Denosumab-related osteonecrosis of the jaw: A literature review

Martwica kości szczęk wywołana denozumabem – przegląd piśmiennictwa

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Abstract

Osteonecrosis of the jaw (ONJ) is a rare treatment-related side effect of anti-resorptive drugs whose risk is increased by concomitant local and systemic factors. The number of cases of medication-related ONJ is constantly increasing as a result of the rising tide of molecular-targeted and immunological drugs used in cancer treatment. Denosumab-related ONJ presents peculiar pathophysiological, histopathological, clinical, and therapeutic features compared to that induced by bisphosphonates-related ONJ.

This study aimed to compare ONJ induced by denosumab to that caused by bisphosphonates. We have reviewed the literature of the last 5 years on denosumab-related ONJ, focusing on reviews and meta-analyses.

The physiopathology of ONJ is unclear. Denosumab acts on receptor activator of nuclear factor kappa-B ligand (RANKL) to inhibit the formation and activity of osteoclasts. The reduction of bone turnover seems to play an important role. Dentists and oral surgeons in the coming years will see an increasing number of patients who are receiving treatment potentially toxic to bone, but also require good dental care. Early recognition of ONJ is essential in the patient's treatment with denosumab, therefore a close collaboration between the dentist and oncologist is fundamental.

Key words: jaw, osteonecrosis, denosumab

Słowa kluczowe: szczęka, martwica kości, denosumab

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In 2003, for the first time Marx described 36 cases of osteonecrosis of the jaw (ONJ) induced by bisphosphonates in cancer patients.[1] Next year, Ruggiero described 63 cases. In the following years, the number of cases has rapidly increased, both as spontaneous reports to the various pharmacovigilance agencies, and as articles and case reports in medical journals.[2] Denosumab-related osteonecrosis of the jaw (DRONJ) was first reported in 2010 by Taylor.[3] Denosumab is a new antiresorptive drug, approved in June 2010 by the US Food and Drug Administration (FDA), under the name Prolia® (Amgen, Thousand Oaks, California, USA) for use in osteoporosis in postmenopausal women, and in November 2010 under the name Xgeva® (Amgen, Thousand Oaks, California, USA) for use in bone metastases cancers. The safety data sheet for this drug reads as follows: "(...) Rare cases of jaw bone necrosis have been reported in clinical trials in patients receiving denosumab; consideration should be given to conducting a dental examination before initiating treatment in patients with co-occurring risk factors; Patients undergoing treatment should avoid invasive dental procedures; during the treatment, special care should be taken during oral hygiene (...)".

This is a systematic critical review of the full-text papers focusing on reviews and meta-analyses published on the topic in the last 5 years in Medline-Pubmed, Google Scholar, Scopus, and Cochrane electronic databases, using the following key words: osteonecrosis of the jaw, denosumab, and metastatic bone cancer.

ONJ is a multifactorial disease characterized by necrotic exposed bone, intra-oral bone or extra-oral fistula in the maxillofacial area persistent for more than 8 weeks when radiotherapy or metastasis causes have been excluded, associated or not with pain and swelling of the soft tissues. Cases of spontaneous appearance have been observed, especially in patients with poor oral hygiene and dental or periodontal diseases, but the frequency is still unknown. In regard to drugs, ONJ was originally described in association with bisphosphonates, but recently their number has increased so much that in 2014 the American Association of Oral and Maxillofacial Surgeons (AAOMS) suggested renaming it "medication-related osteonecrosis of the jaw" (MRONJ). Bisphosphonates (BPs) and denosumab (DMab) are included among the antiresorptive drugs associated with ONJ. More recently, cases due to anti-angiogenic and immunological drugs have also been reported. ONJ's risk is increased by a set of local and systemic factors (Table 1).

ONJ can affect both the mandible and maxilla. Two thirds of cases affect the mandible, a third affect the maxilla and both in only 4% of cases. The physiopathology of ONJ is unclear. The special predisposition for the posterior region of the mandible is due to the increased density, poor blood supply and continuous masticatory stimulation there. Infections are an important factor, although it is not clear whether the infection precedes necrosis or it is rather a super infection of a necrotic base. However, the oral mucosa covering the jawbone is thin and the over 800 types of bacteria that form the dental plaque can pass into the underlying bone, especially in the presence of inflammation or mucosal injury. The presence of bacteria stimulates bone resorption through the production of cytokines which can contribute to bone necrosis. In ONJ lesions, vital bone is mixed irregularly with necrotic bone colonized by *Actinomyces* sp. colonies. The reduction of bone turnover seems to play an important

Table 1. Risk factors for ONJ

Local factors	Systemical factors
Tooth extraction	longer duration of antiresorptive therapy for metastatic neoplasia (breast, lung, prostate, rein and myeloma) or post-menopausal osteoporosis
Dent alveolar surgery	radiotherapy
Periodontal disease	chemotherapy
Trauma	antiangiogenic drugs: bevacizumab, sunitinib
Poor oral hygiene	immunotherapy: ipililumab
Local suppuration	glucocorticoid therapy
Denture use	erythropoietin therapy
	diabetes
	anemia
	hypertension
	hypothyroidism
	hyperparathyroidism
	renal failure and renal dyalisis
	osteoporosis
	smoking
	increasing age

Table 2. Classification of ONJ according to AAOMS 2009[4]

Pre-ONJ	No exposed/necrotic bone in patients who were treated with BPs
Stage 0	No clinical evidence of necrotic bone, but not specific symptoms or radiographic signs
Stage 1	Bone exposed/necrotic in asymptomatic patients who have no evidence of infection
Stage 2	Bone exposed/necrotic associated with infection as evidenced by bone pain and erythema in the exposure region with or without purulent drainage
Stage 3	Bone exposed/necrotic in patients with pain, infection, and one or more of the following conditions: pathologic fracture, extraoral fistula, osteolysis extension beyond the alveolar bone (eg. lower edge and mandibular branch; zygomatic process of the maxilla and maxillary sinus, nasal floor)

role, and this suggests the association of ONJ with antiresorptive drugs and a dose-related risk. However, there are other associated conditions with low bone turnover in which the ONJ problem does not arise. The BPs could act on ONJ through a reduction of the blood supply, thanks to their antiangiogenic properties. Conversely, DMab has no anti-VEGF action. In the last few years, cases of ONJ were reported in association with antiangiogenic agents, suggesting that angiogenesis suppression may play a role in ONJ's pathogenesis. Some experts suggest that there may be elements of a genetic predisposition, such as polymorphisms of farnesyl pyrophosphate synthase and cytochrome CYP450/CYP2C8.

ONJ clinically can be classified into 3 stages[4] (Table 2). Up to 30% of ONJ cases debut in stage 0, characterized by an absence of clinically exposed bone in patients presenting with nonspecific symptoms or radiographic findings, including alveolar bone depletion, trabecular alterations, lamina dura thickening, and narrowing of the alveolar duct. ONJ stage 0 has been described in the course of therapy with antiresorptive drugs, but the diagnosis is difficult and often delayed.

Bedogni et al. have proposed a new classification in 3 stages which includes CT imaging findings and eliminates stage 0 (Table 3).[5] Franco et al. in 2014 proposed a new dimensional staging system, classifying the lesions by size following imaging findings, with a view to making treatment decisions easier (Table 4).[6]

DMab is an antiresorptive drug indicated in post-menopausal osteoporosis and in some cancers with symptomatic bone metastases, hypercalcemia and prevention of skeletal-related events. In 2 phase III clinical trials comparing denosumab and zoledronic acid in patients with metastatic cancer, it appeared that the ONJ frequency is similar. A recent meta-analysis reports that the mean incidence of DRONJ in over 5700 cancer patients is 1.8% vs 1.3% in the zoledronic acid arm.[7] In contrast, during treatment of osteoporosis every 6 months with DMab, the occurrence of ONJ is very rare. In the FREEDOM study, no cases of ONJ occurred in 7000 women within 3 years of follow-up.[8] DMab is a human monoclonal immunoglobulin (IgG2) that binds the cytokine RANKL (receptor of activator of NF kB ligand) produced by osteoblasts, preventing the activation of the RANK receptor on the

Table 3. Classification of ONJ according to Bedogni et al.[5]

Classification of ONJ	
Stage 1	**Focal ONJ** Clinical signs and symptoms: bone exposure, sudden dental mobility, nonhealing postextraction socket, mucosal fistula, swelling, abscess formation, trismus and gross mandible deformity hypoesthesia/paraesthesia of the lips. CT signs: increased bone density limited to the alveolar bone region (trabecular thickening and focal osteosclerosis), with or without the following signs: markedly thickened and sclerotic lamina dura, persisting alveolar socket and cortical disruption
Stage 2	**Diffuse ONJ** Clinical signs and symptoms: same as stage 1. CT signs: increased bone density extended to the basal bone (diffuse osteosclerosis), with or without the following signs: prominence of the inferior alveolar nerve canal, periosteal reaction, sinusitis, sequestra formation and oro-antral fistula
Stage 3	**Complicated ONJ** Same as stage 2, with one or more of the following: Clinical signs and symptoms: extra-oral fistula, displaced mandibular stumps and nasal leakage of fluids. CT signs: osteosclerosis of adjacent bones (zygoma and hard palate), pathologic mandibular fracture and osteolysis extending to the sinus floor

Stage 1a: asymptomatic; stage 1b: symptomatic (pain and purulent discharge). Stage 2a: asymptomatic; stage 2b: symptomatic (pain and purulent discharge). CT: Computed tomography; ONJ: Osteonecrosis of the jaw.

Table 4. Classification of ONJ according to Franco et al.[6]

Classification of ONJ	
Stage 0	No exposed bone, with nonspecific radiographic findings such as osteosclerosis and periosteal hyperplasia, and nonspecific symptoms such as pain
Stage I	Exposed bone and/or radiographic evidence of necrotic bone*, or persistent socket space < 2 cm in greater diameter, with or without pain
Stage II	Exposed bone and/or radiographic evidence of necrotic bone*, between 2–4 cm in major diameter, with pain responsive to NSAIDs, and possible abscesses
Stage III	Exposed bone and/or radiographic evidence of necrotic bone*, > 4 cm in greater diameter, with intense pain that respons or does not respond to NSAIDs, abscesses, orocutaneous and/or maxillary sinus fistulization, with mandibular nerve involvement

* Radiographic evidence of necrotic bone: irregular areas of hypo- and hypercalcification and/or bone sequestration.

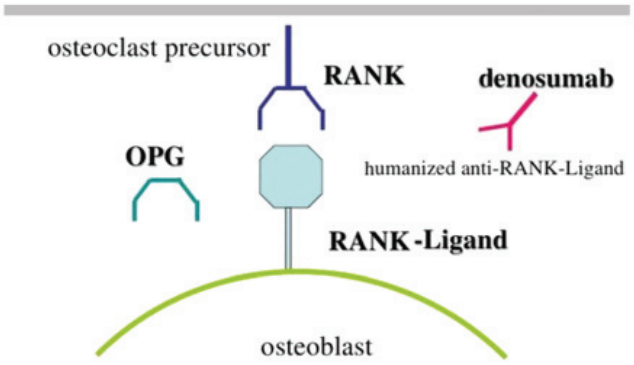

Fig. 1. Mechanism of action of denosumab

osteoclast and the precursor cell surface (Fig. 1). The reduction of the RANK/RANKL interaction inhibits osteoclast formation, its activity and survival. Additionally, bone resorption is reduced and bone mass is enhanced.[9,10]

Bone resorption is essential for the subsequent neoformation step and the correct sequence of resorption and bone formation is essential in the bone remodeling process. The inactivation of RANKL by denosumab also decreases macrophage mobility and chemotaxis. Macrophages are the first line of defense against invading microorganisms and the decrease of host defense mechanisms may predispose to the development and worsening of ONJ.[11] There are some differences between DRONJ and BRONJ (bisphosphonate-related ONJ). The slight prevalence of females in ONJ could be related to the many patients treated with BPs for osteoporosis and breast cancer. However, some authors deny gender differences. DRONJ can occur after a number of lower doses of the drug (8 to 15), compared to BRONJ, whose risk typically depends on the cumulative dose. DMab has a half-life of roughly 32 days and it seems that it does not induce the formation of neutralizing antibodies. After administration of the first dose, the inhibition of osteoclast activity occurs after just 6 hours, ending within 6 months after the last dose. Therefore, it is recommended to postpone any surgery until 4–6 months after termination of the DMab.[12] Unlike BPs, DMab does not accumulate at the bone level, whereby DRONJ is less intense that BRONJ, is rapidly reversible and responds better to conservative treatment. Also, the histopathological appearance of DRONJ is different: the viable bone around the sequestrum is characterized by a decreased number of morphologically immature osteoclasts as indicated by the presence of very few nuclei and this may reflect the inhibition of the formation and maturation of osteoclasts from monocyte cell lineage.

The particular incidence of DRONJ in cancer patients seems related to drug-dependent factors (dose used, duration of the treatment) and to the specific kind of malignancy. A recent meta-analysis suggested that patients with prostate cancer have 3 times higher risk compared to other types of cancer, probably linked to anemia and frequent use of corticosteroid.[7] In the case of breast cancer, concomitant use of drugs that reduce bone turnover (aromatase inhibitors) is an additional risk factor. In any case, the safety profile of DMab after long-term exposure is 19.1 months in breast cancer and 12 months in prostate cancer.[13] Finally, metastatic kidney cancer is a special case. This patient setting is particularly susceptible to ONJ due to the concomitant use of antiangiogenic drugs that block vascular endothelial growth factor (VEGF). In recent years, some cases of ONJ have been reported during treatment with bevacizumab[14,15] and sunitinib.[16] whereby it is possible that the potent antiangiogenic activity of VEGF-targeting agents may inhibit bone remodeling and promote ONJ development. Additionally, it is possible that these drugs may compromise the integrity of the bone and mucosal blood supply. Another group of drugs used in the treatment of these patients and of which one can hypothesize a co-factor role in the development of ONJ is mammalian target of rapamycin (mTOR) inhibitors,[17] such as temsirolimus. Inhibition of mTOR is accomplished through the binding of intracellular protein FKBP-12, which follows a lower expression of D-type cyclins, c-myc and ornithine decarboxylase, regulatory proteins of the cell cycle, which results in the stopping of the cell in G1. It also reduces the phosphorylation of proteins (4E-BP 1 and S6K) of the PI3 kinase/AKT, thus blocking cell division. However, it has the ability to inhibit the production of hypoxia-inducible factors (HIF-1 and HIF-2α) and vascular endothelial growth factor (VEGF), with consequent inhibition of tumoral angiogenesis. mTOR inhibition causes cell growth arrest and often immunosuppression, which explains the infection susceptibility of the treated patients.

Conclusions

ONJ is a rare condition associated with antiresorptive therapy. Denosumab-related ONJ and bisphosphonate-related ONJ have a similar frequency, but have different pathogenetic, clinical and histopathological features. The vast majority of cases (>90%) occurs in cancer patients, and simple preventive procedures are effective at reducing the risk. The growing association of drugs that can act as co-factors in favor of bone resorption, reducing blood supply and promoting infections should be avoided. A close collaboration between the oncologist and dentist is essential for its prevention, early diagnosis and treatment.

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