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Implications in dental treatment during the use of antiresorptive drugs - a literature review

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Abstract:

Introduction: Antiresorptive drugs such as bisphosphonates and denosumab are crucial for treating osteoporosis, metastatic bone disease, and hypercalcemia by inhibiting osteoclast function. They can lead to medication-related osteonecrosis of the jaw (MRONJ) following invasive dental procedures, requiring careful management to mitigate potential adverse effects.

Purpose of work: Synthesis of knowledge about the impact of taking antiresorptive drugs on aspects of dental treatment.

Materials and methods: Materials used in this study were found in the PubMed and Google Scholar database, using the following key words “antiresorptives”, “bisphosphonates”, “dental treatment”, “osteonecrosis of the jaw”

Summary: Antiresorptive drugs like bisphosphonates and denosumab are essential for managing osteoporosis and other bone diseases but pose challenges in dental care, notably with

risks such as medication-related osteonecrosis of the jaw (MRONJ). These medications influence treatment strategies across orthodontics, implantology, periodontal therapy, and endodontics, necessitating careful management to balance therapeutic benefits with potential dental complications.

Key words: antiresorptives, bisphosphonates, osteonecrosis of the jaw, MRONJ,

Introduction

Antiresorptive drugs are commonly prescribed for various bone diseases (including osteoporosis, metastatic bone disease and hypercalcemia of malignancy) due to their proven high therapeutic efficacy. Commonly used antiresorptive drugs today include bisphosphonates and denosumab, while romosozumab has both antiresorptive and osteoanabolic properties. The primary action of these drugs involves the direct or indirect inhibition of osteoclasts, the cells responsible for bone remodeling (1). Bisphosphonates can be administered orally or intravenously, while denosumab is given by subcutaneous injection. Unlike bisphosphonates, which are not metabolized and have a strong affinity for bone with a very long half-life in the bone (months to years), denosumab is an antibody that is metabolized, not specifically stored in the bone, and has a short half-life (weeks) (2). Bisphosphonates have a structure similar to that of native pyrophosphate and are categorized into two groups: those containing nitrogen and those without. The nitrogen-containing bisphosphonates include alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid. The non-nitrogen-containing bisphosphonates are etidronate, clodronate, and tiludronate. All bisphosphonates work by inhibiting bone resorption through their attachment to hydroxyapatite binding sites on the bone, especially in regions of active resorption (3). When administered orally, bisphosphonates are approved for treating non-malignant bone conditions like osteoporosis and osteopenia. Intravenous administration of bisphosphonates has demonstrated effectiveness in managing and preventing metastatic bone disease, highlighting their role as important adjuvants in cancer treatment, particularly for breast and prostate cancers (4). Denosumab, a human monoclonal antibody similar to natural IgG2 immunoglobulin, has been noted for its antiresorptive activity, setting it apart from other antiresorptive medications (5). Denosumab functions by inhibiting the RANK ligand, a signaling molecule crucial for communication between osteoclasts and osteoblasts. This inhibition inactivates osteoclasts, thereby slowing bone resorption. (6) Recently,

denosumab has been used to treat osteoporosis, bone metastases, and malignant hypercalcemia. Unlike bisphosphonates (BF), denosumab does not accumulate in bones, and its effects on bone remodeling are reversible, lasting approximately six months. (1) Romosozumab is a monoclonal antibody that targets and inhibits sclerostin, which is a natural inhibitor of the Wnt signaling pathway. By blocking sclerostin, romosozumab activates the Wnt signaling pathway, resulting in enhanced bone formation and reduced bone resorption (7). It is administered monthly via subcutaneous injection (8). However, antiresorptive drugs also lead to adverse effects, such as medication-related osteonecrosis of the jaw (MRONJ). This condition is characterized by exposed necrotic bone and severe pain following invasive dental procedures, without any prior history of craniofacial radiation therapy (9).

Medication-related osteonecrosis of the jaw (MRONJ)

Osteonecrosis of the jaw (ONJ) is an uncommon yet serious condition that can impact both jaws, although it is more frequently seen in the mandible (10). The initial documented instances of patients experiencing non-healing necrosis in the maxillofacial region were described by Marx et al. in 2003. This condition was linked to the use of bisphosphonates in patients and was thus appropriately termed bisphosphonate-related osteonecrosis of the jaw (BRONJ) (11). Recently, researchers have identified additional medications that can cause osteonecrosis of the jaw (ONJ), including monoclonal antibodies and bone-targeting agents like denosumab (12). Due to these developments, the American Association of Oral and Maxillofacial Surgeons (AAOMS) specialist committee updated the nomenclature from bisphosphonate-related ONJ to medication-related ONJ (MRONJ) in a positional paper released in 2014 (13). MRONJ presents as one or more necrotic bone lesions, typically exposed in the oral cavity, that persist for a minimum of 8 weeks. For a diagnosis of MRONJ, the following criteria must be met:

- Previous or ongoing treatment with antiresorptive or antiangiogenic medications.
- Presence of exposed bone or a deep fistula that has persisted for more than eight weeks.
- No history of radiation therapy to the maxillofacial region (14).

MRONJ often arises following invasive dental procedures like tooth extractions, oral trauma, or infections, especially in the maxilla and mandible where bisphosphonates tend to accumulate. In this condition, even minor injuries can result in impaired repair of the jawbone tissue (15).

However, with increasing available information, it appears that MRONJ is likely multifactorial (16). Multiple hypotheses regarding the pathophysiology of MRONJ have been proposed (11):

- Bone remodeling inhibition. The excessive suppression of osteoclastic bone resorption by antiresorptive medications may contribute to the development of ONJ. Both bisphosphonates (BP) and denosumab are linked to ONJ, despite inhibiting bone turnover through different mechanisms, suggesting that excessive suppression of bone turnover is a significant factor (17). This suppression results in the accumulation of non-renewed, hypermineralized bone and a reduction in microvasculature, making the bone more susceptible to osteonecrosis following injury. The jaw's increased vulnerability to MRONJ is attributed to the higher remodeling rates of alveolar bone compared to the bones of the axial and appendicular skeleton, according to animal studies. Consequently, antiresorptives preferentially affect osteoclasts in the jaws, where turnover is higher. This preference is also observed at local sites with elevated turnover, such as extraction sites or areas with periodontal or periapical inflammation, which show increased accumulation of BPs in mouse studies. Preliminary clinical evidence indicates that teriparatide, a synthetic recombinant human parathyroid hormone, can improve MRONJ symptoms. Teriparatide indirectly stimulates osteoclasts to counteract the suppression caused by antiresorptive therapy, supporting the hypothesis of excessive bone remodeling suppression (18).
- Greater sensitivity of oral cell types, including osteoblasts, periodontal fibroblasts, and mesenchymal stem cells to bisphosphonates (17).
- Inflammation or infection. Even though tooth extraction is commonly cited as the main event leading to MRONJ, it's apparent that most extracted teeth already had underlying periodontal or periapical conditions (19). Infections and inflammation play a significant role in the development of ONJ and are considered major risk factors. The proinflammatory cytokine IL-36α is crucial in the incidence of MRONJ and is notably upregulated in infected periodontal tissue and gingival crevicular fluid. Additionally, there is evidence of crosstalk between IL-36α and TGF-β within these signaling pathways (20).
- Anti-angiogenesis. Bisphosphonates such as zoledronic acid have been found to directly impede angiogenesis both in vitro and in vivo, as evidenced by various studies. Animal models have shown reduced vascularity in MRONJ-affected sites, along with a decrease in microvessel numbers during the initial stages of bone healing (21). Furthermore, the natural process of angiogenesis observed during socket healing after tooth extraction is hindered by bisphosphonates. Both bisphosphonates and denosumab have been demonstrated to reduce arterial area, venous area, and overall vascularity of periodontal tissues during the early and late stages of MRONJ development (15).

- Genetic Factors. They moderately influence the occurrence of MRONJ. There is a link between the presence of one or more single nucleotide polymorphisms (SNPs) and the development of MRONJ. Many of these SNPs are found in genes related to bone turnover or specific metabolic bone diseases. Additionally, there may be germline sensitivity to bisphosphonates (BPs) (22).
- Affinity of anti-resorption drugs to the jawbones. Specifically, within the jaw, the alveolar crest undergoes a faster rate of remodeling compared to other bones, leading to the buildup of one of the highest concentrations of bisphosphonates. The alveolar bone also relies more on osteoclastic remodeling and renewal than any other bone in the adult skeleton (23). The mandibular and maxilla bones are thinly covered by a mucoperiosteal layer, providing limited protection against oral pathogens. Additionally, the jawbone is susceptible to repetitive microtraumas due to occlusion and chewing activities. This ongoing bone remodeling process enhances the accumulation of bisphosphonates, amplifying their effects. This intricate interplay among immunosuppression, recurrent microtraumas, and the unique anatomical characteristics of the jawbone highlights its particular susceptibility to bisphosphonate-related osteonecrosis (14).

The American Association of Oral and Maxillofacial Surgeons (AAOMS) has proposed a classification of MRONJ into four stages based on the severity of clinical features (24).

- Stage 0. Patients who do not exhibit clinical signs of necrotic bone but may have nonspecific symptoms like toothache, jaw discomfort, or sinus pain. They may also present with clinical indicators such as increased tooth mobility or the presence of a periapical fistula. Radiographically, these patients might show alveolar bone resorption, changes in the trabecular pattern, osteosclerosis, or thickening of the periodontal ligament (25).
- Stage 1. Patients with exposed and necrotic bone or fistulas that lead to bone exposure, who are asymptomatic and show no signs of infection (26).
- Stage 2. Patients present with exposed and necrotic bone or a fistula probing to bone, typically associated with pain and signs of infection (25).
- Stage 3. Patients with exposed and necrotic bone or a fistula probing to bone, who also experience pain and infection, and one or more of the following additional findings: necrotic bone exposure extending beyond the alveolar bone region, such as the inferior border and ramus of the mandible, maxillary sinus, or zygoma in the maxilla, pathologic fractures, extraoral fistulas, oral antral or oral nasal communication, osteolysis reaching the inferior border of the mandible or the sinus floor (20).

Radiological findings are crucial for determining the stage of MRONJ and guiding treatment decisions. Common radiological findings include osteolysis, mixed osteolysis and bone sclerosis, osteosclerosis, bone erosion, bone sequestrum, post-extraction phantom socket,

subperiosteal reaction, increased lamina dura thickness, narrowing of the mandibular canal, increased maxillary antrum density, and pathological fractures. Panoramic radiographs and Cone Beam Computed Tomography (CBCT) are useful for identifying these findings, with CBCT providing more precise, three-dimensional information compared to panoramic radiographs (27). In patients who are treated with antiresorptive medications and undergo tooth extraction, radiographic signs of chronic dental infection appear to predict the onset of MRONJ (28). The condition is more likely to develop in areas with furcation involvement, root remnants, or untreated dentinal or pulpal caries lesions. The bony changes induced by ARDs include the persistence of the alveolar socket and the lamina dura, a heterogeneous bone pattern, and the formation of sequestra. Additionally, sequestrum formation seems to be a pathognomonic feature of MRONJ, as it only occurs in MRONJ+ sites (29).

The American Society of Clinical Oncology recommends that all patients receive a dental examination and appropriate preventive dentistry before starting bone-modifying agent therapy and maintain optimal oral health throughout the treatment (27). For patients prescribed medications associated with MRONJ, stabilizing oral health promptly is crucial, ideally before beginning drug therapy. This process includes a comprehensive evaluation of the teeth and periodontium, along with a radiographic examination. Dentists should perform necessary procedures such as extracting non-viable teeth, scaling and root planing, dental restorations, and promoting good oral hygiene practices (26). Non-restorable teeth or those with a poor prognosis (e.g., exhibiting extensive periapical lesions or moderate-to-advanced periodontal disease) should be extracted, while salvageable teeth should undergo restorative procedures. Additionally, any oral infections should be managed appropriately, such as treating marginal periodontitis with systemic periodontal treatment and addressing apical periodontitis with root canal treatment. Wearing dentures increases the risk of MRONJ due to potential local trauma from the prosthetics. It's essential to regularly examine denture placement and promptly address any pressure points that may develop. Evidence suggests these measures can help prevent or reduce the risk of developing MRONJ (30). Additionally, a key objective of primary prevention is to provide appropriate counseling. Patients should be informed about the risk of MRONJ and made aware of its potential clinical signs, which facilitates early diagnosis (31). After starting bisphosphonate therapy, patients should have check-ups every six months to monitor their oral health and promote good oral hygiene (32). Tooth extractions in patients undergoing denosumab or bisphosphonate treatment, particularly in oncological contexts, should be conducted with antibiotic prophylaxis (e.g., amoxicillin/clavulanic acid).

Additionally, the procedure should involve smoothing of sharp bony edges, wound closure, and subsequent monitoring until full mucosal healing is attained (33). Nevertheless, it is recommended that patients on high doses of AR agents should avoid tooth extractions when possible. If a tooth extraction is unavoidable, a temporary suspension of AR treatment, known as a 'drug holiday,' is suggested or considered. In some countries, national guidelines or position papers, which are based on expert opinions, recommend a drug holiday. However, there is no international agreement on the practice of high-dose AR drug holidays (34). According to a certain meta-analysis conducted, the group of patients taking a drug holiday did not significantly differ from the group of patients without a drug holiday in terms of the development of MRONJ following a tooth extraction procedure (35).

The management of MRONJ, whether through conservative or surgical means, remains a topic of debate (27). It is recommended that treatment decisions be made by a multiprofessional team, taking into account the staging of MRONJ, the patient's overall medical health, and the cancer prognosis. Generally, two main approaches are considered: medical and surgical treatments. However, there is ongoing controversy in the literature regarding the optimal approach. Medical treatment, a more conservative strategy, involves minor local debridement of exposed necrotic bone, smoothing sharp bone edges, and managing infections with antibiotics and topical antibacterial rinses. Some experts suggest using a combination of pentoxifylline and tocopherol (vitamin E), similar to treatments for osteoradionecrosis. For patients who cannot use pentoxifylline, cilostazol can be an alternative (26). In cases of active infection, it is common for patients with ONJ to be prescribed long-term antibiotics. Conservative therapy is also valuable for patients who are not candidates for surgery (36). However, clinical and radiographic improvements with medical treatment may take months or even years to manifest (26). Surgical intervention is advised when conservative treatment fails or the disease progresses further (e.g., mucosal irritation from exposed bone or symptoms from involvement of the inferior alveolar nerve or maxillary sinus). The goal of treatment is to slow disease progression; however, the criteria for initiating surgical treatment are not fully defined (37). Recent research suggests that surgical intervention significantly improves the healing rate in MRONJ patients compared to conservative therapy. Moreover, outcomes are more favorable in patients undergoing major surgery versus minimal surgery. These findings are supported by previous studies, albeit many of them focused on mandibular cases. Given the anatomical and histological disparities between the maxilla and mandible, they may impact MRONJ dynamics and treatment. Thus, this study focuses on analyzing surgical cases in the maxilla. Multivariate

analysis revealed that postoperative residual necrotic bone serves as a poor prognostic indicator for surgical treatment of maxillary MRONJ. The intricate anatomy of the maxilla poses challenges to maxillary bone surgery, particularly due to its unique characteristics. Infections in the maxillary alveolar region can readily extend into the maxillary sinus due to the sparse and thin bone separating these structures. In surgical interventions for maxillary MRONJ, the authors made efforts to conserve the mucous membrane of the maxillary sinus to the greatest extent possible (38).

Influence of antiresorptive drugs in periodontal therapy

A histomorphometrical analysis in rats found no morphological effects of different antiresorptive and antiangiogenic medications on periodontal and oral tissue structures. However, inflammatory cell infiltrates were more frequently observed in animals administered these medications or their combinations. Clinically, this suggests that such medications may induce inflammatory reactions in periodontal tissues (39). The extent of periodontal disease as a co-morbidity in cases of osteonecrosis of the jaw is unclear. While periodontal disease is frequently reported in MRONJ cases, other studies indicate that residual alveolar bone levels are similar in individuals with and without MRONJ. Additionally, periodontal disease has been observed as a precipitant of MRONJ in a significant number of cases. The presence of periodontal disease may require invasive periodontal procedures or dental extractions, thereby increasing the risk of MRONJ (32).

Influence of antiresorptive drugs in endodontic therapy

Non-surgical endodontic treatment is recommended over extraction to reduce the risk of bisphosphonate-related osteonecrosis of the jaw (ONJ) (4). This treatment aims to manage infection and prevent its spread to periapical tissues. However, precautions are advised during the procedure to avoid soft tissue damage, especially when placing rubber dam clamps, as they may potentially trigger ONJ (32). Actinomyces species are commonly found in infections and have been identified in microbial compositions of peripheral lesions resistant to endodontic treatment. Despite adherence to guidelines, debris extrusion beyond the apical foramen is unavoidable during nonsurgical endodontic treatment. Therefore, the question remains unanswered in the literature regarding the necessity of antibiotic prophylaxis during nonsurgical endodontic treatment for necrotic teeth in patients currently or previously treated with bisphosphonates (40).

Influence of antiresorptive drugs in implantology

As dental implant procedures become increasingly common, various dental associations have issued guidelines to help dentists manage patients who are on antiresorptive drugs. The European Federation of Periodontology (EFP) advises against placing implants in individuals who are taking bisphosphonates or denosumab because of the increased risk of medication-related osteonecrosis of the jaw (MRONJ). On the other hand, the American Dental Association (ADA) recommends that patients with nonmalignant diseases who are undergoing antiresorptive therapy can proceed with dental implants, provided that careful consideration is given to factors such as the drug regimen and the duration of therapy. However, for patients with malignant diseases, dental implants are contraindicated during antiresorptive therapy (41). The safety of dental implantology in patients taking antiresorptive medications is critically important, as dental implants can significantly enhance the quality of life for these patients, much like they do for those not on such therapy. However, the risk of medication-related osteonecrosis of the jaw (MRONJ) poses a serious concern due to its severe negative impact on patients' quality of life. Dentures are an alternative to dental implants, but they also carry risks; for instance, pressure sores from dentures can potentially trigger the development of MRONJ (42). Peri-implantitis may serve as a trigger for MRONJ, even in cases where the implant is already osseointegrated. The presence of peri-implantitis, characterized by inflammation and bone loss around the implant, can create a favorable environment for the development of MRONJ (43).

Influence of antiresorptive drugs in orthodontic therapy

There is a general consensus in the literature that orthodontic tooth movement is reduced following bisphosphonate administration, which supports its clinical use in enhancing anchorage (44). In patients receiving orthodontic treatment, alveolar bone metabolism significantly influences the dynamics of orthodontic movements. Low bone turnover can result in slower tooth movements under applied orthodontic force, with crown tipping being more predominant compared to axial displacement (bodily movement). Furthermore, closing post-extraction spaces can be challenging under these conditions. Animal studies have demonstrated that bisphosphonates can inhibit root resorption during orthodontic treatment, enhance

anchorage when administered locally, and reduce the risk of microimplant disintegration (45). Caution is recommended regarding invasive diode laser therapy, the use of miniscrew skeletal anchorage devices, potential mucosal trauma from retainers, orthognathic surgery, and tooth extraction procedures (32).

Summary

Medication-related osteonecrosis of the jaw (MRONJ) presents a significant challenge in dental practice, initially associated with bisphosphonates and now recognized with other medications like denosumab. This condition, characterized by exposed necrotic bone lasting more than eight weeks, primarily follows dental procedures in patients undergoing antiresorptive therapy. Management approaches range from conservative measures to surgical interventions, with ongoing research focusing on optimal treatment strategies and the underlying pathophysiology. Emphasis is placed on preventive dental care and careful management during dental procedures to minimize the risk of MRONJ and ensure optimal oral health outcomes for affected patients. Beyond MRONJ, these medications impact various aspects of dental care, influencing treatment planning in orthodontics, implantology, periodontal therapy, and endodontics. Understanding these implications is crucial for dental professionals to optimize patient care, balancing the therapeutic benefits of antiresorptive drugs with the management of associated dental risks.

Author's contribution

Conceptualization, Aleksandra Dziewulska; methodology, Aleksandra Dziewulska, Laura Pacek; software, Weronika Kiełt; check, Barbara Wajdowicz, Aleksandra Kudła; formal analysis, Klaudia Kowalska, Rozalia Czapiewska; investigation, Aleksandra Wróbel, Gabriela Broniec; resources, Julia Kozłowska; data curation, Weronika Kiełt; writing - rough preparation, Aleksandra Dziewulska; writing - review and editing, Laura Pacek, Barbara Wajdowicz; visualization, Julia Kozłowska, Gabriela Broniec; supervision, Rozalia Czapiewska; project administration, Klaudia Kowalska; receiving funding, Aleksandra Kudła, Aleksandra Wróbel; All authors have read and agreed with the published version of the manuscript .

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