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Review

Medication-Related Osteonecrosis of the Jaw—A Continuing Issue

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Abstract: Introduction: Medication-related osteonecrosis of the jaw (MRONJ) is a condition that is becoming more common in the everyday practice of both dental and maxillofacial surgeons. Materials and methods: This paper aims to provide a comprehensive and easy to read by clinicians presentation of comprehensive, accessible, and up-to-date data on MRONJ. The individual chapters focus on the etiology, epidemiology, diagnosis, prevention, treatment, and recurrence of MRONJ. Results and discussion: It has been observed over the years that among drugs that increase the risk of the disease, apart from bisphosphonates, angiogenesis inhibitors and anti-RANKL monoclonal antibodies should also be included. A thorough physical and subjective examination, periodic correction of dental prostheses, and an adequate preparation for even the simplest of procedures in the oral cavity area can prevent or minimize the risk of MRONJ. Conclusions: It is extremely difficult to treat once it occurs and oftentimes is a recurring problem that leads to a multitude of symptoms that gradually decrease the quality of a patient's life.

Keywords: osteonecrosis; bisphosphonates; angiogenesis inhibitors; MRONJ; BRONJ

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1. Introduction

The diagnosis of medication-related osteonecrosis of the jaw (MRONJ) requires the simultaneous existence of three conditions: (1) history of treatment with anti-resorptive or anti-angiogenic agents; (2) at least 2 months exposure of the facial bones directly or in the form of a fistula; (3) exclusion of radiation or metastatic etiology of the above described exposure [1,2]. MRONJ is a condition that is becoming more common in the everyday practice of both dental and maxillofacial surgeons. The reason behind this is an increasing number of chronically ill patients treated with anti-resorptive drugs [1]. The very first case of postsurgical osteonecrosis in the oral cavity area was described in 2003 by Marx [1]. It had been linked to the intake of anti-resorptive drugs—bisphosphonates: pamidronic and zoledronic acids. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) has been recognized as a result. It has been observed over the years that among the drugs that increase the risk of jaw osteonecrosis, apart from bisphosphonates, angiogenesis inhibitors and anti-RANKL monoclonal antibodies should also be included [2]. In 2014, The American Association of Oral and Maxillofacial Surgeons (AAOMS) recommended that the term medication-related osteonecrosis of the jaw (MRONJ) should be introduced [2].

2. Materials and Methods

We conducted the literature search using two scientific browsers—Google Scholar and PubMed—using the keywords: bisphosphonates, BRONJ, MRONJ and the exact

phrases: angiogenesis inhibitors, anti-RANKL monoclonal antibodies, medication-related osteonecrosis of the jaw. The selected literature, with a few exceptions (definition and mechanisms) covered the years from 2010 to 2021. At the time of the search, the most relevant (both in terms of number of citations as well as etiology, epidemiology, diagnostics, treatment strategy, and recurrence) publications available were selected and discussed in this manuscript.

3. Results and Discussion

3.1. Etiology

Bisphosphonates (BP) play a significant role in the treatment of diseases that result in osteoclastic bone loss. The aforementioned group of medicines is most commonly used for treating osteoporosis, innate bone fragility, osteopenia, and bone metastases [2]. Bisphosphonates decrease the metabolic rate of the bone and as a result its resorption rate is also reduced. This group of medicines inhibit vascular calcification and osteoclast-dependent bone resorption [3]. The retention period of these drugs in the bone tissue is very long, for example the biological half-life of alendronic acid is approx. 10–15 years [4]. Other examples of BPs are: zoledronate, etidronate, and clodronate [3]. The meta-analysis of Cochrane data from 2012 shows that BP treatment in patients suffering from breast cancer with bone metastases resulted in: decreasing the risk of SRE (skeletal-related events) by 15%, extending the time in between episodes of pain, which had a positive influence on the overall quality of a patient's life [5].

In addition to bisphosphonates, there are numerous other drugs that are etiological agents of MRONJ. Among them, there are angiogenesis inhibitors, tyrosine kinase inhibitors, and immunosuppressants, e.g., tocilizumab. In addition, intake of monoclonal antibodies, radiopharmaceuticals, mammalian target of rapamycin inhibitors, or selective estrogen receptor modulators can lead to MRONJ [6]. The angiogenesis inhibitors either block the vascular growth factor receptor (bevacizumab) or connect with the tyrosine kinase receptor (sunitinib, sorafenib), impairing the rebuilding and healing process of the bone tissue. They are applicable in cancer treatment through angiogenesis inhibition that limits the cancerous tumor growth. The RANK ligand inhibitor—denosumab, decreases the bone tissue resorption by inhibiting the growth and activity of the osteoclasts. It is used in treatment of osteoporosis and bone metastases [7]. The results of a 10 year observation of patients treated with denosumab as well as previously treated with BP, have proven denosumab to be more effective in comparison with BP (alendronate acid, risedronate, zoledronate) [7].

According to AAOMS the criteria for MRONJ are: no previous radiotherapy, no metastases to the jaw bones, current or previous treatment with angiogenesis inhibitors, bone exposure or intra-/extraoral fistula persisting for over 8 weeks [2]. MRONJ should be differentiated from periodontal and periapical diseases, chronic osteitis and diseases of the paranasal sinuses. The risk factors for MRONJ occurrence can be divided into three groups. The first group consists of drug-related agents—the nature of the drug and its dose, therapy length, and route of administration. The second group contains traumatizing local agents such as: ill-fitting prostheses, atypical anatomical conditions, and local inflammation. The last group of risk factors are systemic diseases and comorbidities such as: diabetes, hypercalcemia, genetic factors, erythropoietic disorders, osteomalacia, and chronic steroid therapy [8].

MRONJ origins are not entirely understood. There are a few hypotheses that could explain its location that is exclusive in jaw bones. The most probable causes that should be included are: the presence of microtrauma, the toxicity of BP in the soft tissue, various infections, specific oral cavity biofilm, high bone turnover, terminal mandibular vascularization, the possibility of bone exposure during dental procedures, and lesions dependent on the type of medication used (resorption and remodeling of the bone and angiogenesis inhibition) [9].

3.2. Epidemiology

Early MRONJ symptoms include: redness of the mucosa, pain, ulceration, and bone exposure within the lesion area [10]. Purulent leakage and loosening of the teeth are observed in more advanced stages of the illness. The mandible is the most common location for the lesions in 2/3 of the patients [11]. The second most frequent localization of medication-related osteonecrosis is within the alveolar processes of the maxillae, which accounts for about 1/3 of the cases [11]. Sporadically, necrotic lesions caused by pharmacotherapy can also occur in the hard palate [11]. Tooth extraction causes MRONJ in approx. 60% to 73% of patients, however cases of spontaneous (not related to tooth extraction) onset of the disease are also described in the literature [12,13]. Van Cann et al. calculated that the incident of MRONJ in the group of patients treated with anti-resorptive agents during the first year of therapy is about 1%, and in the case of combined therapy with an anti-angiogenic agent this percentage increases 6-fold [13]. MRONJ frequency is the highest among oncological patients (between 1 and 15%) where high doses of these drugs are used in regular time intervals [14]. The frequency of MRONJ occurrence amongst osteoporotic patients is estimated to be around 0.001–0.01%, which is only slightly higher than its frequency in overall population (<0.001%) [14]. Oncological patients are at 10 times the risk of MRONJ occurrence in comparison with the patients that undergo anti-resorptive treatment due to osteoporosis [15].

3.3. Diagnostics

The MRONJ diagnostic process, according to the AAOMS guidelines, is based on medical history, clinical examination, and imaging tests [2]. A typical symptom of MRONJ is pain, the odontogenic etiology of which should be excluded, and which may radiate to the temporomandibular joint and maxillary sinus [2]. Neurosensory sensations other than pain are also possible [2]. One of the prodromal factors of MRONJ may be chin numbness, which must be differentiated from malignant changes each time [16]. In a clinical examination, one of the symptoms is loosening of the teeth, for which periodontitis should be excluded [2]. Moreover, the presence of exposed bone or fistulas is a significant clinical symptom in determining the severity of MRONJ [2,10]. The latter should be differentiated from fistulas resulting from pulp necrosis [2].

Orthopantomogram (OPG) is a common type of examination used in diagnosing MRONJ. Taking an OPG radiogram allows for making an initial diagnosis and serves as a helpful tool in monitoring the progress of the disease and the therapeutic process. In questionable cases, referring the patient to three dimensional imaging diagnostics (i.e., a conventional computed tomography [CT] as well as cone beam computed tomography [CBCT]) is the gold standard in MRONJ diagnosis [17,18]. Those examinations enable more accurate bone density assessments in the area affected by necrotic lesions and allow for more precise determination of its extent and presence of possible pathological fractures. These factors are crucial for qualifying for potential surgery and planning its scope [17].

3.4. Prophylaxis

In recent years, the attempts to evaluate the validity of determining the marker levels of bone turnover in the serum before any surgical intervention in patients treated with anti-resorptive drugs have been made to predict the risk of medication-related osteonecrosis in the postoperative period. The indicators that are marked include: s-CTX (C-terminal cross-linked telopeptide of the alpha chain type I collagen), s-OC (osteoclacin), s-PTH (parathormone), and s-BAP (bone isoform of the alkaline phosphatase) [19,20]. The results of conducted research are pointing to differences in s-CTX, s-OC, s-PTH, and s-BAP levels in patients undergoing anti-resorptive treatment in comparison with the control group [19,20]. Due to insufficient data from small study groups, there is no hard evidence that would justify a routine marking of those indicators in patients that are at a risk of developing MRONJ [19,20].

A research of Salgueiro et al. shows that even a 5 month break from intravenous BP therapy is not effective in osteonecrosis prevention [20]. Other studies show statistically significant differences in the incidence of MRONJ as a result of implementing the so-called "drug holiday," although anti-resorption therapy may not always be discontinued [21]. On the basis of animal studies, Otto et al. demonstrated the validity of local management (bone plasty and wound closure), antibiotic therapy, and the implementation of a break in the use of bisphosphonate (i.e., zoledronic acid) [21].

Patients that belong to the MRONJ risk group are absolutely required to maintain proper oral hygiene as well as systematically visit the dental office for regular hygienization [21,22]. Dental checkups should be completed every 3 to 4 months [21]. All conservative or endodontic dental procedures should be carried out in accordance with a standard protocol and should not be postponed in order to avoid any surgical intervention [21,22]. Prosthetic and orthodontic treatment, if properly performed, is classified as low risk for MRONJ occurrence [23]. The implantoprosthetic treatment, on the other hand, has been proven to increase the risk of MRONJ both before and during the anti-resorptive therapy [24].

When a surgical intervention is required in the oral cavity area it ought to be minimally invasive. According to some authors, teeth extractions should be singular and atraumatic, others believe that multiple extractions completed under antibiotic prophylaxis and completed with a tight flap plastic surgery are completely safe [25]. A mucoperiosteal flap should be created when needed and its base should be as wide as possible for maintaining sufficient blood supply [25]. In each case of mucous membrane disruption, the wound requires closure with surgical sutures avoiding tissue overtension [25]. One week prior to the scheduled surgical procedure the patient should implement 0.12% chlorhexidine (CHX) mouth rinsing three times per day and continue with it until the wound is completely healed [25].

The recommendations of the Polish Dental Association and National Programme to Protect Antibiotics Working Group (PDA/NPPAWG) concerning the use of antibiotics in dentistry from 2019 suggest routine antibiotic prophylaxis in patients treated with bisphosphonates, denosumab, or bevacizumab before all surgical procedures on the jaw bones (teeth extraction, surgery performed on the alveolar process, endodontic or periodontal surgery), which is in line with other guidelines [25–27]. The antibiotic prophylaxis, according to PDA/NPPAWG protocol, should be implemented one day prior to the procedure and continued for 3 days postsurgery (the so-called short term prophylaxis); in cases of coexisting risk factors for osteonecrosis in the jaw bones, it is advised to prolong the antibiotic therapy up to 14 days (long term prophylaxis) [26]. Detailed risk factors include taking the zoledronic acid orally, bisphosphonates intravenously, using this medication for at least 3 years, and having a history of inflammation or osteonecrosis [26]. The recommended antibiotics are amoxicillin with clavulanic acid 875 mg + 125 mg in 12 h intervals and in case of a penicillin allergy the antibiotic of choice should be clindamycin: 300 mg every 8 h [26]. For healing evaluation purposes, frequent control visits are recommended—two to three times a week [26].

AAOMS proposed a staging system helpful in preoperative evaluation of MRONJ which highlights the progress of the disease as follows [2]:

- Stage 0—no evident clinical signs of osteonecrosis, the symptoms are nonspecific, radiographic changes are present. Recommended treatment focuses on comorbidities, incorporating analgesics and antibiotics.
- Stage 1—exposed and necrotic bone, fistulas that penetrate the bone, the patient is asymptomatic and there are no signs of infection. Treatment should include antibacterial rinses (0.12% CHX), quarterly checkups, and determining possible indications for further bisphosphonate therapy.
- Stage 2—exposed and necrotic bone, fistulas that penetrate the bone, the infection is present, pain and erythema in the exposed bone area with or without purulent

contents. In this stage symptomatic antibiotic therapy, antibacterial rinses, pain control, and wound dressing is applied.

- Stage 3—exposed and necrotic bone, fistulas that penetrate the bone and one of the following symptoms: exposed and necrotic bone that spreads beyond the alveolar part of the maxilla and mandible resulting in pathological fractures, extraoral fistulas, oronasal fistula, and osteolysis in maxillary sinus. The treatment of this stage includes: surgical dressing of the wound and resection procedures, antibacterial rinses, antibiotic therapy, and pain relief [2,27].

3.5. Treatment

It is assumed that conservative treatment and minor surgical procedures can be performed in outpatient mode [2]. A special case of MRONJ in the vicinity of dental implants is highlighted as an indication for a surgical procedure that can be performed with local anesthesia [28]. The treatment of the aforementioned peri-implant MRONJ consists of implant removal, sequestrectomy, and soft tissue cleanup which leads to a complete recovery in 87% of patients (100% if MRONJ occurred only in the maxillary area) [28,29]. Nevertheless, patients at a stage so advanced that they require both the resection surgery and later reconstructive procedures need to be referred to a hospital ward [2]. Some authors indicate that the treatment of MRONJ stage III using extensive resectional procedures in conjunction with microvascular flap reconstruction has shown very positive results [30–35]. The invasive approach with microvascular flap reconstruction has been proven to be successful, with the mucous membrane healing index reaching 97%, however, the possibility of performing free flap surgery depends on the general condition of the patient [36,37]. However, it should be taken into consideration that such extensive surgical procedures can be followed by serious possible complications. Mücke et al. point out that as many as 25% of all patients who underwent such procedures suffered from difficulty in postoperative wound healing [38]. Authors who favor the invasive surgical treatment with microvascular flap reconstruction employ both the soft-tissue (anterolateral thigh flap and the radial forearm flap) [38] as well as bone-component flaps (deep circumflexing iliac artery flap, fibular free flap, and scapular free flap) [39,40]. Those authors, however, do not indicate in what types of clinical situations each flap should be used. They also do not specify what the different success rates are between cases concerning soft-tissue only and those that apply to both soft and hard tissue defects [41].

Choukorun et al. have introduced an autogenic leukocyte- and platelet-rich fibrin L-PRF that has been widely used in regenerative dentistry [42]. According to the literature, when used for wound closure after surgical procedures in MRONJ patients, it shows good results, especially in conjunction with bone morphogenetic protein 2 (BMP-2) [43]. This is an autogenous material that releases growth factors in extensive time periods and at the same time accelerates the healing processes in soft tissue as well as in the bone [10,43]. Moreover, it supports hemostasis and reduces postoperative swelling and pain [43]. Fibrin concentrate stimulates the activation of mesenchymal stem cells, which drastically intensifies angiogenesis and tissue regeneration [43]. Some scientists observe a very high effectiveness of this therapy even in individuals that have been treated with intravenous bisphosphonates [44,45]. Controlled studies of leukocyte-platelet rich fibrin (LPRF) have shown 60–100% success rates [36,44]. However, a systematic review of studies on the use of autologous platelet concentrates did not give unequivocal results on the effectiveness of this type of therapy [45]. Thus, Fortunato et al. believe that there is currently insufficient evidence for the effectiveness of the use of platelet concentrates in the prevention and treatment of MRONJ, although they do not exclude that further studies will show such effectiveness [45]. Fluorescence-guided surgery can be helpful in determining resection margins; however, it has not been shown to improve the quality of life of patients who have had it used in place of conventional surgical techniques. [46].

Some of the proposed MRONJ prophylaxis and therapy methods are still in the research phase. The role of hyperbaric oxygen therapy is still unclear but some benefits

coming from implementation of this treatment have been described in patients that did not respond to standard procedures [47]. Yalcin-Ulker conducted research showing that periprocedural administration of pentoxifylline both pre- and posttreatment has a positive impact in regards to the healing process of a postextraction wound in MRONJ patients [48]. Such treatment is beneficial to the bone tissue healing process and inflammatory reaction reduction [48]. It has been proven that bisphosphonate intake is linked to the increase in the vascular endothelial growth factor (VEGF) which leads to healing impairment [48]. Pentoxifylline is a powerful vasodilator that is able to reduce VEGF levels in the bones reversing the effect previously induced by bisphosphonates [48]. Bedogni et al. presented research concerning a link between vitamin D3 deficiency and a higher risk of MRONJ in oncological patients that are currently in the active stage of the disease [49]. According to Bedogini et al., vitamin D3 deficiency is not an MRONJ risk factor [49]. Other research on vitamin D has shown that this secosteroid can play a potentially significant role in various etiological paths of MRONJ [50,51]. There are a number of comorbid diseases that correlate between MRONJ occurrence and deficit of this vitamin [50].

The recurrence rate of MRONJ is high, however, it can be reduced with proper procedures [52–55]. According to an analysis made in eight Japanese units in the years 2006–2016, in 361 patients that were observed for approximately 15 months each, a complete recovery was obtained in 25.2% of patients that underwent conservative treatment. On the other hand, 76.7% of patients who had surgical treatment experienced a complete recovery [56]. Jakiel et al. carried out a study on 49 patients that required surgical treatment in the oral cavity area both before and during BP and denosumab therapy [57]. In the course of the described study, there were no signs of MRONJ during a 2 year observation period [57]. Proper healing of the soft tissue and absence of pain were noted by Jakiel et al. [57]. Despite growing knowledge about the risk of MRONJ occurrence and ability to properly treat patients, it is still a highly relapsing disease, and according to various studies, it can affect 11.8% to 45% of the risk group patients [58].

4. Conclusions

MRONJ is a disease that is more and more commonly diagnosed. It significantly decreases the patient's quality of life, therefore, it is crucial for the clinicians to better understand the risk factors in order to be able to predict both anti-resorptive as well as anti-angiogenic therapy results. The importance of raising awareness among medical practitioners and constant updates of knowledge on that matter are invaluable. Each year, new articles are being published that touch on the subject of etiology, diagnostics, prophylaxis, and treatment of MRONJ, which when combined with quick development of comprehensive knowledge allow for improving the prevention and treatment of this condition.

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