Immune Dysfunction in Medication-Related Osteonecrosis of the Jaw

Subjects: Dentistry, Oral Surgery & Medicine

Contributor: Ilaria Roato, Rodolfo Mauceri, Vincenzo Notaro, Tullio Genova, Vittorio Fusco, Federico Mussano

The pathogenesis of medication-related osteonecrosis of the jaw (MRONJ) is multifactorial and there is a substantial consensus on the role of antiresorptive drugs (ARDs), including bisphosphonates (BPs) and denosumab (Dmab), as one of the main determinants. The time exposure, cumulative dose and administration intensity of these drugs are critical parameters to be considered in the treatment of patients, as cancer patients show the highest incidence of MRONJ. BPs and Dmab have distinct mechanisms of action on bone, but they also exert different effects on immune subsets which interact with bone cells, thus contributing to the onset of MRONJ.

Keywords: medication-related osteonecrosis of the jaw ; osteoclast ; osteoblast

1. Introduction

Osteonecrosis of the jaw (ONJ) is a multifaceted disease that has been known since 2003 in patients exposed to BPs (bisphosphonate-related ONJ (BRONJ)), but was renamed medication-related ONJ (MRONJ) [1] after the observation of cases due to the receptor activator of the nuclear factor κB ligand (RANKL) antibody, denosumab (Dmab), and other drugs [2][3][4]. Indeed, due to the continuous evolution in cancer treatment, MRONJ has been associated in smaller measure to antiangiogenic and cyclin inhibitor drugs [2][5].

To date, there is still open discussion about the definition, diagnosis, staging and treatment strategy of MRONJ [5][6][7][8][9][10]. The pathogenesis of MRONJ appears multifactorial [11]. MRONJ has the peculiarity of occurring in the jaw (often, albeit not exclusively, at a tooth extraction site), but not in other bones. A possible reason is the strong mechanical stimulation to which jaws are subjected that leads to a high bone turnover rate, which is approximately 3- to 6-times faster than those observed in long bones of beagle dogs [12][13].

There is a substantial consensus on the important role of antiresorptive drugs (ARDs), such as BPs and Dmab, in the pathogenesis of MRONJ [1][4][14]. With regard to zoledronic acid (Zol), which is an amino-bisphosphonate (N-BP), and denosumab (Dmab), time exposure, cumulative dose and administration intensity are all parameters that increase MRONJ risk. Of course, MRONJ reduces the quality of life of the affected patients [15]; thus, measures aimed to reduce the disease risk that contribute to patients' oral health have been adopted by clinicians.

The coexistence of more factors increases the risk for MRONJ, which is higher for oncologic than osteoporotic patients likely due to the higher and more frequent doses of ARDs that can lead to an intense suppression of bone turnover [16]. One of the main causes of MRONJ is represented by the inhibition of osteoclast (OC) and osteoblast (OB) activity due to the ARDs, which causes suppressed bone turnover with compromised bone healing [17]. Microcirculation dysfunctions with angiogenesis inhibition [18], mucosal damage secondary to toxic exposure of the bone, bacterial infection and immune dysfunction all come together to lead to MRONJ [17][19].

2. An Immunosuppressed Milieu Favors ONJ Induced by ARDs

Both N-BPs and Dmab cause an immune dysfunction in MRONJ patients [20][21][22] by hindering their capability to respond properly to immunological stress independently of the oral microbiome [23]. It is also noteworthy that a large number of patients that develop MRONJ have other disease conditions or partake in many pharmacological treatments (chemotherapy, steroids, antiviral drugs, etc.), which may contribute to their immune system impairment [23][24].

The role of immune responses and inflammation in the onset and/or progression of MRONJ has been recently reported since a massive infiltration of lymphocytes mixed with inflammatory cells within tissue affected by MRONJ has been documented [25]. Moreover, it has been found that N-BPs increased the production of acute general inflammatory

mediators in vitro [26] and in vivo [27], modifying the immune cell subset of patients [28][29], but they did not change inflammatory bone markers. Tooth extraction is comparable, for some aspects, to a bone fracture, where inflammation and fracture healing are parallel processes, because both need a focus and a resolution. Initially, at the damage site, the T-cell subset releases cytokines, such as IL-17, which directly support the proliferation and differentiation of local mesenchymal stem cells into OBs. Later, another specific subgroup of T cells blocks the secretion of pro-inflammatory factors to allow for lesion healing. In pathological conditions, the over production of IL-17 elicits an opposite effect on OBs by inhibiting their differentiation and activity, and by promoting OC bone resorption [30][31]. Thus, the correct cross-talk among immune cells and bone cells is fundamental to avoid both bone and immune alterations [32]. In mice treated with Zol, tooth extraction increases inflammatory cytokine levels and osteocyte apoptosis in the extraction site, promoting osteonecrosis [33]. These data confirm other previously published data, showing that the serum level of inflammatory cytokines was increased in MRONJ patients and that the administration of anti-inflammatory cytokines, such as antitumor necrosis factor-α (TNFα) and anti-interleukin 6 (IL-6), were effective in preventing a cytokine storm induced by N-BPs [33]. Recently, it has been reported in a murine model that the administration of either anti-inflammatory or antibiotic drugs significantly blocked Zol-induced osteonecrosis following tooth extraction [34], suggesting that this type of treatment should be considered to prevent MRONJ onset.

3. Bacterial Infections as Both Cause and Consequence of Immune Dysfunction in MRONJ

The role of commensal oral microbiota and bacterial infections, either associated or not to tissue damage induced by invasive dental procedures, in MRONJ is debated [35]. It is noteworthy that the jawbone is the peculiarly susceptible to infections compared to other bones, which are not as easily exposed to microorganisms as they occur in the oral cavity. Breaching the mucosal barrier during or after antiresorptive treatment may cause infection and hinder the healing process, thus leading to bone necrosis [36][37]. The most common surgical procedure associated with the onset of osteonecrosis is tooth extraction [6]. After N-BP treatment, bacteria are known to stimulate bone resorption [38][39]. A growing number of scientific papers have suggested the possible role of Actinomyces species [40][41], which are ubiquitous Gram-positive, non-spore-forming bacteria, that were found in more than 80% of bone samples from MRONJ patients in two retrospective studies [37][42]. Bacterial microfilms that are detectable in N-BP-related sites of osteonecrosis may stimulate OC activity on the bone surface, supporting the concept that microorganisms may directly contribute to bone necrosis [43][44].

Several studies highlighted oral cavity infection as a major event that stimulates a chronic inflammatory immune response, with the increase in cytokines leading to the upregulation of β-defensin 3 [45]. Defensins are antimicrobial peptides (AMPs) that are important in the innate immunity response against microbial pathogens [46], and they exert a protective action on oral cavity integrity against the invasion by microbes [47]. In the animal model, it has been reported that infectious osteomyelitis and ARD administration synergize in promoting MRONJ, with an increased release of pro-inflammatory cytokines. The same authors suggested that ”pro-inflammatory cytokines may represent therapeutic targets to prevent osteonecrosis induced by infectious osteomyelitis in patients treated with anti-resorptive therapy” [48][49]. Increased levels of β-defensins were also described in osteomyelitis of the jaw compared to uninfected healthy jaws, while in infected osteoradionecrosis (ORN), their levels were significantly reduced [50]. This observation suggests that, in MRONJ, bone displays not only necrotic characteristics similar to the ORN samples, but it shows the previously described aspect of bone affected by bacterial infections [51]. Thus, Stockman et al. concluded that “The increased expression of human β-defensins in bone samples of N-BP-induced ONJ can be interpreted as a sign of unimpaired metabolic activity and can therefore be seen as a reaction of vital bone to microbial invasion” [50]. Furthermore, β-defensins are expressed by OBs, stimulating their proliferation and differentiation process [52], and, in patients with infection, the level of expression of β-defensin-2 by OBs has been found to increase, suggesting that antimicrobial peptides play a central role in the prevention of bone infection. Looking at patients treated with immunosuppressive drugs, an increased susceptibility to bone infection seems to occur due to decreasing antimicrobial peptide expression levels [53]. Considering all these data and the fact that an intrinsic basal level of β-defensin 3 expression is independent of exposure to bacterial stimuli, it is still unclear whether AMP expression contributes to the MRONJ pathogenesis or if it is simply an after-effect of the disease [54].

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