other organs[d]	4 out of 11 common signs of the disease. Most have a positive test for ANA[d]	Anti-inflammatory medicines, hydroxychloroquine, corticosteroids. If severe rituximab and belimumab[d]
Diffuse connective tissue disease, e.g., scleroderma, primary lupus, and polymyositis	A group of inflammatory diseases with the potential of involvement of many organ systems[f]	Serological markers[f]	immune modulation using cyclosporin A and monoclonal antibodies[f]
Rheumatoid arthritis	A long-term condition that causes pain, swelling, and stiffness in the joints[d]	No definitive test[d]	Disease-modifying antirheumatic drugs including methotrexate, leflunomide, hydroxychloroquine, sulfasalazined
Inflammatory spondylopathies	A group of inflammatory rheumatic diseases that includes ankylosing spondylitis and psoriatic arthritis[g]	Combination of physical examination, radiography, MRI, and blood tests for HLA-B27 gene[g]	Exercise, surgery, medication including NSAIDs and disease-modifying antirheumatic drugs[g]
Polymyalgia rheumatica	A rare rheumatologic disease characterized by bilateral morning stiffness which lasts >45-60 min of duration associated with a subacute-onset of severe pain with active movements[f]	Diagnosis of exclusion with blood tests including ESR and CRP[d]	Corticosteroids[d]

[a]WHO. Fact Sheets; 2020. Available from: https://www.who.int/news-room/fact-sheets. [Last accessed on 2020 May 07], [b]U.S Department of Health and Human Services. FDA-Approved HIV Medicines; 2020. Available from: https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/21/58/fda-approved-hiv-medicines. [Last accessed on 2020 May 07], [c]National Kidney Foundation. Immunosuppressants. Available from: https://www.kidney.org/atoz/content/immuno. [Last accessed on 2020 May 07], [d]NHS. Conditions; 2020. Available from: https://www.nhs.uk/conditions/. [Last accessed on 2020 May 07], [e]American Academy of Allergy, Astham and Immunology. Conditions and Treatments. Available from: https://www.aaaai.org/conditions-and-treatments/primary-immunodeficiency-disease/selective-iga-deficiency. [Last accessed on 2020 May 07], [f]OrphaNet. The Portal for Rare Diseases and Orphan Drugs; 2020. Available from: https://www.orpha.net/consor/cgi-bin/Disease.php?lng=EN. [Last accessed on 2020 May 07], [g]Arthritis Foundation. Spondylopathies; 2020. Available from: https://www.arthritis.org/diseases/spondyloarthritis. [Last accessed on 2020 May 07]. HIV=Human immunodeficiency viruses; NRTIs=Nucleoside reverse transcriptase inhibitors; NNRTIs=Nonnucleoside reverse transcriptase inhibitors; PIs=Protease inhibitors; AIDS=Acquired immunodeficiency syndrome; CVID=Common variable immune deficiency; IgG: Immunoglobulin G, DPP-4=Dipeptidyl peptidase IV, GLP-1=Glucagon-like peptide-1; SGLT2=Sodium-glucose cotransporter 2; SCID=Severe combined immunodeficiency syndrome; ADA=Adenosine deaminase; ERT=Enzyme replacement therapy; HSCT=Hematopoietic stem cell transplant; GT=Gene therapy; PNP=Purine nucleoside phosphorylase; ASAs=Aminosalicylates; ANA=Antinuclear antibody; MRI=Magnetic resonance imaging; HLA-B27=Human leukocyte antigen B27; NSAID=Nonsteroidal anti-inflammatory drugs; ESR=Erythrocyte sedimentation rate; CRP=C-reactive protein; mTOR=Mammalian target of rapamycin

were considered, e.g., fracture of osteosynthesis material, exposure of the reconstruction plate, etc.

Data extracted

Data extracted from the studies included the number of patients; patient gender and age; predisposing factors and localization of MRONJ; type of antiresorptive drug therapy and its cumulative dose; clinical indications for the drug or combined therapy; complications; follow-up time; and MRONJ recurrence.

All selected papers were carefully read to identify author(s); year of publication; study design; population; and treatment characteristics.

In the case of missing information, authors were contacted and 6 weeks was given for a response. If the information was still missing, missing data were presented as "not reported (NR)" in the results.

Review quality assessment data

Two review authors (RS and OA) appraised the risk of bias in the included study with the Cochrane Handbook for Systematic Reviews of Interventions.[20] The authors used the consensus-based clinical case reporting guidelines development (CARE checklist) for case reports and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for case series/longitudinal studies.[21,22] Any disagreements in the risk of bias assessments were referred to the third author of the review team (VP) and subsequently resolved by discussion. Levels of evidence were assessed according to the levels of evidence for therapeutic studies adapted from the American Society of Plastic Surgeons.[23]

RESULTS

Results were expressed as descriptive statistics because of the significant heterogeneity in the published data. There were no randomized controlled trials or case–controlled studies identified. A total of 27 articles were included in this review. All the published data described patients treated from 2009 to 2020. The types of articles that included within this review were case series (n = 8); case reports (n = 10); and retrospective observational studies (n = 9) [Table 4].[24-50]

List of excluded studies

Following the initial search, we considered 68 studies to be potentially eligible for inclusion, but after a thorough inspection of the full-text articles, 41 were excluded for not meeting the inclusion criteria for this review [Table 5].[17,50-89] The remaining 27 papers were then analyzed for data extraction.

Table 4: Studies included in the systematic review, including the number of patients and evidence level

Study	Type of study	Level of evidence*
Alsalleeh *et al*., 2014[40]	CR	V
Bocanegra-Pérez *et al*., 2009[27]	CS	IV
Chiu *et al*., 2013[35]	CR	V
Chiu *et al*., 2014[39]	ROS	III
Di Fede *et al*., 2013[38]	ROS	III
Di Fede *et al*., 2016[43]	CS	IV
Favia *et al*., 2017[44]	CR	V
Friedrich and Blake, 2007[25]	CS	IV
Fujieda *et al*., 2020[50]	ROS	III
Furukawa *et al*., 2018[46]	CR	V
Furuya *et al*., 2017[45]	ROS	III
Junquera *et al*., 2009a[28]	CS	IV
Junquera *et al*., 2009b[29]	CR	V
Katz and Ordoveza, 2014[41]	CS	IV
Khamaisi *et al*., 2007[24]	ROS	III
Liao *et al*., 2019[48]	ROS	III
Longato *et al*., 2013[36]	CR	V
Mathai *et al*., 2018[47]	CS	IV
Mehanna and Goddard, 2010[31]	CR	V
Molcho *et al*., 2013[37]	ROS	III
Nomura *et al*., 2013[34]	CS	IV
O'Ryan and Lo, 2012[32]	ROS	III
Park *et al*., 2010[30]	CS	IV
Park *et al*., 2012[33]	ROS	III
Preidl *et al*., 2014[42]	CR	V
Song *et al*., 2008[26]	CR	V
Steybe *et al*., 2019[49]	CR	V

*Levels of Evidence for Prognostic Studies Adapted from the American Society of Plastic Surgeons. Available from: https://www.plasticsurgery.org/documents/medical-professionals/health-policy/evidence-practice/ASPS-Rating-Scale-March-2011.pdf. [Last accessed on 2020 May 10]. CS=Case series; CR=Case report; ROS=Retrospective observational study

Immunosuppressed patients and medication-related osteonecrosis of the jaw data analysis

All 27 studies were published from 2009 to 2020 with results expressed as descriptive statistics.

A total of 206 patients with a mean age of 67.1 years (range 24–90 years) were included. One hundred and seventy-four patients were female (84.47%) and eight were male (3.88%). It was unclear for twenty patients (9.71%) and four patients did not have gender reported (1.94%) [Table 6].

The indications for treatment with an antiresorptive medication were osteoporosis (n = 181); prophylactically in combination with steroid therapy for rheumatoid arthritis (n = 11); Crohn's disease (n = 2); and sarcoidosis (n = 1). The indication for providing antiresorptive medication was not reported for one patient (n = 1). The most common antiresorptive medication was alendronate (n = 161). This was followed by risedronate (n = 12); clodronate (n = 7); ibandronate (n = 5); zoledronate (n = 4); and minodronate (n = 2). It was unclear what antiresorptive

Table 5: List of excluded studies

Authors	Type of study	Reason of exclusion
Aviles *et al.*, 2013[68]	RCT	Oncology study
Badros *et al.*, 2006[51]	Prospective observation	Oncology study
Badros *et al.*, 2013[66]	Poster	Oncology study and study type
Bagur *et al.*, 2010[58]	Abstract	Study type
Bejhed *et al.*, 2016[78]	Case control	Unclear sample (oncology)
Boonyapakorn *et al.*, 2008[53]	Prospective study	Oncology study
Borromeo *et al.*, 2011[62]	Case control	Unclear sample (oncology)
Brahim *et al.*, 2011[61]	Abstract	Oncology study and study type
Freire *et al.*, 2020[89]	Abstract	Study type
Freire *et al.*, 2020[50]	Abstract	Study type
Ebker *et al.*, 2013[67]	Letter to editor	Study type
Estilo *et al.*, 2008[52]	Retrospective study	Oncology study
Favia *et al.*, 2015[72]	Case report	Oncology study
Felsenberg *et al.*, 2009[54]	Abstract	Study type
Gambino *et al.*, 2016[80]	Abstract	Oncology study and sample type
Hayashi *et al.*, 2018[83]	Retrospective cohort	Unclear sample (oncology)
Horauf *et al.*, 2010[57]	Abstract	Oncology study and study type
Jarnbring *et al.*, 2015[75]	Retrospective case control	Oncology study
Kos *et al.*, 2010[59]	Retrospective observational	Unclear sample (oncology)
Lazarovici *et al.*, 2009[55]	Case control	Unclear sample (oncology)
Lazarovici *et al.*, 2010[56]	Case control	Unclear sample (oncology)
Mizohata *et al.*, 2014[71]	Poster	Oncology study and study type
Medeiros *et al.*, 2018[84]	Abstract	Study type
Otto *et al.*, 2012[17]	Retrospective observational	Oncology study
Paek *et al.*, 2016[79]	Retrospective observational	Unclear methodology and results
Patel, 2017[82]	Letter to editor	Study type
Pichardo *et al.*, 2013[70]	Case report	Unclear sample (oncology)
Pilanci *et al.*, 2015[73]	Retrospective observational	Oncology study
Rahimi-Nedjat *et al.*, 2016[77]	Retrospective observational	Unclear sample (oncology)
Shudo *et al.*, 2018[85]	Prospective	No BRONJ cases
Soares *et al.*, 2020[87]	Cross-sectional observational	Oncology study
Son *et al.*, 2019[88]	Retrospective observational	Unclear sample (oncology)
Suzuki *et al.*, 2017[81]	Abstract	Study type
Then *et al.*, 2012[63]	Retrospective observational	Oncology study
Thumbiegere-Math *et al.*, 2012[66]	Retrospective observational	Oncology study
Toro *et al.*, 2011[60]	Abstract	Oncology study and study type
Vestergaard *et al.*, 2012[64]	Cohort	Unclear sample (oncology)
Vidal Real *et al.*, 2015[74]	Cohort	Unclear sample (oncology)
Watters *et al.*, 2013[69]	Prospective observational	Unclear sample (oncology)
Wazzan *et al.*, 2018[86]	Retrospective observational	Oncology study

BRONJ=Bisphosphonate-related osteonecrosis of the jaw; RCT=Randomized controlled trials

medication was used for 14 patients (n = 14) and not reported for one patient (n = 1). The mean time of exposure of antiresorptive medication prior to the presentation with MRONJ was 53.0 months (range 9–144 months) [Table 7].

All patients had some form of immunosuppression as defined by the WHO. In some patients, they featured more than one disorder of immunosuppression. The most common disorder of immunosuppression was rheumatoid arthritis (n = 56). This was followed by diabetes (n = 49); a nonspecified diffuse disease of connective tissue (n = 7); Sjogren's syndrome (n = 5); a history of a transplant (n = 3), Crohn's disease (n = 2); sarcoidosis (n = 2); scleroderma (n = 1); and hypothyroidism (n = 1) [Table 7].

Of the papers reporting the etiology of MRONJ (n = 197), the most common trigger was an extraction (63.11%). This was followed by spontaneous development (13.59%); periodontal disease (4.37%); implant-related (2.43%); removable prosthesis-induced (1.94%); and trauma (0.49%). There was no identifiable trigger reported for ten patients (n = 10) [Table 6]. The staging of MRONJ was identified based on a reported diagnosis using the AAOMS diagnostic criteria or classified using the AAOMS diagnostic

Table 6: Preoperative epidemiologic analysis (age, sex, predisposing factors, and site of the necrosis involved)

Study	Patients number	Age/sex	Sex	Trigging cause	MRONJ Stage	Jaws involved
Alsalleeh *et al*., 2014[40]	1	66	Female	Extraction	II	Maxilla
Bocanegra-Pérez *et al*., 2009[27]	1	69	Female	Extraction	II	Both
Chiu *et al*., 2013[35]	1	63	Female	Implant	III	Maxilla
Chiu *et al*., 2014[39]	40	59.6-86.6 mean 74.9	39 female 1 male	Extraction 22	Nonreported	Nonreported
Di Fede *et al*., 2013[38]	87	53-92 mean 70.7	87 female	Extraction 57 spontaneous 26 denture 2 perio 2	0 (15) I (12) II (53) III (7)	Maxilla (23) mandible (61) both (3)
Di Fede *et al*., 2016[43]	18	63-72 mean 68.0	16 female 2 male	Extraction 9 denture 1 implant 3 perio 5	I (4) II (11) III (3)	Maxilla (12) mandible (6)
Favia *et al*., 2017[44]	1	49	Male	Extraction	III	Mandible
Friedrich and Blake, 2007[25]	1	75	Female	Extraction	Unclear	Mandible
Fujieda *et al*., 2020[50]	9	24-90 median 66	Unclear	Extraction 9	Nonreported	Nonreported
Furukawa *et al*., 2018[46]	1	81	Female	Trauma	III	Maxilla
Furuya *et al*., 2017[45]	5	65-79 mean 75.4	5 female	Nonreported	Nonreported	Nonreported
Junquera *et al*., 2009a[28]	1	73	Male	Extraction	II	Mandible
Junquera *et al*., 2009b[29]	1	73	Male	Extraction	II	Mandible
Katz and Ordoveza, 2014[41]	1	74	Female	Extraction	II	Mandible
Khamaisi *et al*., 2007[24]	1	73	Female	Nonreported	Nonreported	Mandible
Liao *et al*., 2019[48]	4	Nonreported	Nonreported	Extraction 4	Nonreported	Nonreported
Longato *et al*., 2013[36]	1	73	Female	Perio	II	Mandible
Mathai *et al*., 2018[47]	3	50-70 mean 60	3 female	Extraction	III	Maxilla
Mehanna and Goddard, 2010[31]	1	55	Female	Spontaneous	II	Mandible
Molcho *et al*., 2013[37]	3	63-70 mean 66.3	3 female	Nonreported	Nonreported	Maxilla
Nomura *et al*., 2013[34]	4	72-84 mean 78.3	4 female	Extraction	II	Mandible
O'Ryan and Lo, 2012[32]	11	54-89 median 70	Unclear	Extraction	Unclear	Unclear
Park *et al*., 2010[30]	4	68-81 mean 70.5	4 female	Perio	II	Mandible
Park *et al*., 2012[33]	3	51-61 mean 54.7	2 male 1 female	Extraction	II	Maxilla
Preidl *et al*., 2014[42]	1	36	Female	Extraction	II	Mandible
Song *et al*., 2008[26]	1	74	Female	Extraction	II	Mandible
Steybe *et al*., 2019[49]	1	77	Female	Extraction	II	Mandible

MRONJ=Medication related of osteonecrosis of the jaw

criteria based on the clinical and radiographical features reported in the papers. This was unclear or not reported for 74 patients ($n = 74$). For the remaining patients ($n = 132$), the majority of patients were identified as presenting with stage II MRONJ (63.64%). This was followed by presentations at stage I (13.64%); stage 0 (11.36%); and stage III (11.36%) [Table 6].

The site of MRONJ was reported for 137 patients ($n = 137$). Of those reported, MRONJ was most commonly reported in the mandible (63.50%), followed by the maxilla (32.85%). It was found in both the maxilla and mandible in five patients (3.65%). The region within the mandible or maxilla of MRONJ was not reported or unclear in 187 patients ($n = 187$) [Table 6].

Method of treatment; complications and recurrence were not well reported in the papers analyzed. Of the 28 patients that reported treatment, surgical treatment was the most common modality ($n = 17$), followed by conservative treatment ($n = 7$) and finally resection ($n = 4$). Of the eight patients with reported complications following treatment, infection was most common ($n = 6$), followed by progression of MRONJ ($n = 2$). It was reported that 31 patients did not develop any postoperative complications. Thirty-two did not have any recurrence of MRONJ following treatment (84.21%) [Table 8].

Risk of bias and review quality assessment

In the ten case report studies, a lack of clarity and missing data was identified in some of the 13 domains of the CARE Checklist. The lack of clarity was predominantly on reporting recurrence and the type of diagnostic procedures used at follow-up. Therefore, the level of bias for all the included case reports was graded as high. Regarding the retrospective and longitudinal case studies, there was a consistent lack of clarity in multiple domains of the STROBE Checklist. These were predominantly a result of the outcome measurement methods and inaccurate reporting of the

Table 7: Preoperative pharmacological analysis: type of drugs, indication for drug therapy, and time of drug exposure

Study	Type antiresorptive drug	Indication of drug therapy	Time of antiresorptive drug exposure (months)	Type of Immunosuppression disorder or immunosuppression drug
Alsalleeh *et al*., 2014[40]	Alendronate	Osteoporosis	36	RA
Bocanegra-Pérez *et al*., 2009[27]	Alendronate	Osteoporosis	32	RA, diabetes
Chiu *et al*., 2013[35]	Alendronate	Osteoporosis	84	RA, diabetes
Chiu *et al*., 2014[39]	Alendronate (40)	Osteoporosis (40)	Mean 48	RA (5), diabetes (14) diffuse disease of connective tissue (5)
Di Fede *et al*., 2013[38]	Ibandronate (1) Clodronate (7) Risedronate (1) Alendronate (77)	Osteoporosis (87)	Median 38	Diabetes (8)
Di Fede *et al*., 2016[43]	Ibandronate (4) Zolendronate (1) Risedronate (2) Alendronate (11)	Osteoporosis (18)	Median 69	RA (18) diabetes (unclear)
Favia *et al*., 2017[44]	Infliximab	Steroid therapy (Crohn's)	144	Crohn's
Friedrich and Blake, 2007[25]	Zoledronate	Steroid therapy (Sarcoidosis)	36	Diabetes, sarcoidosis
Fujieda *et al*., 2020[50]	Unclear (9)	Nonreported	Unclear (9)	RA (7), diffuse disease of connective tissue (2)
Furukawa *et al*., 2018[46]	Alendronate	Steroid therapy (RA)	84	RA
Furuya *et al*., 2017[45]	Mindronate (2) Risedronate (1) Alendronate (1) Nonreported (1)	Steroid therapy (RA) (4)	84	RA (3) RA and diabetes (2)
Junquera *et al*., 2009a[28]	Alendronate	Steroid therapy (RA)	Nonreported	RA
Junquera *et al*., 2009b[29]	Alendronate	Steroid therapy (RA)	46	RA
Katz and Ordoveza, 2014[41]	Zoledronate	Osteoporosis	24	Diabetes, scleroderma
Khamaisi *et al*., 2007[24]	Alendronate	Steroid therapy (RA)	Nonreported	RA
Liao *et al*., 2019[48]	Unclear (4)	Osteoporosis	Nonreported	Sjogrens (4)
Longato *et al*., 2013[36]	Alendronate	Steroid therapy (RA)	48	RA
Mathai *et al*., 2018[47]	Alendronate (3)	Osteoporosis (3)	12 (3)	RA (3)
Mehanna and Goddard, 2010[31]	Unclear	Steroid therapy (RA)	12	RA
Molcho *et al*., 2013[37]	Alendronate (3)	Osteoporosis (3)	36 (2) nonreported (1)	Diabetes (3)
Nomura *et al*., 2013[34]	Risedronate (2) Alendronate (2)	Osteoporosis (4)	9-69 mean 38	RA (1) RA and diabetes (2) diabetes (1)
O'Ryan and Lo 2012[32]	Alendronate (11)	Osteoporosis (11)	36	Diabetes (10) RA (4) sarcoidosis (1) Sjogrens (1)
Park *et al*., 2010[30]	Risedronate (4)	Osteoporosis (4)	60-120 mean 78	RA (3) hypothyroidism (1)
Park *et al*., 2012[33]	Alendronate (3)	Osteoporosis (3)	24-92 mean 58.7	Transplant and diabetes (3)
Preidl *et al*., 2014[42]	Zoledronate and Risedronate	Steroid therapy (Crohn's)	Ris 36, Zol 2 infusions	Crohn's
Song *et al*., 2008[26]	Alendronate	Osteoporosis	60	Diabetes
Steybe *et al*., 2019[49]	Alendronate	Osteoporosis	84	Diabetes

RA=Rheumatoid arthritis

frequency of recurrence and complications. Therefore, a high level of bias was considered for all retrospective and longitudinal case studies. Hence, the level of risk of bias across the case series, retrospective, and longitudinal studies was deemed to be high [Table 4].

According to the levels of evidence for therapeutic studies adapted from the American Society of Plastic Surgeons, we found that the quality of the studies included in this systematic review was ranging from level III to level V. Most of the articles included were level V (n = 10) which have resulted in limiting the quality of evidence described in the MRONJ literature. Hence, the need for improving the quality level by performing randomized controlled trials to confirm the hypothesis that immunosuppressed diseases can highly increase the chances of developing MORNJ in nononcologic patients.

DISCUSSION

The increased use of antiresorptive drugs has resulted in an increased incidence of patients suffering from MRONJ. Although the incidence of ONJ is rare, the development of ONJ can be devastating and the management extremely difficult.[18] Recognition of patients who are at higher risk is therefore crucial. The epidemiology and pathogenesis are

Table 8: Treatment and complications during the follow-up time

Study	Type of MRONJ treatment	Complications during follow-up (included plate removal)	MRONJ recurrence (*n*°)
Alsalleeh *et al*., 2014[40]	Conservative	Nil	No
Bocanegra-Pérez *et al*., 2009[27]	Resection	Nil	No
Chiu *et al*., 2013[35]	Surgical	Nil	No
Chiu *et al*., 2014[39]	Nonreported	Nonreported	Nonreported
Di Fede *et al*., 2013[38]	Nonreported	Nonreported	Nonreported
Di Fede *et al*., 2016[43]	Nonreported	Nonreported	Nonreported
Favia *et al*., 2017[44]	Resection	Nil	No
Friedrich and Blake, 2007[25]	Resection	Nil	No
Fujieda *et al*., 2020[50]	Surgical/conservative (unclear)	Nonreported	Nonreported
Furukawa *et al*., 2018[46]	Conservative	Nil	No
Furuya *et al*., 2017[45]	Nonreported	Nonreported	Nonreported
Junquera *et al*., 2009a[28]	Conservative	Nil	No
Junquera *et al*., 2009b[29]	Conservative then resection	Progression of MRONJ	Yes
Katz and Ordoveza, 2014[41]	Conservative	Nil	No
Khamaisi *et al*., 2007[24]	Nonreported	Nonreported	Nonreported
Liao *et al*., 2019[48]	Nonreported	Nonreported	Nonreported
Longato *et al*., 2013[36]	Surgical	Nil	No
Mathai *et al*., 2018[47]	Surgical (3)	Nil	No
Mehanna and Goddard, 2010[31]	Conservative	Nil	No
Molcho *et al*., 2013[37]	Nonreported	Nonreported	Nonreported
Nomura *et al*., 2013[34]	Surgical (3) nonreported (1)	Infection (2) nil (2)	No
O'Ryan and Lo, 2012[32]	Unclear	Infection (3) nil (9)	Yes (4)
Park *et al*., 2010[30]	Surgical (4)	Nil	No
Park *et al*., 2012[33]	Surgical (2) unclear (1)	Nil (2) nonreported (1)	No (2) nonreported (1)
Preidl *et al*., 2014[42]	Surgical twice	Progression of MRONJ	Yes
Song *et al*., 2008[26]	Conservative	Nil	No
Steybe *et al*., 2019[49]	Surgical	1 (necrotizing fasciitis)	No

MRONJ=Medication related of osteonecrosis of the jaw

becoming clearer, but for the most part, remain unclear with many unknowns. Improvements have been made regarding its definition, diagnosis and staging, prevention strategies, and treatment in the last two decades.[18] Additional risk factors have been recognized, such as intravenous bisphosphonate therapy, associated treatment with systemic steroids, and the literature suggests that local and systemic factors (such as periodontal disease and diabetes) might act as predisposing factors in the development of MRONJ, however it is unclear of the concomitant effect of immunosuppressive disorders on the development of MRONJ.[38,90-92]

The purpose of this systematic review was to evaluate the current state of knowledge regarding the risk of ONJ as it relates to dose, duration, and rate of occurrence in the immunosuppressed category of patients.

This review demonstrated a variety of articles with patients suffering from different disorders of immunosuppression. Rheumatoid arthritis and diabetes were the most common of these. Interestingly, the other immunosuppressive disorders all involve therapeutic management with corticosteroids, an already known risk factor in the development of MRONJ. Despite this interesting finding, it is unclear on the degree of involvement of these disorders and so difficult to draw definite assumptions.

Similar to previous literature, this review demonstrated a larger proportion of female patients suffering from MRONJ, albeit an even higher proportion of the data set.[92] Osteoporosis is more common in females and antiresorptive therapy is one of the most common management strategies for this disorder. This is one of the suggested explanations to explain the heightened frequency of MRONJ in females.[92] However, it is unclear why the proportion of females is so much higher in the immunosuppressed category of patients as demonstrated in this study.

In this review, it was surprising to discover a high proportion of patients with a spontaneous onset of MRONJ (14.3%). This leads to the suggestion that certain systemic problems may enhance the susceptibility of the spontaneous development of MRONJ when compared to other osteometabolic patients.

Treatment of MRONJ is challenging, and an effective and appropriate therapy that substantially improves the outcome is yet to be determined.[80] The majority of current research on the resolution, complications, and recurrence of MRONJ comes from a report of patients with multiple myeloma who were observed prospectively. MRONJ resolved in 62% of cases and recurred in 12%.[93] This review found higher rates of recurrence (15.8%), which may be explained by the immunosuppression reducing the propensity of a complete and robust immune response.

When considering the mean time of presentation of MRONJ in osteoporotic patients, this review found the mean time in patients with disorders affecting immunosuppression to be shorter than in previous literature (31.1 months).[3,94,95] If any conclusion can be drawn from this finding, it would be that a short time period of BP exposure does not necessarily constitute a safety threshold relating to the risk of MRONJ in patients and any invasive treatment on patients with BP therapy at any stage should involve a thorough risk assessment.

Other clinical findings in this review are mostly in agreement with clinical findings in other reported papers.[38,43,92,94,96] Alendronate (alendronic acid) was the most frequent type of antiresorptive medication prescribed in patients who developed MRONJ. This is likely a result of alendronate being the most commonly delivered oral bisphosphonate for osteoporotic patients.[92,96] This review observed that the majority of MRONJ was located in the mandible, predominantly in the molar region, and most frequently first observed as stage II according to the AAOMS diagnosis, seemingly aligned with previous research.[7]

The significant heterogeneity in data prevented quantitative analysis, and while clear trends were evident in the collected data, these must be carefully interpreted in the context of vastly varied reporting and important voids in the available information pertaining to risk factors. However, the authors still consider the results from this review important and valuable in this poorly understood area of medicine. It is understandable that due to the infrequent incidence of MRONJ, it is difficult to improve the quality of evidence unless a collective effort is employed. Therefore, the authors believe that additional high-level evidence studies, such as multicenter studies, case–controlled studies, or randomized controlled trials, are necessary to determine whether patients in the immunosuppressed category have notable differences regarding the risk of MRONJ. This review sought to determine whether disorders of immunosuppression expose individuals to developing MRONJ and their associated outcomes following management. It seems prudent for further research to also focus on specific disorders of immunosuppression; to consider their physiology and to determine the extent and degree of involvement. In addition, this may allow for the evaluation of the mechanisms of involvement with these disorders of immunosuppression.

The authors advocate, in general, that the following rules should be applied for MRONJ observational studies:

- Diagnosis and staging of the disease should be assessed with standardized reproducible scales and should be calibrated among the clinicians involved in the study
- If randomization is feasible, it should be carried out and described in sufficient detail to allow an assessment of whether it produced comparable groups
- Common, quantifiable, and clinically relevant endpoints (time to complete wound healing, pain, specific investigations, treatment acceptability, and participant satisfaction) should be described in a sufficiently detailed manner
- A long follow-up period is essential to identify a predictable treatment effect
- A predictable special investigation, such as computed tomography (CT), cone-beam CT, or magnetic resonance imaging should be encouraged for the duration of follow-up to determine any local recurrence.

CONCLUSION

This is the first systematic review exploring the complex relationship between immunosuppressed patients with MRONJ. This study has observed and highlighted the absence of high-level evidence in the literature. Although some trends have been demonstrated in this review, it is currently difficult to ascertain quantitatively the susceptibility of immunosuppressed patients in the development of MRONJ. The available data suggest that more well-designed clinical studies are necessary to improve the evidence in managing this serious condition.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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