Medication-Related Osteonecrosis of the Jaws (MRONJ): Etiological Update

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Abstract

Osteonecrosis of the jaws (ONJ) is an uncommon but severe bone disease, can be related to various medicaments (MRONJ) including bisphosphonates (BRONJ), antiangiogenic and antiresorptive medicaments such as Denosumab (DRONJ), human monoclonal antibody to the receptor activator of nuclear factor-kB ligand. The rise in number in the latest years can be explained with many patients treated with all these drugs, assumed for osteometabolic (i.e osteoporosis, osteogenesis imperfecta) or neoplastic diseases (multiple myeloma, metastatic breast, prostate and renal cancer). The onset mechanism of MRONJ is not entirely understood, probably different mechanisms are involved, such as inhibition of the osteoclasts differentiation and function, decrease of the angiogenesis and inflammation/infection of the jaw bones. Some pathogenetic mechanisms are different according to the drugs, for example the cases of the RANK-ligand inhibitor related ONJ may occur without considering the period of medication intake; also the risk of ONJ manifestation after bisphosphonates (BF) is not significantly diminished after interrupting the drug therapy, because BF bind to the bone matrix for many years. Drugs currently implicated in osteonecrosis pathology are various, therefore the term ONJ was currently replaced by MRONJ; it is necessary that the anamnestic phase and management of the patients to be more detailed and correct, not only to prevent osteonecrosis but also to plan all necessary treatments before start of the drug therapy.

Keywords: *Osteonecrosis of the jaws, Bisphosphonates, Antiresorptives, Denosumab, Antiangiogenics*

1.Introduction

Osteonecrosis of the jaws (ONJ) is an uncommon but severe bone disease, can be related to various medicaments including bisphosphonates (BF), antiangiogenic and antiresorptive drugs such as Denosumab, and recently was reproted also some human monoclonal antibody to the receptor activator of nuclear factor-kB ligand. The Special Committee on medication-related osteonecrosis of the jaws, created by American Association of Oral and Maxillofacial Surgeons, favors the term Medication related osteonecrosis of the jaws (MRONJ) alternatively at Bisphosphonate related osteonecrosis of the jaws (BRONJ) [1]. MRONJ can really affect quality of life, so it is very important to immediately identify the pathology and risk factors.

The clinical classification and treatment of MRONJ are significantly unchanged. In order to diagnose patients with MRONJ, all these manifestations must be demonstrated: no patient history of radiotherapy or prominent metastatic disease of the jaws, [2] patient treated or still being treated with antiresorptive or antiangiogenic medicaments, bone exposure (Fig 1) or presence of an intraoral or extraoral fistula in the maxillofacial region which persisted for more than 8 weeks (Fig 2a, 2b). This definition is totally clinical and bone exposure is a late sign of this disease.

About medicaments that can cause ONJ, two different categories can be distinguished: antiresoptive (including Bisphosphonates and RANK-L inhibitors) and

antiangiogenic medications (Tab 1). Intravenous bisphosphonates (IV BPs) are used to manage cancer-related conditions, including skeletal-related events (SRE) associated with bone metastases in the context of solid tumors such as breast cancer, prostate cancer, lung cancers and for the management of lytic lesions in the setting of multiple myeloma. Oral bisphosphonates (OBPs) instead, are used to treat osteometabolic diseases, such as osteoporosis, osteopenia and other less common syndromes such as Paget's disease of bone and osteogenesis imperfecta [3-4].

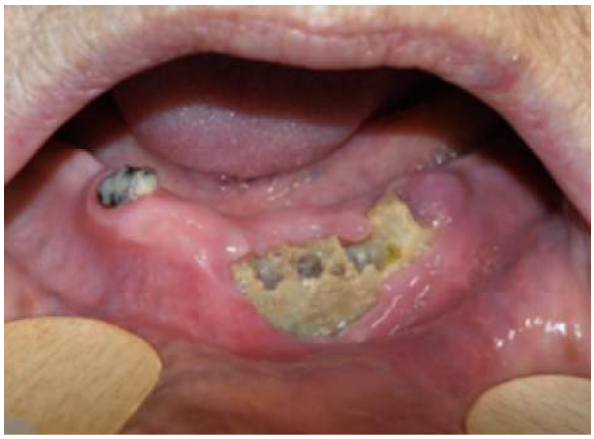

Figure 1. MRONJ

BPs can also be divided into aminobisphosphonates (NBPs) (Zolendronate, Pamidronate, Alendronate, Risendronate, Ibandronate, Neridronate) and non-aminobisphosphonates (Clodronate, Tiludronate, Etidronate), depending on the presence of an amine functional group in the molecule. NBPs are the only kind of bisphosphonates associated with osteonecrosis [5-6].

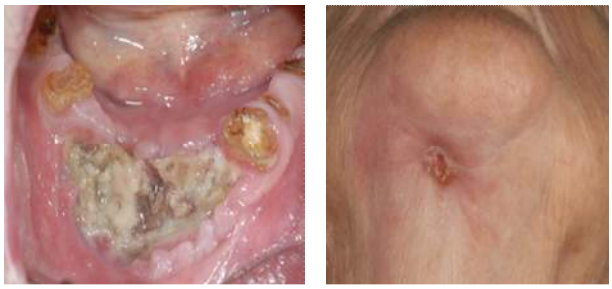

Figure 2a,2b. MRONJ complicated: osteonecrosis of the jaw with extraoral fistula.

RANK ligand inhibitor (Denosumab) is considered an antiresorptive medication and hinders the development, activity of osteoclasts, decreases bone resorption and increases bone density [7-8] and it is used effectively for the management of osteoporosis and metastatic bone diseases.

These medications can improve the quality of life of patients, even though their positive effects on the cancer-specific survival are not demonstrated.

Differently from BPs, whose osteonecrotic effects endure for years depending on the cumulative dose, the way of administration and the effects of RANK ligand inhibitors decreases very quickly after the end of administration [9-10].

Table 1 : MRONJ Related Medications.

Category	Molecule	Trade name
Biphosphonate	Alendronate	Fosamax, Merck
Biphosphonate	Ibandronate	Bonviva, Roche
Biphosphonate	Neridronate	Nerixia, Abiogen Pharma
Biphosphonate	Pamidronate	Aredia, Novartis
Biphosphonate	Risedronate	Actonel, Procter and Gamble
Biphosphonate	Zolendronate	Zometa, Novartis
Biphosphonate	Tiludronate	Skelid, Sanofi-Aventis
RANK-L inhibitors	Denosumab	Prolia/Xgeva, Amgen
Antiangiogenic medicament	Bevacizumab	Avastin, Roche/Genentec
Antiangiogenic medicament	Vatalanib	Investigational Status

Antiangiogenetic medications interferes with the formation of new blood vessels rather than arrest tumor cells growth; the main mechanism of action of this class of medicaments involves the angiogenic growth factor (Vascular Endothelial Growth Factor, VEGF) and its receptor (VEGFR).

There are basically two types of drugs: monoclonal antibodies (administered intravenously) that block the receptor or growth factor (Bevacizumab) and small molecules, which determine the block by binding the tyrosine kinase receptor (Sunitinib and Sorafenib). It has been hypothesized that these drugs facilitate the delivery of other anticancer agents. Therefore, this therapy may need to be administered over a long time [11].

The aim of this etiological update is to emphasize the early detection of risk factors and describes all drugs involved in MRONJ and their mechanism of action considered in the recent literature.

2. Physiopathology and risk factors

The onset mechanism of MRONJ is not entirely understood. There are some hypothesis that could explain the localization exclusively to the jaws, such as presence of microtrauma, soft tissue BPs toxicity,

infections, peculiar biofilm of the oral cavity, high bony turnover, terminal vascularization of the mandible, possibility of bone exposition during oral treatments and alterations medicament-dependent (bone resorption and remodeling, angiogenesis inhibition) [12-13].

The most popular hypothesis blames the higher turnover of the jawbones and antiresorptive drugs that causes oversuppression. As osteonecrosis does not manifest itself in other sites, the turnover of the jawbone consequently has to be higher than other bone sites; in addition, there has to be a disproportionate inhibition of turnover in the jawbone compared with the rest of the skeleton after regular use of denosumab or bisphosphonates. In contrast, recent studies state that turnover of the jawbone is not changed either by a bisphosphonate or denosumab, so it seems unlikely that over suppression of turnover in the jawbones plays an important role in the pathogenesis of MRONJ [14].

Table 2 : MRONJ Risk Factors.

	Risk factors
Medication-related	Molecule
	Way of administration (IV; IM; OS)
	Total Amount
	Length of the therapy
Underlying pathology-related	Disease
	Steroid therapy
	Eritropoietic factors
	Tobacco
	Alcohol
	Sex
	Age
	Obesity
	Genetic factors
	Concurrent pathologies
	(Diabetes, anemia, dialysis, osteomalacia, hypocalcemia,
	Rheumatoid arthritis, immunosuppression)
Local factors-related	Oral surgery
	Osteointegrated implantology
	Removable prosthesis
	Microtrauma
	Inflammatory disease
	Anatomic conditions

This pathology could be caused by the inhibition of osteoclast differentiation and function and by the increase of apoptosis in order to limit the growth of the tumor. In fact, drugs remain bonded to the hydroxyapatite for a long time, so their effects remain for years, depending on the amount of medicament administered and on the duration of the therapy. During osteoclastic bone resorption, drugs are released from the bone mineral and internalized via endocytosis by osteoclasts. However, accumulating evidence indicates that not only osteoclasts but also other phagocytes are capable of taking up small amounts of molecules. Medicaments use this action mechanism are: Zoledronate, Pamidronate, Ibandronate, Residronate, Alendronate, Tiludronate, Etidronate. N-BPs inhibit farnesyl diphosphonate synthase and block prenylation of small GTPases.

Table 3: The ONJ risk.

Cancer patients		Osteoporotic patients	
Therapy	Cases x patients	Therapy	Cases x patients
Placebo	0-1,9 x 10,000	Placebo	0-2x 10,000
Zolendronate	100 x 10,000	Oral bisphosphonates < 4 years	10x 10,000
Denosumab	70/90 x 10,000	Oral bisphosphonates > 4 years	21x 10,000
Bevacizumab	20 x 10,000	Zolendronate for 3 years	1,7x10,000
Zolendronate+ Bevacizumab	90 x 10,000	Denosumab	4x10,000

Deregulation of small GTPase signaling causes disruption of cytoskeletal organization, vesicle transport, loss of the sealing zone and ruffled border resulting in the detachment of osteoclasts from bone surfaces leading to the loss of function and survival. ONJ can occur after dental procedures, such as teeth extraction, since the possible infection of the wound. The infection extends into bone and bone cells are no more capable to react and limit the process [15-16].

On these bases, both systemic and oral infections/inflammations are implicated in ONJ pathogenesis. In fact, patients with periodontitis and abscesses presence a higher risk of developing ONJ, because the infection triggers necrosis. Moreover, it is appropriate to report inhibition of angiogenesis as a possible mechanism that can cause ONJ. This mechanism is useful to interfere with the growth of the tumor but it can also cause ischemia and then necrosis. If this process occurs in the jaws the patient may present circulating VEGF levels, reduction in vascularization and eventually necrosis. Medicaments using this action mechanism are Sorafenib (Nexavar®),Sunitinib (Sutent®),

Pazopanib (Votrient®), and Everolimus (Afinitor®) and Bevacizumab (Avastin®). Even some BPs use this mechanism, such as zolendronic acid, but angiogenesis's inhibition has not been reported with denosumab [17].

Another hypothesis is based on soft tissue toxicity: multiple cell types underwent increased apoptosis or decreased proliferation after exposure to medicaments, especially BPs, even though their concentration in tissues outside bone is minimal. In contrast to BPs, no soft tissue toxicity has been reported with denosumab [18].

As a cause of ONJ we can also consider innate or acquired immune dysfunction: immune dysfunction can cause mucosal ulceration, delayed healing, exposed bone, histologic necrosis, inflammation when BPs and chemiotherapy are administered. For this concern, three risk factors have to be considered: underlying disease, type of medication and local factors (Tab 2).

Therapeutic indications are classified into two categories: osteoporosis/osteopenia or malignancy. Medications instead are classified into two types: BPs and non-BPs (other antiresorptive and antiangiogenic medications) [18].

A higher risk of developing ONJ in patients with cancer exposed to zolendronate than cancer patients treated with placebo (risk between 50-100 times higher) is feasible. Among cancer patients, exposed to denosumab, the risk of MRONJ is comparable to the risk of ONJ in patients exposed to zolendronate, even if with denosumab there is no antiangiogenic effect.

Bone turnover in patients treated with bisphosphonates remains low and resembling a memory effect, according to observations that in patients being treated with BFs tooth extraction sockets were not remodeled and remained visible for months or years. Indeed, this is most probably because BFs covalently bind to bone and remain there for years. In contrast, the effect of denosumab as an antibody is temporary. It has been shown that remodeling of the jaw-bone is resumed when denosumab is stopped.

This is in line with the concept that there is an increase in bone turnover when denosumab is being administered [14].

As Ruggero e coll. reported in the Position paper of the AAOMS this year [1], the risk of MRONJ is different if we consider the medications and the administrations. We can resume the ONJ risk in the table 3.

Although the epidemiologic data report similar results, it is important to underline a significant difference between BRONJ and DRONJ. While the BRONJ is reported to occur after a mean administration of 33 months (intravenous oncological dosing) or 48 months (oral osteoporosis dosing), the RANKL-ligand inhibitor related osteonecrosis occurs early after the administration, independent on the number of previous administrations [1].

At the same time, risk of developing an ONJ after each RANKL inhibitor administration decreases from month to month, while risk of developing BRONJ remains stable for years. In fact, the risk of developing BRONJ is related to the total amount of drug assumed, and to the duration of the therapy. The concomitant assumption of antiangiogenic, especially bevacizumab and antiresorptive therapies increases the risk of MRONJ.

Another risk factor that should be taken into account is administration of steroid therapy and erithropoietic factors. Which increase the risk of MRONJ in patients with myeloma. Even assumption of tobacco and alcohol is mentioned as a potential risk factor, even if it is not evidence-based. There are not sufficient studies about the role of sex, age and obesity in developing MRONJ.

The risk is higher with the presence of concurrent pathologies such as diabetes, anemia, dialysis, osteomalacia, hypocalcemia, rheumatoid arthritis and immunosuppression. Analyzing local factors, concomitant oral disease, operative treatment and anatomic factors are important in determining the risk of developing ONJ. [19-20]

Several studies report that among patients with MRONJ, tooth extraction is a common predisposing event ranging from 52 to 61% of patients reporting tooth extraction as the precipitating event, while limited information regarding anatomic risk factors for MRONJ is available. MRONJ is more likely to appear in the mandible (73%) than the maxilla (22.5%) but can appear in both jaws (4.5%). Denture use was associated with an increased risk of the ONJ among cancer patients exposed to zolendronate. Pre-existing inflammatory dental disease such as periodontal disease or periapical pathology is a well-recognized risk factor. Among cancer patients with MRONJ and pre-existing inflammatory dental disease was a risk factor among 50% of the cases [1].

3. Conclusions

MRONJ is a complication multi drugs-related that can lead to oncologic treatment interruptions as well as diminished quality of life, it is therefore necessary that the anamnestic phase and patient management are more detailed and correct, both to prevent osteonecrosis but also to plan all necessary treatments before drug therapy.

For this reason, many research groups on Osteonecrosis of the jaw were performed. One of this is CROMa (Coordination of Research on Osteonecrosis of the Jaw), set up in 2007 at the Department of Oral and Maxillofacial Sciences of "Sapienza" University of Rome; the aim of CROMa is to prevent or to treat established MRONJ and to give relevant pieces of information and

advice both to patients and to bisphosphonates prescribing providers, in order to provide a comprehensive patient-centered oral care delivery; in particular all patients with past, current, or planned BPs therapy, follow three possible care pathways, consisting in prevention, surgery and oral clinics. In the prevention path patients receive oral hygiene and personal oral hygiene instructions every 4 months, surgery procedures are performed in case of hopeless teeth recommending a

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