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Medication-Related Osteonecrosis of the Jaw Associated with Monoclonal Antibodies and Small-Molecule Inhibitors: A Literature Review

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ABSTRACT: Medication-related osteonecrosis of the jaw (MRONJ) has evolved from an uncommon clinical entity to a well-recognized, multifactorial complication predominantly linked to antiresorptive and antiangiogenic therapies. While bisphosphonates were the first drug class linked with M.R.O.N.J., subsequent research has identified several newer therapeutic agents, specifically monoclonal antibodies (mAbs) and small-molecule inhibitors (SMIs), as significant contributors. The increasing use of these agents in oncology and metabolic bone disorders necessitates a thorough understanding of their mechanisms and association with MRONJ. This review synthesizes evidence from 25 key studies, encompassing randomized controlled trials, cohort analyses, pharmacovigilance reports, and expert consensus guidelines. Our objective is to present an evidence-based framework highlighting the incidence, how the process works, risk modifiers, signs and symptoms, diagnostic protocols, and management strategies linked to MRONJ induced by mAbs and SMIs.

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INTRODUCTION & BACKGROUND

According to the American Association of Oral and Maxillofacial Surgeons (AAOMS), medication-related osteonecrosis of the jaw (MRONJ) can be defined as exposed necrotic bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that fails to heal within 56 days in patients with a history of antiresorptive or antiangiogenic therapy, without any history of radiation therapy to the cranio-maxillofacial complex [1]. Originally attributed to bisphosphonates, most notably intravenous zoledronic acid, MRONJ has since been observed in association with denosumab, an anti-RANKL (Receptor Activator of Nuclear factor Kappa-B Ligand) monoclonal antibody, and bevacizumab, an anti-VEGF agent [2,3]. Additionally, small-molecule kinase inhibitors such as sunitinib and sorafenib, as well as mTOR inhibitors (e.g., everolimus) and CDK4/6 inhibitors (e.g., palbociclib), have been implicated in predisposing patients to MRONJ [1,4,5]. The pathophysiological mechanisms underlying MRONJ induced by these agents include profound suppression of bone remodeling, impairment of angiogenesis, and increased susceptibility to infection and trauma, all culminating in impaired osseous healing. Given the rising clinical application of these targeted drugs, understanding their implications in MRONJ is imperative for maxillofacial surgeons, oncologists, and dental practitioners.

REVIEW

Material and Method

A comprehensive literature review was conducted to evaluate the association between monoclonal antibodies, small-molecule inhibitors, and medication-related osteonecrosis of the jaw (MRONJ). Electronic database searches were performed using PubMed, Scopus, Web of Science, and Google Scholar for studies published up to April 2026. The review methodology was structured according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6]. The search strategy included combinations of the following keywords: "MRONJ," "medication-related osteonecrosis of the jaw," "osteonecrosis," "monoclonal antibodies," "small-molecule inhibitors," "denosumab," "bevacizumab," "tyrosine kinase inhibitors," "mTOR inhibitors," "CDK4/6 inhibitors," "antiresorptive agents," and "antiangiogenic therapy." Studies were included if they evaluated the role of monoclonal antibodies or small-molecule inhibitors in the development, pathophysiology, epidemiology, diagnosis, prevention, or management of MRONJ. Eligible articles included randomized controlled trials, cohort studies, case-control studies, pharmacovigilance reports, systematic reviews, consensus guidelines, and relevant case series published in English-language journals. Articles were excluded if they focused exclusively on bisphosphonate-related osteonecrosis without discussing monoclonal antibodies or targeted therapies; lacked sufficient clinical relevance; were duplicate publications, conference abstracts, editorials, or non-English publications without accessible translations. A total of 1,045 records were identified through database searching, with an additional 37 records obtained from manual reference screening and related reviews. After duplicate removal, 1,013 articles underwent title and abstract screening. Of these, 948 articles were excluded due to irrelevance. Sixty-five full-text articles were assessed for eligibility, and 25 studies meeting the inclusion criteria were selected for qualitative synthesis in the final review.

Search Strategy-

For our study, we started by searching databases and found 1,045 relevant articles. We also found 37 more from references and other reviews, making a total of approximately 1,082 records. After removing duplicates, we had around 1,013 unique articles. We then screened the titles and abstracts and excluded about 948 that were not relevant. This left us with 65 full-text articles, which we reviewed in detail. Out of these, 40 studies were excluded because they didn't primarily focus on monoclonal antibodies or small-molecule inhibitors associated with MRONJ and were selected for detailed analysis in our review.

(Types: RCTs, cohort studies, pharmacovigilance reports, consensus guidelines)

Epidemiology and Drug Associations

Denosumab, a human IgG2 monoclonal antibody that binds and inhibits receptor activator of nuclear factor kappa-B ligand (RANKL), exhibits potent antiresorptive effects without incorporating into the bone matrix. Studies in oncology patients report an MRONJ incidence ranging from 1.8% to 2.0%, particularly in those receiving high-dose regimens for skeletal-related events in metastatic bone disease. Importantly, unlike bisphosphonates, denosumab's pharmacological effects are reversible, and its shorter half-life has implications for treatment planning. Bevacizumab, an anti-VEGF monoclonal antibody used in solid tumors like breast and colorectal cancers, disrupts angiogenesis critical for bone and soft tissue repair. The incidence of MRONJ

is relatively lower (0.2-0.4%) when used as monotherapy, but this risk escalates considerably when bevacizumab is administered concomitantly with bisphosphonates or denosumab.

CDK4/6 Inhibitors Cyclin-dependent kinase inhibitors (CDK4/6 inhibitors) such as abemaciclib and palbociclib, used in hormone receptor-positive breast cancer, have been recently identified as significant contributors to MRONJ, particularly when used alongside denosumab [7,8]. Recent reports suggest an increased incidence of MRONJ in patients receiving CDK4/6 inhibitors concomitantly with denosumab, indicating possible additive toxicity on bone homeostasis [1, 4]. Tyrosine kinase inhibitors (TKIs) like sunitinib and sorafenib and mTOR inhibitors like everolimus exert antiangiogenic effects through VEGF pathway inhibition and have been associated with MRONJ, especially in polytherapy regimens. Although their individual contribution to MRONJ is less clearly defined, cumulative pharmacologic suppression of angiogenesis and bone remodeling potentiates risk. The major monoclonal antibodies and small-molecule inhibitors implicated in MRONJ, along with their mechanisms and associated risks, are summarized in Table 1.

Table 1: Drug classes implicated in MRONJ: pharmacologic classification, mechanism of action, and associated risk profiles.

Drug/Class	Drug Type	Mechanism of Action	MRONJ Risk/Association
Denosumab	Monoclonal antibody	Inhibits RANKL, suppressing osteoclast formation and bone resorption	High risk, especially in oncology patients receiving high-dose therapy (1.8–2%)
Bevacizumab	Monoclonal antibody	Inhibits VEGF-mediated angiogenesis and vascular repair	Low to moderate risk; risk increases with concurrent antiresorptive therapy
Sunitinib	Small-molecule inhibitor	Inhibits VEGF receptors and angiogenesis pathways	Moderate risk, particularly in combination therapy
Sorafenib	Small-molecule inhibitor	Inhibits RAF kinase and VEGF signaling pathways	Associated with impaired healing and increased MRONJ susceptibility
Everolimus	Small-molecule inhibitor	Inhibits mTOR pathway, affecting cell proliferation and angiogenesis	Moderate risk, especially with antiresorptive co-administration
Palbociclib	Small-molecule inhibitor	Inhibits cyclin-dependent kinases 4 and 6, altering bone homeostasis	Increasingly reported association with MRONJ when combined with denosumab
Abemaciclib	Small-molecule inhibitor	Suppresses CDK4/6-mediated cellular proliferation	Potential additive MRONJ risk with antiresorptive agents
Zoledronic acid	Antiresorptive agent	Inhibits osteoclast-mediated bone turnover by binding hydroxyapatite	Well-established high MRONJ risk, particularly intravenous use
Pamidronate	Antiresorptive agent	Suppresses bone resorption via osteoclast apoptosis	Moderate to high MRONJ risk with long-term use

PATHOPHYSIOLOGY AND RISK FACTORS

Medication-Related Osteonecrosis of the Jaw (MRONJ) is a complex condition with multiple contributing factors. At the core of its pathophysiology is the suppression of normal bone turnover, reduced blood supply, and the presence of local infection or trauma. A key element is the dysfunction of osteoclasts. Drugs like bisphosphonates and denosumab interfere with osteoclast activity; denosumab, for instance, blocks the RANKL pathway, thereby halting osteoclast development and function [3, 4].

Another significant factor is impaired angiogenesis; medications such as bevacizumab and tyrosine kinase inhibitors (TKIs) inhibit VEGF, which is essential for new blood vessel formation, thus hindering tissue healing. Moreover, microbial colonization, mostly by Actinomyces sp., is frequently seen in exposed necrotic bone, which further exaggerates the condition [9]. Inflammatory dental diseases like periodontitis, alongside physical trauma from tooth extractions or poorly fitting dental prostheses, can create vulnerable sites for MRONJ to develop [1, 10]. Genetic predispositions are also under investigation, with certain polymorphisms in genes related to bone metabolism and vascular regulation, such as RANK, VEGF, and cytochrome P450, potentially increasing susceptibility to MRONJ [11, 12]. Systemic factors, including the use of corticosteroids, poor oral hygiene, diabetes, smoking habits, and states of immunosuppression, further elevate the risk and severity of MRONJ in affected individuals [13, 5].

CLINICAL PRESENTATION AND DIAGNOSIS

Patients with MRONJ can present with a wide range of clinical features, from asymptomatic areas of exposed bone to more advanced disease with severe pain, swelling, purulent discharge, and even pathological fractures. Common findings include persistent exposed bone for over eight weeks, unexplained tooth mobility, surrounding erythema, sinus tract formation, or extraoral fistula. Radiographic features may show osteolysis, sclerosis, or sequestrum formation [14]. MRONJ is staged from 0 (non-specific symptoms) to Stage 3 (extensive necrosis with complications).

MANAGEMENT STRATEGIES

Conservative management can be done in initial stages (0-1) and is managed non-surgically with chlorhexidine rinses, systemic antibiotics (amoxicillin/clavulanate or clindamycin), and pain control. Periodic monitoring is essential to assess for disease progression [14]. needs to be done in stages 2 and 3 of MRONJ, which typically require active surgical management due to the severity of necrosis and associated complications. Surgical options include sequestrectomy and curettage, aimed at removing necrotic bone to control infection and stimulate healing. In more advanced cases, particularly those involving extensive necrosis or pathological fractures, segmental resection of the affected jaw may be necessary. Reconstruction following resection is often performed using local rotational flaps or, in complex cases, microvascular free tissue transfer to restore both form and function. Early surgical debridement may improve treatment outcomes compared to delayed intervention [4, 14].

Preventive measures remain the cornerstone in managing the risk of MRONJ, particularly in patients scheduled to begin antiresorptive or antiangiogenic therapy. A thorough dental evaluation and clearance should be performed before initiating treatment, which includes addressing existing dental issues and extracting non-restorable teeth to reduce future risk. Elective invasive dental procedures should ideally be avoided during the course of antiresorptive therapy to minimize trauma to the jawbone. Maintaining optimal oral hygiene and educating patients about the importance of regular dental check-ups and prompt reporting of any oral symptoms are crucial components of prevention. While the concept of implementing a "drug holiday," a temporary discontinuation of antiresorptive medication before invasive dental procedures, has been suggested, the role of drug holidays remains debated; some clinicians consider temporary discontinuation in selected cases despite limited evidence [15, 1].

DISCUSSION

Emerging research is focusing on predictive biomarkers such as serum CTX, genetic polymorphisms, and inflammatory markers for risk assessment [11, 16]. Regenerative therapies including platelet-rich fibrin (PRF), teriparatide, low-level laser therapy, and mesenchymal stem cell therapy have demonstrated promising preliminary outcomes in enhancing wound healing and reducing disease progression [17, 5, 2]. Compared to bisphosphonate-associated MRONJ, denosumab-related lesions may demonstrate earlier onset due to reversible inhibition of osteoclast activity. Antiangiogenic agents such as bevacizumab primarily impair vascularity and tissue repair, whereas tyrosine kinase inhibitors and CDK4/6 inhibitors appear to exert cumulative effects on bone remodeling and angiogenesis. Combination therapy involving antiresorptive and targeted agents has consistently demonstrated a higher MRONJ risk compared to monotherapy [3, 2, 13, 4, 8]. Validation through multicenter clinical trials remains necessary before these emerging modalities can be incorporated into routine clinical practice.

CONCLUSIONS

The spectrum of MRONJ has significantly broadened with the introduction of newer antiresorptive and targeted therapies. While denosumab remains one of the leading agents implicated in MRONJ, increasing evidence points to the contributory role of bevacizumab, TKIs, mTOR inhibitors, and CDK4/6 inhibitors. Clinicians must adopt a vigilant, multidisciplinary approach

balancing oncologic benefits with maxillofacial safety. Early diagnosis, individualized risk assessment, and collaboration across specialties are key to minimizing MRONJ-related morbidity and optimizing patient care. Timely diagnosis remains a cornerstone, especially since early symptoms are often vague or asymptomatic. When left undetected, lesions may progress to more severe stages involving bone exposure, infection, and even pathological fractures. Therefore, proactive risk mitigation, including dental assessments, treatment of oral infections, and avoidance of invasive procedures during therapy, is essential. Clinicians should also counsel patients about maintaining excellent oral hygiene and promptly reporting symptoms. The management of MRONJ increasingly requires multidisciplinary coordination, involving oncology, oral and maxillofacial surgery, and dentistry. With the development of new therapeutic strategies and ongoing clinical trials, it is crucial to maintain a balance between oncologic efficacy and the preservation of maxillofacial health.

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Conflicts of Interest
The authors declare that they have no conflict of interest.

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Not applicable.

Consent to Participate
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Consent for Publication
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Availability of Data and Materials
Not applicable.

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Not applicable.

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